

Validity of Different Fibrosis Scores for Assessment of Hepatic Fibrosis in Chronic Hepatitis B Patients

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Abstract

Background and aim: Severity of liver fibrosis could be discriminated through biological and physical method. This study was conducted to evaluate the diagnostic value of serum markers of fibrosis and ARFI elastography for CHB related liver fibrosis compared to liver biopsy.

Methods: A total of 92 CHB adult Egyptian patients were included in this study, all were subjected to liver biopsy with staging of fibrosis using METAVIR scoring system.

Liver stiffness measured through acoustic radiation force impulse (ARFI) and non-invasive fibrosis scores including AST/ALT ratio (AAR), AST/platelet ratio (APRI), fibrosis index based on four factors (FIB-4), fibro-Q test, King's score, BARD score, cirrhosis discriminate score (CDS), S index and APAG score were compared to biopsy result.

Results: Among the studied scores, APRI score, FIB-4, Fibro-Q test and King's score were significant predictors for advanced fibrosis in CHB patients, with King's score showing the highest AUROCs for predicting advanced fibrosis. The optimal King's score cut off value for predicting advanced fibrosis was >9.62 with 58.33% sensitivity and 98.75 specificity. ARFI elastography was not effective predictor for advanced fibrosis in CHB patients. Multivariate analysis showed that diabetes mellitus (D.M) was the only predictor for advanced fibrosis in CHB patients.

Keywords: AAR, APRI, ARFI, chronic hepatitis B, FIB-4, King's score, non-invasive scores.

Abbreviations

AAR=AST/ALT ratio, ALT= alanine transaminase, Anti HBe= hepatitis B e antibody, APAG=age, platelets, albumin and gamma glutamyltransferase, APRI= AST/platelet ratio, ARFI= acoustic radiation force impulse imaging, AST= aspartate transaminase, BMI= body mass index, CBC= complete blood count, CDS=Cirrhosis Discriminate Score, CHB=chronic hepatitis B, CHC= chronic hepatitis C, D.M=diabetes mellitus, DNA= deoxyribonucleic acid, ECM= extracellular matrix, FIB-4= fibrosis index based on four factors, GGT= gammaglutamyltransferase, HB=hemoglobin, HBeAg= hepatitis B e antigen, HBsAg= hepatitis B surface antigen, HBV= Hepatitis B virus, HCV= hepatitis C virus infection, HSCs= hepatic stellate cells, INR= international randomized ratio, IQR= interquartile range, mL= milliliters, MRE= magnetic resonance elastography, NAFLD= non-alcoholic fatty liver disease, PCR= polymerase chain reaction, PT=prothrombin time, ROC= Receiver operating characteristic, ROI= region of interest, SSI= supersonic shear wave imaging, TE= transient elastography.

1. INTRODUCTION

Hepatitis B virus (HBV) infection is one of the world's most significant public health problems [1]. Globally, about 260 million people are estimated to be chronically infected with HBV. Liver fibrogenesis; a consequence of chronic hepatitis B (CHB) infection, is a dynamic, process responsible for driving the progressive excess accumulation of extracellular matrix (ECM) components (i.e., liver fibrosis) and sustained by the activation of hepatic stellate cells (HSCs) [2,3]. Liver biopsy has traditionally been considered the reference

method for evaluation of hepatic fibrosis in patients with chronic liver disease.

However, it is costly and invasive procedure that requires physicians and pathologists to be sufficiently trained in order to obtain adequate and representative results. These limitations have led to the development of non-invasive methods for assessment of liver fibrosis. These methods rely on two different approaches: a "biological" approach based on the quantification of biomarkers in serum samples or a "physical" approach based on the measurement of liver stiffness [4].

Serum markers are grouped into two main categories: direct and indirect biomarkers. Direct Markers are either linked to matrix deposition, or cytokines and chemokines linked to liver fibrosis [5]. Indirect markers are numerous indices based on routine biochemical blood tests that reflect liver injury. Examples are AST/ALT ratio (AAR), AST/platelet ratio (APRI), fibrosis index based on four factors (FIB-4), King's score [5], S index, age, platelets, albumin and gamma glutamyltransferase (APAG) score [6], and BARD score [7].

Liver stiffness, which may change significantly as fibrosis develops, can be measured by a noninvasive imaging-based technique called elastography. Research over the past two decades has led to significant developments in elastographic methods, including magnetic resonance elastography (MRE), transient elastography (TE), and acoustic radiation force impulse imaging (ARFI), shear wave elasticity (SWE) and supersonic shear wave imaging (SSI) [8].

The aim of the current study was to evaluate the diagnostic value of serum markers of fibrosis and ARFI elastography for CHB related liver fibrosis compared to liver biopsy.

2. PATIENTS AND METHODS

2.1. Selection of Patients

This cross sectional study was performed on a total of 92 patients recruited from attendants to Tropical Medicine and Gastroenterology outpatient clinic, Sohag University Hospital during the period from December 2016 to June 2018. ARFI elastography was performed in Sohag Cardiology and Gastroenterology Centre.

Inclusion criteria were patients with symptomatic or asymptomatic CHB infection based on positive hepatitis B surface antigen (HBsAg) for more than 6 months. Exclusion criteria were: Patients with serological evidence of hepatitis C virus infection (HCV) or human immunodeficiency virus infection, HBV patients who had received or currently under anti-viral therapy, alcohol consumption, decompensated liver disease, Patients with hepatocellular carcinoma, Patients known to have other chronic liver disease (e.g. autoimmune hepatitis, primary biliary cirrhosis, Wilson's disease, haemochromatosis, non-alcoholic fatty liver disease (NAFLD), or drug induced chronic hepatitis), and patients with a contraindication to liver biopsy such as: uncooperative patient, Prothrombin time >4 seconds more than

control, INR greater than 1.6 [9], platelets count <100.000/mm [10].

According to histological staging of fibrosis, patients were grouped into 2 groups: Group 1: included 80 patients with mild to moderate fibrosis (F0, F1 and F2 METAVIR score), Group 2: included 12 patients with advanced fibrosis (F3 and F4 METAVIR score).

2.2. Clinical Assessment

Baseline patient characteristics including age, gender, body mass index (BMI), Symptoms suggestive of chronic liver disease or liver cell failure and presence of diabetes mellitus (D.M) or systemic hypertension were collected from all participants.

2.3. Laboratory Investigations

Peripheral venous blood sample of 5 milliliters (mL) was collected from each participant, and HBsAg, hepatitis B e antigen (HBeAg), hepatitis B e antibody (Anti HBe), polymerase chain reaction (PCR) for HBV deoxyribonucleic acid (DNA), gammaglutamyltransferase (GGT), HCV antibody, Complete blood count (CBC), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, prothrombin time (PT) and international randomized ratio (INR) were measured.

2.4. Calculation Of Fibrosis Scores

The score were calculated as described in the original articles.

- **AAR:** $AAR = AST \text{ (IU/L)} / ALT \text{ (IU/L)}$ [11].
- **APRI:** $APRI = (AST \text{ level (IU/L)} / AST \text{ ULN (IU/L)}) \times 100 / PLT \text{ (10}^9\text{/L)}$ [12].
- **FIB-4 score:** $FIB-4 = (Age \text{ (years)} \times AST \text{ (IU/L)}) / (\text{platelets (10}^9\text{/L)} \times \sqrt{ALT})$ [13].
- **The Fibro-Q test:** $FibroQ = 10 \times (\text{age (years)} \times AST \text{ (IU/L)} \times PT\text{-INR}) / (ALT \text{ (IU/L)} \times \text{platelets (10}^9\text{/L)})$ [14].
- **King's score:** $\text{king' score} = (Age \text{ (years)} \times AST \text{ (IU/L)} \times INR) / \text{platelets (10}^9\text{/L)}$ [15].
- **BARD score:** The BARD score is composed of three variables and the possible score ranges from 0 to 4 points, that is AST/ALT ratio at least 0.8 (2 points); a BMI at least 28 kg/m² (1 point); and presence of type 2 DM (1 point) [16].
- **Cirrhosis Discriminate Score (CDS):** CDS is composed of three variables: AST/ALT, PT-INR and platelet count. Different points

are given to ingredients of this index and the possible score ranges from 0 to 11 points^[17].

- **S index:** $S \text{ index} = (1000 \times \text{GGT (IU/L)} / (\text{platelets (10}^9\text{/L)} \times \text{albumin}^2 \text{ (g/dl)}))^{[18]}$.

- **APAG:** $\text{APAG} = e^P / (1 + e^P)$

$$P = -9.340 + 0.997 \times \ln(\text{age}) + 6.355 \times \ln(\text{PT}) - 3.372 \times \ln(\text{albumin(g/L)}) + 0.677 \times \ln(\text{GGT (IU/L)})^{[19]}$$

2.5. Liver Stiffness Measurement using ARFI Elastography

Liver stiffness was measured by ARFI elastography using a Siemens ACUSON S2000 Ultrasound System (Siemens AG) with a 6C1 HD transducer, by using Virtual Touch Tissue Quantification application in all patients. The measurement was performed in the right liver

lobe over segments 8[20]. Under fasting conditions for at least 8 hour [21], 10 valid ARFI measurements were performed for each patient by the intercostal approach. The patient was placed in supine position with the right arm in maximum abduction. Minimal scanning pressure was applied by the operator; the patient was asked to stop normal breathing for a moment to minimize breathing motion [22].

ARFI measurements were obtained in a selected region of interest(ROI; a box with dimension of 1 cm × 0.5 cm), at a depth of 1 to 2 cm from the liver capsule, avoiding large vessels and bile ducts [23]. Reliable measurements were defined as a median of 10 valid measurements with an interquartile range (IQR) to median value ratio less than 30% and the result is expressed in m/s[24](Figure 1, Figure 2).



Figure1. Acoustic radiation force impulse of the liver performed with the Siemens system through intercostal access. The measurement is given in meters per seconds^[25].

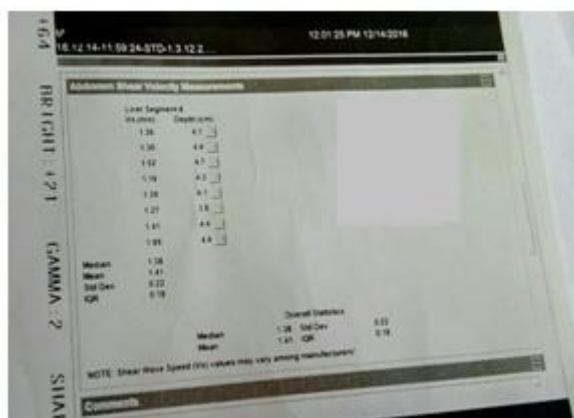


Figure2. Output report of ARFI examination with means, median and standard deviation.

2.6. Ultrasound Guided Percutaneous Liver Biopsy

Ninety two liver biopsy specimens were included in the study.

The obtained tissue cores (15 mm in length each) were fixed in 10 % formaldehyde, processed as usual, embedded in paraffin and sections of 4 μm thickness were prepared and stained with hematoxylin and eosin to assess

both the grade and the stage of chronic viral hepatitis using METAVIR staging systems [26]. Liver biopsies were examined by a single pathologist.

2.7. Data Analysis

Data were analyzed using IBM SPSS Statistics for Windows version 20 and Medcalc version 15.8.0. Quantitative data were expressed as means ± standard deviation for normally

distributed data, median and IQR for skewed data. Qualitative data was expressed as number and percentage. Quantitative data was tested for normality by Shapiro–Wilk test. Mann–Whitney U test and Spearman's correlation were used for data which wasn't normally distributed. Chi-square (χ^2) test and Fisher's Exact Test were used for comparison of qualitative variables as appropriate. Univariate and multivariate analysis were used to evaluate the predictors of advanced liver fibrosis. Receiver operating characteristic (ROC) curve was constructed for fibrosis markers, for optimum cut off point in predicting advanced fibrosis, and the area under the ROC curve value with 95% CI was calculated. Optimal cut-off value was determined; sensitivity, specificity, positive predictive value, negative predictive value were calculated. A 5% level was chosen as a level of significance in all statistical tests used in the study.

2.8. Ethical Considerations

The study protocol was approved by the ethical committee of Sohag Faculty of Medicine, Sohag University, Egypt. A written informed consent was obtained from each patient before enrollment in this study.

3. RESULTS

From December 2016 to June 2018, 92 patients (73 males and 19 females) were included in the study. The mean age of the participants was 36.41 ± 11.03 . Based on METAVIR score, patients were categorized into 2 groups: patients with advanced fibrosis (12 patients (13%), mean age 44.83 ± 11.74 , 10 males (83.3%)), and patients with mild to moderate fibrosis (80 patients (87%), mean age 35.15 ± 10.42 , 63 males (78.8%)). Liver fibrosis stage and inflammation grade by METAVIR score in studied patients are summarized in Table 1.

Baseline characteristics of the studied groups are shown in Table 2 which shows statistically significant differences among: age ($P = 0.006$), D.M ($P = 0.045$) and AST ($P = 0.042$).

Table 3 summarizes non-invasive markers of fibrosis in the studied groups. Mean shear wave velocity tends to be higher among patients with advanced fibrosis (mean velocity $1.64 \text{ m/sec} \pm 0.56$) compared to patients with mild to moderate fibrosis (mean velocity $1.39 \text{ m/sec} \pm 0.33$) but without statistically significant difference between both groups. APRI score showed statistically significant difference between patients with mild to moderate fibrosis and patients with advanced fibrosis ($P = 0.23$)

which can be also seen in Figure 3, Table 3. As seen in Figure 4, Table 3, FIB-4 model can significantly distinguish between patients with mild to moderate fibrosis and patients with advanced fibrosis ($P = 0.02$). Figure 5, Table 3 demonstrates the statistically significant difference of fibro-Q test between the studied groups ($P = 0.024$). King's score also showed statistically significant difference between both groups ($P = 0.013$) and this was demonstrated in Figure 6, Table 3.

Table 4 shows the diagnostic ability of the studied markers as presented by AUROCs for advanced fibrosis. King's score had the highest AUROCs (0.723) in predicting advanced fibrosis. It had 98.75% specificity and 58.33% sensitivity at a cutoff value >9.62 . APRI score had the next AUROCs (0.707) in predicting advanced fibrosis. It had 87.5% specificity and 58.33% sensitivity at a cutoff value >0.43 . FIB-4 had an AUROC of 0.706 in predicting advanced fibrosis with 98.75% specificity and 50% sensitivity at a cutoff value >1.83 . Fibro-Q test had an AUROC of 0.703 in predicting advanced fibrosis with 92.5% specificity and 50% sensitivity at a cutoff value >3.43 .

Table 5 summarizes the correlation between shear wave velocity and serum markers of fibrosis among the studied patients. There was a statistically significant positive correlation between shear wave velocity and APRI score ($r = 0.226$) ($P = 0.031$) (Figure 7). There was positive correlation between shear wave velocity and GGT level, AAR, FIB-4 model, fibro Q test, King's score, CDS and S index but without statistical significance.

Multivariate logistic regression analysis for predictors of advanced liver fibrosis is summarized in Table 6. Presence of D.M was the only independent predictor for advanced fibrosis with an odds ratio (OR) of 23.51 ($P = 0.028$).

4. DISCUSSION

Previous studies have shown that the severity of liver fibrosis could be discriminated through measurement of shear wave velocity by ARFI image [27], and also blood-based indices such as APRI [28] and Fib-4 score [29-30]. However, the performance of these indices in guiding indications for antiviral therapy in CHB has not been elucidated [20].

Our study evaluated the validity of ten noninvasive serum markers and ARFI elastography to predict advanced fibrosis compared to liver biopsy in Egyptian patients with HBV related liver disease. Our results showed that APRI score, FIB-4, Fibro-Q test and King's score were significant predictors of advanced fibrosis. AUROC analysis showed that King's score was superior to APRI, FIB-4 and Fibro-Q test in predicting advanced fibrosis at a cutoff value of >9.62 with 0.723 AUROC, 58.33% sensitivity and 98.75% specificity. To our knowledge, the relationship between King's score and the severity of fibrosis in CHB patients was first studied by [31]. His study compared between the performances of five noninvasive models in distinguishing high fibrosis from low fibrosis. These models included King's score, AAR, APRI, CDS and age/platelet index. He found that King's score had the highest correlation with liver fibrosis but AUROC analysis showed that the other four indices were superior to King's score in predicting high fibrosis. Hamidi et al [32] and Liu et al [33] found that King's score could successfully predict advanced fibrosis in CHB patients. A cutoff value of ≥ 8.16 was determined by Hamidi et al [32] with 0.629% sensitivity and 0.576% specificity. On the other hand, Dong et al [34] documented that King's score was one of the best noninvasive models for discriminating significant fibrosis but it was less accurate in predicting advanced fibrosis. Moreover, Dong et al [35] reported that King's score had moderate diagnostic value in prediction of advanced fibrosis in both treatment-naïve and treated CHB patients.

Our results also showed that the APRI model was effective in distinguishing advanced fibrosis from mild to moderate fibrosis in CHB patients at a cutoff value >0.43 . The diagnostic performance of APRI score for staging of fibrosis in CHB patients was studied by many authors. Eminler et al [31], Ma et al [36], Hamidi et al [32] Wu et al [37] and Lang et al [38] found that the APRI score could effectively predict advanced fibrosis at variable cutoff values. Eminler et al [31] described a cutoff value of >0.58 , with sensitivity and specificity of 57% and 76% respectively. Hamidi et al [32] documented a similar cutoff value with 60% sensitivity and 55.3% specificity. Moreover, Wu et al [37] reported that APRI and FIB-4 models had better diagnostic performance for advanced fibrosis than that for significant fibrosis.

Our results showed a good diagnostic performance of the FIB-4 for predicting advanced fibrosis in CHB patients at cutoff value of >1.83 (an AUROC 0.706, sensitivity 50% and specificity 98.75%). This is in agreement with many authors. Liu et al [39] evaluated the optimum cut off values of FIB-4 to predict different stages of fibrosis in CHB patients. For advanced fibrosis, the cutoff value was >1.727 with 65.8% sensitivity and 78.9% specificity. Addissouky et al [40] reported that FIB-4 was an efficient predictor of advanced fibrosis at a cut off value of >3.92 (AUROC 0.880, sensitivity 87.5% and specificity 82.35%). An AUROC of 0.81 was found by Mallet et al [41] at a cutoff value of >1.45 .

Our results also showed that the Fibro-Q model could predict advanced fibrosis at a cutoff value of >3.43 with AUROC 0.703, but it were inferior to King's score, APRI and FIB-4 models. Fibro-Q test was first proposed by Hsieh et al [14] to predict significant fibrosis ($\geq F2$ METAVIR score) and cirrhosis in chronic viral hepatitis patients. He found that it was better than APRI and similar to AAR for predicting significant fibrosis and cirrhosis. El-Saeid et al [42] evaluated the diagnostic performance of Fibro-Q test in both CHB and CHC patients and he found that the test could significantly distinguish mild fibrosis from advanced fibrosis. The AUROC was 0.91 at a cutoff point of 2.795. Ma et al. [36] and Coskun et al [43] reported that Fibro-Q could distinguish marked fibrosis but FIB-4 was more precise.

According to our results, serum GGT levels, AAR, CDS, BARD score and S index could not significantly distinguish advanced fibrosis. Our results agree with Eminler et al [31], Lang et al [38], Dong et al [34], Hamidi et al [32] and Chen et al [44] who reported a poor performance of AAR in predicting severe fibrosis. Our results also agree with Demir et al [45] who found that serum GGT level was not a predictor of severe fibrosis in CHB patients.

To our knowledge, CDS was extensively evaluated in patients with alcoholic liver disease and NAFLD with few studies in CHB patients. Our results agree with Dong et al [34] and Hamidi et al [32] who found a poor performance of CDS in discriminating advanced fibrosis in CHB patients. S-index was designed especially for CHB patients by Zhou et al [18] and he proved an accurate diagnostic performance of the test for predicting significant fibrosis and

cirrhosis. On the other hand, Dong et al[35]found that in CHB patients with ALT <2 ULN the performance of the test was accurate for predicting cirrhosis rather than staging of fibrosis. The BARD scoring system was proposed to evaluate fibrosis in NAFLD patients [16], and to our knowledge; data in CHB patients are limited. Our study showed that BARD score could not significantly discriminate advanced fibrosis. On the contrary, Zhang et al [7] found that BARD score could reliably detect advanced fibrosis in CHB patients. The association of this marker with fibrosis in CHB patients needs further study.

According to our knowledge, many studies investigating the performance of ARFI in patients with chronic hepatitis C (CHC)have been carried out [22,46-47] with less study examining the technique only in cases with CHB. The results of the current study showed a poor diagnostic performance of ARFI in predicting advanced fibrosis in CHB patients. This agrees with Hsu et al[48] who documented a relatively poor diagnostic performance of ARFI in CHB patients compared to other etiologies of chronic liver disease. Xu et al[49]found that the diagnostic performance of ARFI in CHB patients could be improved when combined with serum markers of fibrosis. On the contrary, the results of Ye et al[50],

Friedrich- Rust et al[51] Dong et al[52],Li et al[21] and Ozturker et al [53]showed a good diagnostic performance of ARFI in predicting severe fibrosis in CHB patients. Liu et al [54] reported that the performance of ARFI in diagnosing liver fibrosis in CHB patients is superior to that of serum markers. ARFI based assessment of liver fibrosis in CHB is complicated due to many factors. First, CHB infection is characterized by intermittent acute exacerbations during immune clearance stage [55]. Second, the unpredictable liver inflammation and injury may also bring different degree of liver stiffness [56]. In addition, advanced fibrosis stage (F3- 4) and BMI were also reported to affect the accuracy of ARFI in CHB [57]. In the current study, a positive significant correlation was found between ARFI measurements and APRI score, which agree with the results of Liu et al[58] and Lei et al[59].

To conclude, King's score has the best diagnostic performance among the studied scores in predicting advanced fibrosis in CHB patients; however, its validation in a larger number of patients is recommended. Also, further studyisrecommended to evaluate the diagnostic performance of ARFI elastographyin staging fibrosis in CHB patients.

Table1. Liver fibrosis stage and inflammation grade by METAVIR score in studied patients (No. = 92)

Variables	Summary statistics
Fibrosis	
F0	6 (6.5%)
F1	36 (39.1%)
F2	38 (41.3%)
F3	4 (4.3%)
F4	8 (8.7%)
Fibrosis	
Mild to moderate (F0, F1, F2)	80 (87%)
Advanced (F3, F4)	12 (13%)
Cirrhosis	
No (F0, F1, F2, F3)	84 (91.3%)
Yes (F4)	8 (8.7%)
Inflammation	
A0	4 (4.3%)
A1	43 (46.8%)
A2	39 (42.4%)
A3	6 (6.5%)

Table2. Baseline characteristics of the studied groups

Variables	Total (N=92)	Group (fibrosis)		P-value
		Mild to moderate (N= 80)	advanced (N= 12)	
Age				
Mean± S.D.	36.41 ± 11.03	35.15 ± 10.42	44.83 ± 11.74	0.006
Gender				

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Female	19 (20.7%)	17 (21.2%)	2 (16.7%)	1
Male	73 (79.3%)	63 (78.8%)	10 (83.3%)	
Diabetes Mellitus				0.045
No	85 (92.4%)	76 (95%)	9 (75%)	
Yes	7 (7.6%)	4 (5%)	3 (25%)	
Hypertension				0.346
No	89 (96.7%)	78 (97.5%)	11 (91.7%)	
Yes	3 (3.3%)	2 (2.5%)	1 (8.3%)	
BMI				0.135
Mean± S.D.	25.51 ± 4.74	25.3 ± 4.86	26.96 ± 3.74	
HBV DNA				0.114
Mean± S.D.	6426399.64±30583121.65	5244005.06±27051969.14	14309030.17±49030971.99	
HBe Ag				1
Negative	81 (88%)	70 (87.5%)	11 (91.7%)	
Positive	11 (12%)	10 (12.5%)	1 (8.3%)	
Anti HB e				0.502
Negative	25 (27.2%)	23 (28.8%)	2 (16.7%)	
Positive	67 (72.8%)	57 (71.2%)	10 (83.3%)	
ALT (IU/l)				0.378
Median (IQR)	24.85 (18.93 – 41)	24.6 (18.93 – 40.5)	38 (16 – 47)	
AST (IU/l)				0.042
Mean± S.D.	27.08 ± 12.09	25.65 ± 10.26	36.63 ± 18.44	
Total bilirubin (mg/dl)				0.498
Mean± S.D.	0.74 ± 0.24	0.73 ± 0.24	0.78 ± 0.19	
Prothrombin time (seconds)				0.223
Mean± S.D.	12.88 ± 1.02	12.85 ± 1.01	13.03 ± 1.08	
INR				0.286
Mean± S.D.	1.05 ± 0.11	1.04 ± 0.11	1.07 ± 0.1	
HB (g/dl)				0.16
Mean± S.D.	13.98 ± 1.73	14.08 ± 1.69	13.25 ± 1.83	
Platelets (x1,000/mm ³)				0.056
Mean± S.D.	227.74 ± 67.45	232.74 ± 64.45	194.42 ± 80.05	

BMI: body mass index, HBV DNA: hepatitis B virus deoxyribonucleic acid, HbeAg: hepatitis B e antigen, Anti-HBe: hepatitis B e antibody, ALT: alanine transaminase, AST: aspartate transaminase, INR: international randomized ratio, HB: hemoglobin.

Table3. non-invasive markers of fibrosis in the studied groups.

Marker	Total (N=92)	Group (fibrosis)		P-value
		Mild to moderate (N=80)	Advanced (N=12)	
Shear wave velocity (m/sec)				0.171
Mean± S.D.	1.43 ± 0.37	1.39 ± 0.33	1.64 ± 0.56	
GGT(U/L)				0.27
Median (IQR)	17 (14 – 28)	17 (13.25 – 27.75)	22.5 (14.5 – 32.75)	
AAR				0.706
Mean± S.D.	1.03 ± 0.41	1.01 ± 0.35	1.17 ± 0.72	
APRI				0.023
Median (IQR)	0.28 (0.19 – 0.39)	0.26 (0.19 – 0.37)	0.51 (0.21 – 0.95)	
FIB-4				0.02
Median (IQR)	0.71 (0.55 – 1.12)	0.69 (0.54 – 1.01)	1.67 (0.59 – 2.85)	
BARD				0.181
0	22 (23.9%)	19 (23.8%)	3 (25%)	

1	50 (54.3%)	46 (57.5%)	4 (33.35%)	
2	18 (19.6%)	14 (17.5%)	4 (33.35%)	
3	2 (2.2%)	1 (1.2%)	1 (8.3%)	
Fibro-Q Median (IQ range)	1.44 (1.03 – 2.27)	1.42 (1.02 – 2.14)	2.84 (1.23 – 5.14)	0.024
King's score Median (IQR)	3.93 (2.75 – 5.54)	3.87 (2.73 – 5.06)	12.99 (3.19 – 16.23)	0.013
CDS				0.233
0	1 (1.1%)	1 (1.2%)	0 (0.0%)	
1	1 (1.1%)	1 (1.2%)	0 (0.0%)	
2	5 (5.4%)	4 (5%)	1 (8.3%)	
3	12 (13%)	12 (15%)	0 (0.0%)	
4	26 (28.3%)	23 (28.8%)	3 (25%)	
5	31 (33.7%)	27 (33.8%)	4 (33.3%)	
6	13 (14.1%)	10 (12.5%)	3 (25%)	
7	1 (1.1%)	0 (0.0%)	1 (8.3%)	
8	2 (2.2%)	2 (2.5%)	0 (0.0%)	
APAG				
1	92 (100%)	80 (100%)	12 (100%)	NA
S index Median (IQ R)	4.38 (3.17 – 6.49)	4.35 (3.05 – 6.45)	5.31 (4.09 – 9.17)	0.082

GGT: gamma glutamyltransferase, AAR: AST/ALT, APRI: AST/platelets, Fib-4: the fibrosis index based on the four factors, fibro Q: fibro-quotient, CDS: cirrhosis discriminant score, APAG: age, platelets, albumin and gamma glutamyltransferase, NA- not applicable.

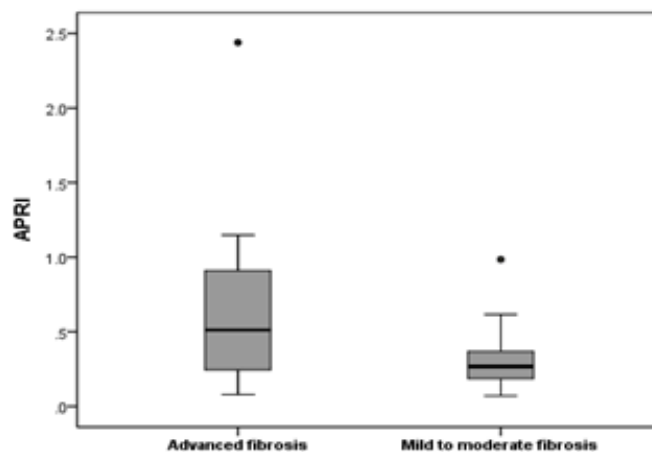


Figure3. comparison between the studied groups regarding APRI measures.
APRI: AST/platelets ratio

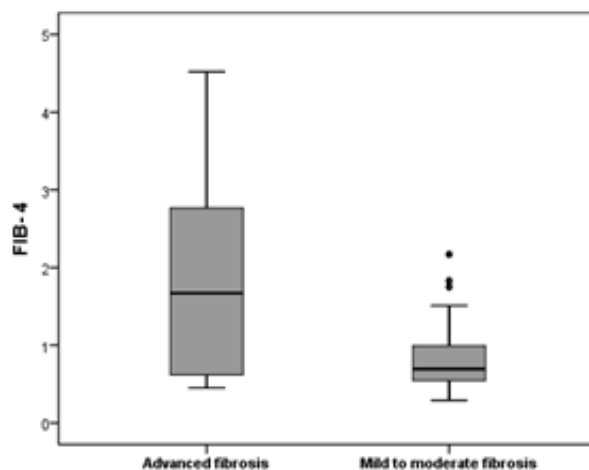


Figure4. comparison between the studied groups regarding FIB-4 measures.
Fib-4: The fibrosis index based on the four factors

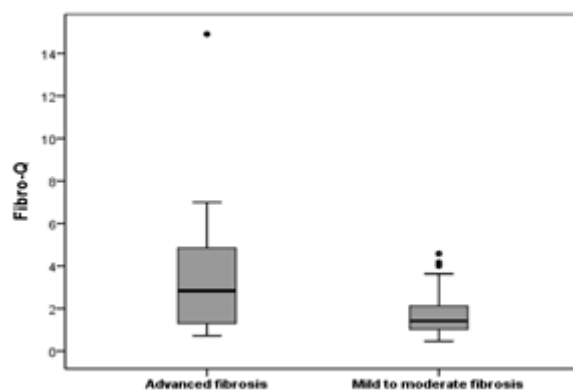


Figure5. comparison between the studied groups regarding Fibro-Q measures.
Fibro Q: fibro-quotient.

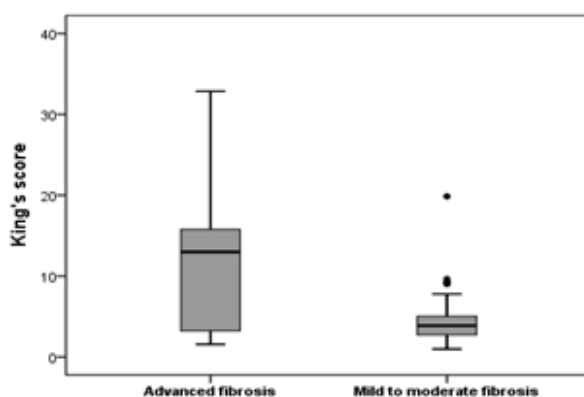


Figure6 comparison between the studied groups regarding King's score.

Table4. Comparison between AUROCs of the studied markers for prediction of advanced fibrosis.

Measures	Cutoff	AUC	CI	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P-value
GGT(U/L)	>31	0.599	0.492 to 0.7	41.67	87.50	33.3	90.9	0.297
AAR	>1.3	0.534	0.427 to 0.639	33.33	83.75	23.5	89.3	0.719
APRI	>0.43	0.707	0.603 to 0.797	58.33	87.50	41.2	93.3	0.023
FIB-4	>1.83	0.706	0.602 to 0.796	50	98.75	85.7	92.9	0.022
BARD	>1	0.588	0.480 to 0.689	41.67	81.25	25	90.3	0.379
Fibro-Q	>3.43	0.703	0.599 to 0.794	50	92.5	50	92.5	0.041
King's score	>9.62	0.723	0.620 to 0.811	58.33	98.75	87.5	94	0.042
CDS	>5	0.633	0.526 to 0.731	33.33	85	25	89.5	0.334
S index	>3.98	0.656	0.550 to 0.752	91.67	47.5	20.8	97.4	0.082
Shear wave velocity	>2.24	0.601	0.493 to 0.701	33.33	98.75	80	97.4	0.357

AUROCs: area under the receiver operator characteristic curve, AUC: area under the curve, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value, GGT: gamma glutamyltransferase, AAR: AST/ALT, APRI: AST/platelets, FIB-4: the fibrosis index based on the four factors, fibro Q: fibro-quotient, CDS: cirrhosis discriminant score.

Table5. Correlation between shear wave velocity and serum fibrosis markers among the studied patient

Fibrosis markers	Shear wave velocity	
	r	P-value
GGT(U/L)	0.017	0.870
AAR	0.087	0.407
APRI	0.226	0.031
FIB-4	0.169	0.108
BARD	-0.025	0.813
Fibro-Q	0.133	0.208
King's score	0.149	0.156
CDS	0.170	0.104

S index	0.202	0.054
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r = spearman correlation coefficient, GGT: gamma glutamyltransferase, AAR: AST/ALT, APRI: AST/platelets, FIB-4: the fibrosis index based on the four factors, fibro Q: fibro-quotient, CDS: cirrhosis discriminant score.

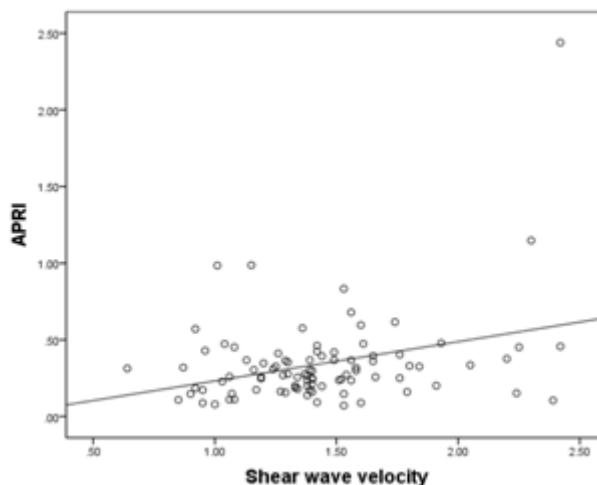


Figure7. Correlation between shear wave velocity and APRI score among the studied patient
APRI: AST/platelet ratio.

Table6. Univariate and multivariate binary logistic regression analysis of predictor variables of advanced fibrosis.

Characteristics	Univariate		Multivariate	
	OR (CI 95%)	P - value	OR (CI 95%)	P - value
Age	1.08 (1.02 – 1.14)	0.008	1.12 (0.93 – 1.36)	0.222
Sex				
Male	1	0.715		
Female	0.74 (0.15 – 3.71)			
Diabetes Mellitus				
No	1	0.028	1	
Yes	6.33 (1.22 – 32.93)		23.51 (1.4 – 393.99)	0.028
Hypertension				
No	1			
Yes	3.55 (0.3 - 42.42)	0.318		
ALT (IU/l)	1.03 (0.99 - 1.06)	0.11		
AST (IU/l)	1.06 (1.02 - 1.11)	0.007	0.99 (0.84 - 1.16)	0.874
GGT(U/L)	1.02 (0.97 - 1.07)	0.491		
AAR	2.13 (0.62 - 7.3)	0.227		
APRI	82.09 (4.5 -1498.03)	0.003	116.73 (0 – 2.49E+12)	0.704
FIB-4	5.85 (2.05 - 16.68)	0.001	0.001 (0 – 9.39)	0.144
BARD	1.71 (0.75 - 3.91)	0.204		
Fibro-Q	1.96 (1.22 - 3.16)	0.006	2.47 (0.46 - 13.19)	0.289
King's score	1.3 (1.12 - 1.52)	0.001	1.89 (0.63 - 5.67)	0.255
CDS	1.4 (0.86 - 2.28)	0.174		
S index	1.06 (0.95 - 1.19)	0.315		
Shear wave velocity	4.93 (1.06 - 22.92)	0.042	9.02 (0.69 - 117.45)	0.093

OR: odds ratio, CI: confidence interval, ALT: alanine transaminase, AST: aspartate transaminase, GGT: gamma glutamyltransferase, AAR: AST/ ALT, APRI: AST/ platelet, FIB-4: the fibrosis index based on the four factors, fibro Q: fibro-quotient, CDS: cirrhosis discriminant score.

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