



Comparison of invasive and non-invasive methods for assessment of liver fibrosis in patients with chronic hepatitis B and hepatitis C virus infections

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Abstract

Introduction: Different methods are employed to determine the severity of chronic viral hepatitis and liver fibrosis. **Objectives:** This study was conducted to compare invasive and non-invasive tests for assessment of liver fibrosis in the patients with chronic hepatitis B and C.

Patients and Methods: In this study, the results of liver biopsy based on the METAVIR scoring system were compared with biomarkers, including fibrosis-4 (FIB-4) and aspartate aminotransferase-to-platelet ratio index (APRI) for identifying liver fibrosis.

Results: Out of 194 patients, 63 and 131 patients had hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, respectively. There was a significant difference between patients with METAVIR stages 0-1 and patients with METAVIR stages 2-3, based on the FIB-4, aspartate aminotransferase (AST) to platelet ratio index (APRI) and the mean prothrombin time (PT), international normalized ratio (INR), platelet (PLT), alanine transaminase (ALT) and AST. A correlation was found between the FIB-4 and APRI indices and the METAVIR score of patients with hepatitis. The FIB-4 index, with a cut-off value <1.1 for detecting liver fibrosis in patients with HBV infection, showed sensitivity of 83.3%, specificity of 64.7%. Further, a positive predictive value (PPV) of 35.7%, and a negative predictive value (NPV) of 94.3% was detected. On the other hand, the APRI index, with a cut-off value <0.73, showed 59% sensitivity, 76.5% specificity, PPV of 33.3% and NPV of 86.7%. The FIB-4 index, with a cut-off value <1.47 for detecting liver fibrosis in patients with HCV infection, showed 73.7% sensitivity, 73.2% specificity, PPV of 31.8%, and NPV of 94.3%. Additionally, the APRI index, with a cut-off value <1.7, showed 42.1% sensitivity, 97.3% specificity, PPV of 72.7% and NPV of 90.8%.

Conclusion: According to the results, in patients with chronic hepatitis, the severity of liver fibrosis increased with an increase in the APRI and FIB-4 indices. Therefore, these two indices can replace biopsy under certain circumstances.



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Introduction

The most common causes of chronic liver disease, in order of prevalence, include chronic hepatitis C, chronic hepatitis B, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis and Wilson's disease. Chronic hepatitis is characterized by liver abnormalities with different causes and variable severity, in which inflammation and liver necrosis persist for at least six months (1). Patients with chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) infections without therapy may experience liver fibrosis progression and cirrhosis. Although in some cases, liver

Key point

Different methods are used to determine the severity of chronic viral hepatitis and liver fibrosis. In this study, the results of liver biopsy were compared with biomarkers, including fibrosis-4 (FIB-4) and aspartate aminotransferase-to-platelet ratio index (APRI) for identifying liver fibrosis.

biopsy is conducted as the gold standard for diagnosis of hepatic disease (1-6). This method is mostly applied to evaluate the severity, prognosis, indications, response to treatment and staging of liver damage (1).

The most popular histological staging

system is the histological activity index (HAI) in the United States and the METAVIR scoring system in Europe (stages F0-6 in the HAI system and stages F0-4 in the METAVIR system) (1,2). Almost 257 million people are living with HBV infection around the world, with 887000 deaths reported annually, mostly due to HBV complications, such as cirrhosis and hepatocellular carcinoma (HCC) (11). The prevalence of chronic acute hepatitis is variable depending on age. More than 90% of infants with HBV infection at birth have a risk of developing chronic HBV later in life (3, 4). Globally, it is estimated that 71 million people have chronic HCV infection, 399000 of whom die each year, mostly due to factors, such as chronic HBV infection (11). The most common route of HCV transmission is drug injection using a shared syringe or needle. According to reports, 85% of patients with chronic HCV infection without treatment develop chronic infection, and 20% of them develop cirrhosis and HCC after 20 years (5).

Early diagnosis and analysis of liver fibrosis in patients with chronic HBV or HCV infection can be very helpful in selecting proper treatments for patients and preventing complications. Liver biopsy is the gold standard for grading inflammation, staging of fibrosis and finally, scoring of chronic liver disease (6-11). Biopsy is not only an invasive method associated with complications, such as pain, bleeding, pneumothorax and hemothorax, but is also influenced by interpretation of different pathologists (15-17). Since some patients do not prefer an invasive method because of its complications, therefore the use of non-invasive methods, such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and fibrosis-4 (FIB-4) indices, has become more popular for the evaluation of liver fibrosis (18,19). If the results of these tests are reliable enough for the evaluation and onset of treatment, they can replace liver biopsy (8).

Objectives

This study aimed to compare invasive and non-invasive methods for diagnosis of liver fibrosis in patients with chronic HBV or HCV infection.

Patients and Methods

Study design

In this cross-sectional study, a total of 194 patients with chronic HBV or HCV infection, who underwent liver biopsy at Sina hospital in Hamadan, Iran, during 2007-2016, were enrolled. Patients with end-stage liver failure, alcoholic liver disease, thalassemia, HIV, coinfection of HBV and HCV and HDV were excluded. According to a study by Stibbe et al (14), at a confidence interval of 95% and statistical power of 95%, a sample size of 58 was measured for patients with chronic HCV infection. In addition, for patients with chronic HBV infection, a sample size of 35 was calculated at statistical power of 80%. All data were obtained at the time of diagnosis (before therapeutic interventions). Pathological analysis of liver

biopsies was conducted at the pathology department of Sina hospital. Moreover, demographic characteristics, such as age, gender, hepatitis type (HBV or HCV) and laboratory biomarkers, including the platelet count (PLT), AST, alanine aminotransferase (ALT), hemoglobin (Hb), white blood cell count (WBC), international normalized ratio (INR). Accordingly, the pathology reports of liver biopsies graded by the modified HAI system from F-0 to F-6 (Knodel score), were extracted from the patients' medical files and recorded in the designed checklists.

Fibrosis scores based on the modified HAI system were graded on a F0-F4 scale (METAVIR system), where F0 indicates no fibrosis, F1 indicates portal fibrosis without septa, F2 indicates portal fibrosis with few septa, F3 indicates numerous septa without cirrhosis and F4 represents cirrhosis, as described in a study by Shiha et al (10). The APRI and FIB-4 indices were calculated based on the laboratory results using the following formulae;

$$APRI = \frac{\frac{AST \text{ Level}}{AST(\text{Upper Limit of Normal})}}{\text{Platelet Count } (10^9/L)} \times 100$$

$$FIB - 4 = \frac{\text{Age(years)} \times AST(U/L)}{\text{Platelet Count } (10^9/L) \times \sqrt{ALT(U/L)}}$$

To determine the correlation of FIB-4 and APRI indices with the METAVIR score, Spearman's correlation coefficient and box plots were employed. A logistic regression analysis was also carried out to determine the cut-off points of FIB-4 and APRI for HBV, HCV and all hepatitis cases separately. Along with the cut-off points, the lower and upper bounds were also determined. Consequently, sensitivity, specificity, area under the ROC (Receiver operating characteristic) curve surface, and Youden index (sensitivity and specificity) were calculated.

Statistical analysis

Statistical analysis was performed in SPSS version 21 (SPSS Inc., Chicago, IL, USA). *P* value less than 0.05 was considered statistically significant.

Results

In the present study, 194 patients (77.32% male and 22.68% female) with chronic viral hepatitis were enrolled, including 63 (32.5%) patients with HBV infection and 131 (67.53%) patients with HCV infection. Moreover, 38 (60.32%) patients with chronic HBV and 112 (85.49%) patients with chronic HCV were male ($P < 0.001$, $\chi^2 = 15.37$, $df = 1$). The mean age of patients with chronic HBV and HCV infections was 36.79 ± 11.98 (range, 16-61 years) and 40.89 ± 11.23 (range, 19-82 years) years, respectively ($P = 0.001$).

Due to the absence of METAVIR stage four patients and few cases of METAVIR 2 and 3 (31 out of 194 liver biopsy samples), all laboratory tests and non-invasive indices

were calculated for two groups of METAVIR 0-1 with no liver fibrosis or mild liver fibrosis and METAVIR 2-3 with significant liver fibrosis (Table 1).

Figure 1 and Figure 2 present the box plots of fibrosis scores according to the METAVIR fibrosis stage. A significant correlation was found between the METAVIR score of patients with hepatitis and the FIB-4 ($r=0.408$, $P<0.001$) and APRI ($r=0.405$, $P<0.001$) indices. There was a significant difference between METAVIR 0-1 and METAVIR 2-3 groups, based on the FIB-4, APRI, and the mean PT, INR, PLT, ALT, and AST (Table 1).

According to Table 2, at a cut-off value <1.1 , more than 83% of patients with HBV infection did not have liver fibrosis; however, at a cut-off value >3.2 , approximately 75% of patients had fibrosis. The FIB-4 index with a cut-off value <1.1 for detecting liver fibrosis showed 83.3% sensitivity, 64.7% specificity. We also found a positive predictive value (PPV) of 35.7% and a negative predictive value (NPV) of 94.3% in patients with HBV infection. Similarly, the APRI with a cut-off value <0.73 showed 59% sensitivity, 76.5% specificity, PPV of 33.3% and NPP of 86.7% (Table 2).

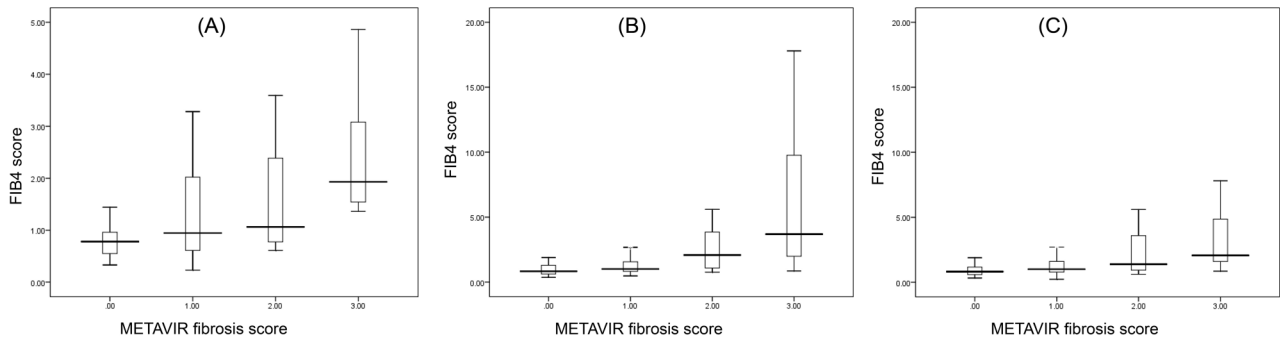


Figure 1. Box plot graph of patients, score values of FIB-4 according to METAVIR fibrosis score in patients with hepatitis B ($r=0.421$, $P<0.001$) (A), hepatitis C ($r=0.395$, $P<0.001$) (B) and all patients ($r=0.408$, $P<0.001$) (C).

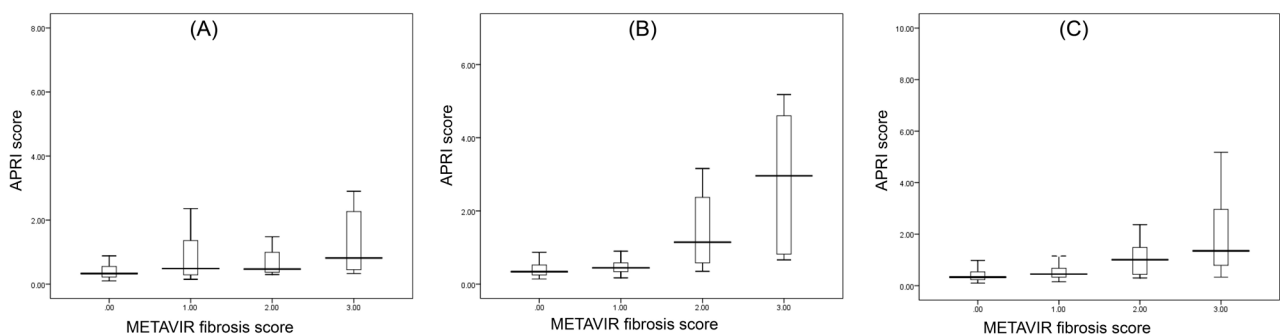


Figure 2. Box plot graph of patients, score values of APRI according to METAVIR fibrosis score in patients with hepatitis B ($r=0.354$, $P<0.004$) (A), hepatitis C ($r=0.442$, $P<0.001$) (B) and all patients ($r=0.405$, $P<0.001$) (C).

Table 1. Clinical and paraclinical characteristics of 194 patients with chronic hepatitis B and C based on METAVIR score

Variables	METAVIR F0-F1		METAVIR F2-F3		P value
	Mean	SD	Mean	SD	
Age (years)	38.47	11.08	45.25	12.77	0.002
APRI	0.67	1.01	1.81	1.70	0.001
FIB-4	1.25	0.87	3.44	3.69	0.001
PT (s)	12.87	1.11	14.05	2.65	0.001
INR	1.07	0.14	1.20	0.23	0.001
PLT ($\times 10^3/\text{mm}^3$)	207.28	59.03	155.64	55.00	0.001
ALT (IU/L)	81.23	130.26	145.74	166.21	0.016
AST (IU/L)	58.57	95.04	109.06	105.06	0.008

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; APRI: AST-to-platelet ratio index; PT: prothrombin time; INR: International normalized ratio; PLT: platelet.

The FIB-4 index with a cut-off value <1.47 for detecting liver fibrosis in patients with HCV infection showed 73.7% sensitivity, 73.2% specificity, PPV of 31.8% and NPV of 94.3%. However, the APRI with a cut-off value <1.7 showed 42.1% sensitivity, 97.3% specificity, PPV of 72.7% and NPV of 90.8% (Table 3). Moreover, the cut-off value, sensitivity, specificity and area under the ROC curve are shown for all hepatitis patients in Table 4.

The highest Youden index revealed the highest sensitivity for both markers (FIB-4 and APRI) (Table 5). Moreover, in patients with HBV infection, the Youden index was 146.9 at a cut-off value <1.1; in other words, at this cut-off point, patients with HBV infection did not have liver fibrosis (Table 5).

Figure 3 presents the ROC curves evaluating the diagnostic accuracy of APRI and FIB-4 indices to determine which scores have the most clinical application for predicting significant fibrosis (\geq F2).

Discussion

Chronic HCV and HBV infections can lead to liver fibrosis progression and cirrhosis. Liver biopsy is the gold

standard for determining the histopathology of chronic hepatitis (6-11). However, some patients are not willing to undergo invasive methods because of their complications. Therefore, non-invasive methods, such as APRI and FIB-4, are considered as more accurate indices for the evaluation of liver fibrosis (18,19).

In the present study, 194 patients with chronic viral hepatitis were enrolled, including 63 (32.5%) patients with HBV infection and 131 (67.53%) patients with HCV infection. The mean age of patients with chronic HBV and HCV infections was 36.79 ± 11.98 and 40.89 ± 11.23 years, respectively. In the present study, a significant difference between the METAVIR F0-F1 and METAVIR F2-F3 groups, based on the FIB-4, APRI, and the mean PT, INR, PLT, ALT, and AST was detected. The study by Teshale et al, revealed the average scores of APRI and FIB-4 indices for the evaluation of fibrosis, especially differentiation of F0-F1 from F2-F4, had good accuracy. This study showed, the average scores of APRI and FIB-4 indices were helpful in evaluating the treatment outcomes of patients and monitoring the prognosis of liver fibrosis (20).

The FIB-4 index, with a cut-off value <1.1 for detecting

Table 2. Sensitivity, specificity, PPV, NPV and area under ROC of different cut-off of FIB-4 and APRI indices for diagnosis of liver fibrosis in the patients with hepatitis B

Variable	Cut off	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Area under ROC
FIB-4	<1.1	83.3	64.7	35.7	94.3	0.740
	<1.9	41.7	80.4	33.3	85.4	0.610
	<3.2	25.0	96.1	60.0	84.5	0.605
APRI	<0.73	50.0	76.5	33.3	86.7	0.632
	<1.1	33.3	84.3	33.3	84.3	0.588
	<1.6	36.4	86.3	33.3	84.6	0.556

PPV, positive predictive value; NPV, negative predictive value; ROC, Receiver operating characteristic.

Table 3. Sensitivity, specificity, PPV, NPV and area under ROC of different cut-off of FIB-4 and APRI indices for diagnosis of liver fibrosis in the patients with hepatitis C

Variable	Cut off	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Area under ROC
FIB-4	<1.47	73.7	73.2	31.8	94.3	0.734
	<2.28	52.6	87.5	41.7	91.6	0.701
	<3.55	42.1	97.3	72.7	90.8	0.697
APRI	<1.7	42.1	97.3	72.7	90.8	0.697
	<3.18	26.3	99.1	83.3	88.8	0.627
	<5.7	5.3	100	100	86.2	0.526

PPV, positive predictive value; NPV, negative predictive value; ROC, Receiver operating characteristic.

Table 4. Sensitivity, specificity, PPV, NPV and area under ROC of different cut-off of FIB-4 and APRI indices for diagnosis of liver fibrosis in all patients with hepatitis

Variable	Cut off	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Area under ROC
FIB-4	<1.5	71.0	75.5	35.5	93.2	0.732
	<2.0	48.4	85.3	38.5	89.7	0.665
	<3.25	35.5	96.3	64.7	88.7	0.659
APRI	<1.3	45.2	92.0	51.9	89.8	0.689
	<1.7	35.5	93.9	52.4	88.4	0.647
	<2.3	32.3	95.7	58.8	88.1	0.640

PPV, positive predictive value; NPV, negative predictive value; ROC, Receiver operating characteristic.

Table 5. Youden index (sum of sensitivity and specificity)-1 according to different cut-off of FIB-4 and APRI indices in the patients with hepatitis B and C

Variable	Hepatitis B		Hepatitis C		All hepatitis patients	
	Cut-off<	Youden index	Cut-off<	Youden index	Cut-off<	Youden index
FIB-4	1.1	147	1.47	146.9	1.5	146.5
	1.9	122.1	2.28	140.1	2	133.7
	3.2	121.1	3.55	139.4	3.25	131.8
APRI	0.77	126.5	1.7	139.4	1.3	137.2
	1.1	117.6	3.18	125.4	1.7	129.4
	1.6	122.7	5.7	105.3	2.3	128

liver fibrosis in patients with HBV infection, showed sensitivity of 83.3%, specificity of 64.7%, PPV of 35.7% and NPV of 94.3%. However, the APRI index, with a cut-off value <0.73, showed sensitivity of 59%, specificity of 76.5%, PPV of 33.3%, and NPV of 86.7%.

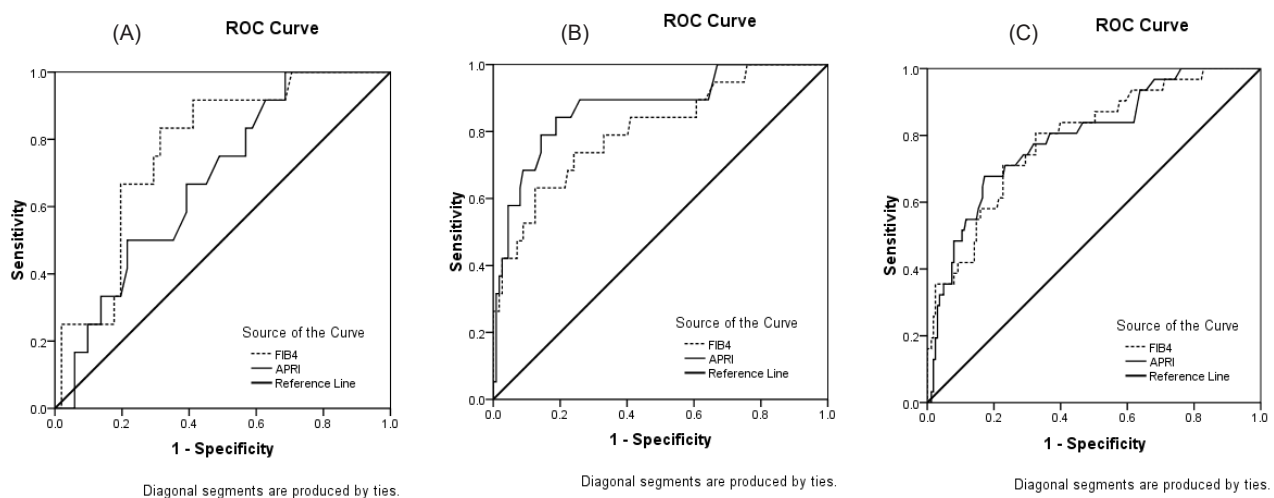
In a study by Zhao et al, new scoring system is helpful in early identification and selection of patients for proper treatment. This is critical for early identification of candidates for liver transplantation (6). Moreover, in a study by Li et al, the FIB-4 index indicated adequate accuracy for detecting liver fibrosis and cirrhosis in chronic HBV patients; however, it was not optimal for differentiating fibrosis from cirrhosis (21).

The FIB-4 index, with a cut-off value <1.47 for detecting liver fibrosis in patients with HCV, disclosed sensitivity of 73.7%, specificity of 73.2%, PPV of 31.8% and NPV of 94.3%; however, the APRI, with a cut-off value <1.7, showed sensitivity of 42.1%, specificity of 97.3%, PPV of 72.7% and NPV of 90.8%. According to a study by Hassanien et al, in patients with chronic HCV genotype 4, a good relationship between the liver fibrosis stage and the FIB-4 and APRI indices was detected. They also detected a gradual increase in the FIB-4 and APRI indices with fibrosis stage. Moreover, the FIB-4 index had the highest diagnostic accuracy for severe fibrosis (18). Our results are consistent with the finding of the study by Hassanien and

colleagues.

Moreover, Yosry et al demonstrated that, non-invasive tests, such as APRI, FIB-4 and FibroScan, are suitable for predicting the stage of liver fibrosis in patients with chronic HCV (22). In another study by Kim et al, the APRI and FIB-4 indices were correlated with liver biopsy, according to the Ishak stage in HBV patients ($P < 0.01$). However, these indices were not appropriate for the assessment of liver fibrosis in HBV patients in the follow-up of treatment (23). The results of these studies are in line with our results. The highest Youden index for both markers, including the FIB-4 and APRI, showed the highest sensitivity. In patients with HBV infection, the Youden index was 146.9 at a cut-off value <1.1; in other words, at this cut-off point, patients with HBV did not have liver fibrosis.

In another study by Gökcan et al on patients with HCV infection, the APRI and FIB-4 indices could be conducted to identify patients with mild fibrosis with a high negative predictive value for differentiation of severe liver fibrosis from mild to moderate liver fibrosis (24). Furthermore, in a study by Hsieh et al, on 237 patients with HCV infection, 41 patients were identified with METAVIR stage F1 fibrosis, 85 with METAVIR stage F2 fibrosis, 98 with METAVIR stage F3 fibrosis and 13 with METAVIR stage F4 fibrosis. The Fibro-Q, FIB-4, and API results increased significantly as fibrosis advanced (25).

**Figure 3.** Receiver operating characteristic (ROC) curves analysis of biomarkers (FIB-4 and APRI) in the patients with hepatitis B (A), C (B) and all hepatitis(C).

In the current study, the FIB-4 index showed sensitivity of 73.7% and specificity of 73.2% at a cut-off value <1.47 in patients with HCV infection. However, the APRI index indicated sensitivity of 42.1% and specificity of 97.3% at a cut-off value <1.7. In a study by Li et al, 236 patients with chronic HBV infection were enrolled. In their study, the area under the ROC curve of APRI was lower than that of the FIB-4 index (0.62 versus 0.69; $P = 0.019$) for diagnosing significant fibrosis. Nevertheless, at an APRI cut-off point >2.0 proposed by the World Health Organization (WHO), no cirrhotic cases were correctly predicted. The WHO suggested, a cut-off point of 3.25 for the FIB-4 index correctly identified significant fibrosis in 83% of cases. Based on the ROC curve analysis, the optimal cut-off points of the APRI index were 0.46 and 0.65. Since, the optimal cut-off points of the FIB-4 index were 1.05 and 1.29 for diagnosing significant fibrosis and cirrhosis, respectively (26).

In our study also, in patients with HBV infection, the FIB-4 index, with a cut-off point <1.1, showed sensitivity of 83.3%, specificity of 64.7%, PPV of 35.7% and NPV of 94.3%. Likewise, the APRI index displayed sensitivity of 59% and specificity of 76.5% at a cut-off point <0.73. The WHO guideline for chronic HBV proposed a new cut-off value for the APRI (APRI >2.0). This new cut-off point (>0.65) pointed higher sensitivity (82% versus 0%) and specificity (65% versus 1%) for diagnosis of cirrhosis in hepatitis Be antigen (HBeAg)-negative chronic HBV patients with ALT<2×ULN. In this study, when the new cut-off point of APRI (>0.65) was used, 14/17 (82%) cirrhotic patients were correctly predicted based on the proposed WHO cut-off point (FIB-4>3.25) (27). This study had some limitations. The number of patients with moderate to severe liver fibrosis was low, and there was no patient with cirrhosis or HCC.

In our study, there were no patients with severe liver fibrosis; therefore, in moderate to severe cases of liver fibrosis (F3), the FIB-4 and APRI indices showed adequate sensitivity and specificity. However, in mild cases of liver fibrosis or cases without liver fibrosis, the determined cut-off points showed adequate sensitivity and specificity; therefore, they can be used to replace liver biopsy.

Conclusion

According to the present results, in patients with chronic HBV and HCV infections, the severity of liver fibrosis increased as the stage of APRI and FIB-4 indices increased. Therefore, these non-invasive indices can be used to replace invasive diagnostic methods under certain circumstances, especially for differentiating moderate to severe fibrosis from normal to mild fibrosis.

Limitations of the study

The limitation of the study was the failure to refer some patients to perform the requested tests, which maximum participation was achieved by educating and justifying

the patients about the importance and consequences of the disease and following up the patients with contact numbers.

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Authors' contribution

MMM and HRGB were the principal investigators of the study. FK, PE and BH were included in preparing the concept and design. PE and ARS revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical issues

This study was approved by the ethics committee of Hamadan university of medical sciences (IR.UMSHA.REC.1396.608). The study also complies with the tenets of Declaration of Helsinki. Informed consent was obtained for studying the patients' medical records. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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