HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2024.69345
Haydarpasa Numune Med J 2025;65(1):1–7

hnhtipdergisi.com

ORIGINAL ARTICLE

Comparison and Value of Non-Invasive Tests in Chronic Hepatitis B and C Versus Liver Biopsy

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Abstract

Introduction: The aim of this study is to evaluate the performance of non-invasive tests, including APRI, FIB-4, and FibroIndex, in detecting fibrosis in patients with chronic hepatitis B and C compared to liver biopsy.

Methods: This study enrolled 236 patients with CHB/CHC who underwent ultrasound-guided liver biopsies between January 2007 and May 2014 at Katip Çelebi University Atatürk Training and Research Hospital. Histological grading of necroinflammation and fibrosis was performed according to the Knodell and ISHAK scoring systems. APRI, FIB-4, and FibroIndex scores were calculated based on their respective formulas. Optimal cutoffs were determined using the Youden method. Sensitivity and specificity were calculated for significant fibrosis and cirrhosis. Statistical analyses were performed using SPSS.

Results: This study evaluated 236 patients with chronic hepatitis B (CHB) and C (CHC) using non-invasive tests to diagnose liver fibrosis and cirrhosis. CHB was more prevalent, accounting for 77.5% of cases, with a slight male predominance in the cohort. Non-invasive tests such as APRI, FIB-4, and FibroIndex demonstrated moderate to good diagnostic accuracy, with better performance generally observed in CHC patients. For instance, APRI exhibited excellent sensitivity and specificity for cirrhosis in CHC. These findings suggest that the effectiveness of these tests varies based on hepatitis type, highlighting the potential need for different diagnostic strategies depending on viral etiology.

Discussion and Conclusion: Non-invasive tests proved to be useful tools for detecting significant fibrosis and cirrhosis. Additionally, FibroIndex demonstrated superior performance with higher sensitivity and specificity compared to other non-invasive tests.

Keywords: APRI; Chronic hepatitis B; Chronic hepatitis C; FibroIndex; FIB-4; Liver fibrosis; Non-invasive fibrosis marker.

The common feature of almost all chronic liver diseases is that they result in progressive hepatic fibrosis.[1] The goal of the treatment is to protect patients from cirrhosis and hepatocellular carcinoma.[2] Percutaneous liver biopsy is the reference test for assessing the stage of fibrosis in both chronic hepatitis C (CHC) and B (CHB).[3] However, biopsy is an invasive and expensive procedure associated with patient discomfort and a risk of major complications

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Submitted Date: 13.09.2023 **Revised Date:** 15.05.2024 **Accepted Date:** 27.05.2024
Haydarpaşa Numune Medical Journal

(0.3%-0.5%), as well as death (0.03%-0.1%).[4–6] Moreover, sampling errors and intraobserver/interobserver variability may lead to an underestimation of the underlying liver disease,[7] particularly when biopsy samples are small or fragmented.[8] These issues have driven extensive research on non-invasive alternatives.[9]

Thus, there is a need to develop accurate non-invasive tests to predict clinically significant fibrosis. Ideally, such tests should be easy to perform, rapid, accessible, cost-effective, and reliable, providing precise results for assessing the degree of liver fibrosis.[3,10,11] The ideal model should also effectively distinguish between the presence and absence of cirrhosis.[12]

In the past 10 years, non-invasive tests have demonstrated their ability to estimate the severity of liver disease by distinguishing patients with low-stage fibrosis from those with significant fibrosis and cirrhosis.[13,14] Several investigators have reported various non-invasive methods for the quantitative analysis of liver fibrosis. The simplest score, APRI, is calculated using AST serum activity and platelet count.[15] Koda et al.[16] described a unique model, the Fibroindex, comprising AST, platelet count, and gamma globulin levels.

Therefore, the aim of our study was to compare the diagnostic performance of three non-invasive blood tests—APRI, FIB-4, and Fibroindex—with liver biopsy findings in CHB and CHC patients.

Materials and Methods

Patients

In this study, 236 qualified patients with chronic hepatitis B and C who underwent ultrasound-guided liver biopsies between January 2007 and May 2014 at Katip Çelebi University Atatürk Training and Research Hospital, Infectious Diseases Clinic, İzmir, were enrolled. The study was approved by the Ethics Committee of Katip Çelebi University.

The diagnosis of chronic hepatitis was based on the presence of HBsAg and HBV DNA for CHB or HCV antibodies and HCV RNA for CHC for more than six months. During the inclusion period, a liver biopsy was deliberately proposed and performed as part of clinical care for staging and grading liver disease.

Patients with the following conditions were excluded: age under 18 years, HCV-HBV co-infection, co-infection with human immunodeficiency virus, hepatitis delta virus, other causes of liver disease, hepatocellular carcinoma, prior interferon or antiviral therapy, presence of other liver diseases, end-stage renal disease, insufficient liver tissue for fibrosis staging, and incomplete data on blood counts. Demographic information was recorded.

The study protocol adhered to the ethical guidelines of the 2013 Helsinki Declaration and was approved by our institutional review board. Data of all HBV/HCV patients who underwent a liver biopsy in our hospital were analyzed, and demographic, laboratory, and other clinical variables were obtained from medical records.

The APRI was defined as follows:

APRI=(AST/AST ULN)/(platelet count)×100.

FIB-4 was calculated as follows:

FIB-4=(Age [years] × AST [U/L])/((platelet count [10^9/L]) × (ALT [U/L])$^{1/2}$).

Fibroindex was defined as follows:

Fibroindex=1.738-(0.064 × platelet count [10^4/mm^3]) + (0.005 × AST [IU/L]) + (0.463 × gamma globulin [g/dL]).

Histological Analysis

The Association for the Study of Liver Diseases (AASLD) criteria were used to define biopsy requirements. All liver specimens were reviewed by pathologists. A minimum

Table 1. Demographic, laboratory and histological features of patients

	Chronic Hepatitis B	Chronic Hepatitis C	p
Age	41.26±12.89	54.89±12.15	<0.001
Sex (Male, %)	106 (58.2)	30 (56.6)	
Length of biopsy (mm)	2.25	2.36	
ALT	106.15±142.66	74.7±64.4	0.297
AST	63.53±75.86	54.77±47.35	0.753
GGT	47.7±61.49	75.04±96.07	0.001
ALP	85.76±31.54	83.83±30.15	0.659
Albumin	4.19±0.46	4.33±0.48	0.039
Globulin	3.18±0.62	3.21±0.64	0.756
Total bilirubin	0.94±0.83	1.08±1.6	0.868
Direct bilirubin	0.39±0.62	0.49±1.18	0.577
Indirect bilirubin	0.57±0.53	0.59±0.63	0.682
PT	11.89±1.58	11.3±0.82	0.002
INR	1.02±0.1	0.97±0.08	0.005
Platelet count	217.41±65.18	210.81±69.05	0.547
HBV DNA (Log IU/ml)	264866953.71		
HCV RNA (Log IU/ml)		2487376.19	
Fibrosis stage	1.87±1.59	1.75±1.63	0.573
Activity index	5.08±3.066	5.47±2.650	0.396
APRI	0.97±1.3	0.94±1.13	0.875
FIB-4	0.17±0.18	0.24±0.15	0.009
Fibro Index	2.13±0.64	2.15±0.67	0.876

of five portal tracts in the specimen was required for the appropriate assessment of histological data.

Histological grading of necroinflammation was performed using the Knodell inflammatory score. The degree of fibrosis was staged according to the ISHAK system as follows:

- F0-2: Low-stage fibrosis
- F3-4: High-stage fibrosis
- F5-6: Cirrhosis

Statistical Analysis

Descriptive results were expressed as a median (standard deviation) or as a number (percentage) of patients. Pearson correlation analysis was used to assess correlations.

The predictive accuracy of APRI, Fibroindex, and FIB-4 was tested using the areas under the receiver operating characteristic curves (AUROC). Based on the ROC analysis, the best cutoff points to predict the absence or presence of significant fibrosis and cirrhosis were determined. For each diagnostic target, optimal cutoffs were established according to the Youden method.

Diagnostic accuracy was evaluated by calculating sensitivity, specificity, and positive and negative predictive values. Statistical analyses were performed using SPSS v.23.0 (SPSS, Inc., Chicago, IL, USA) for Windows.

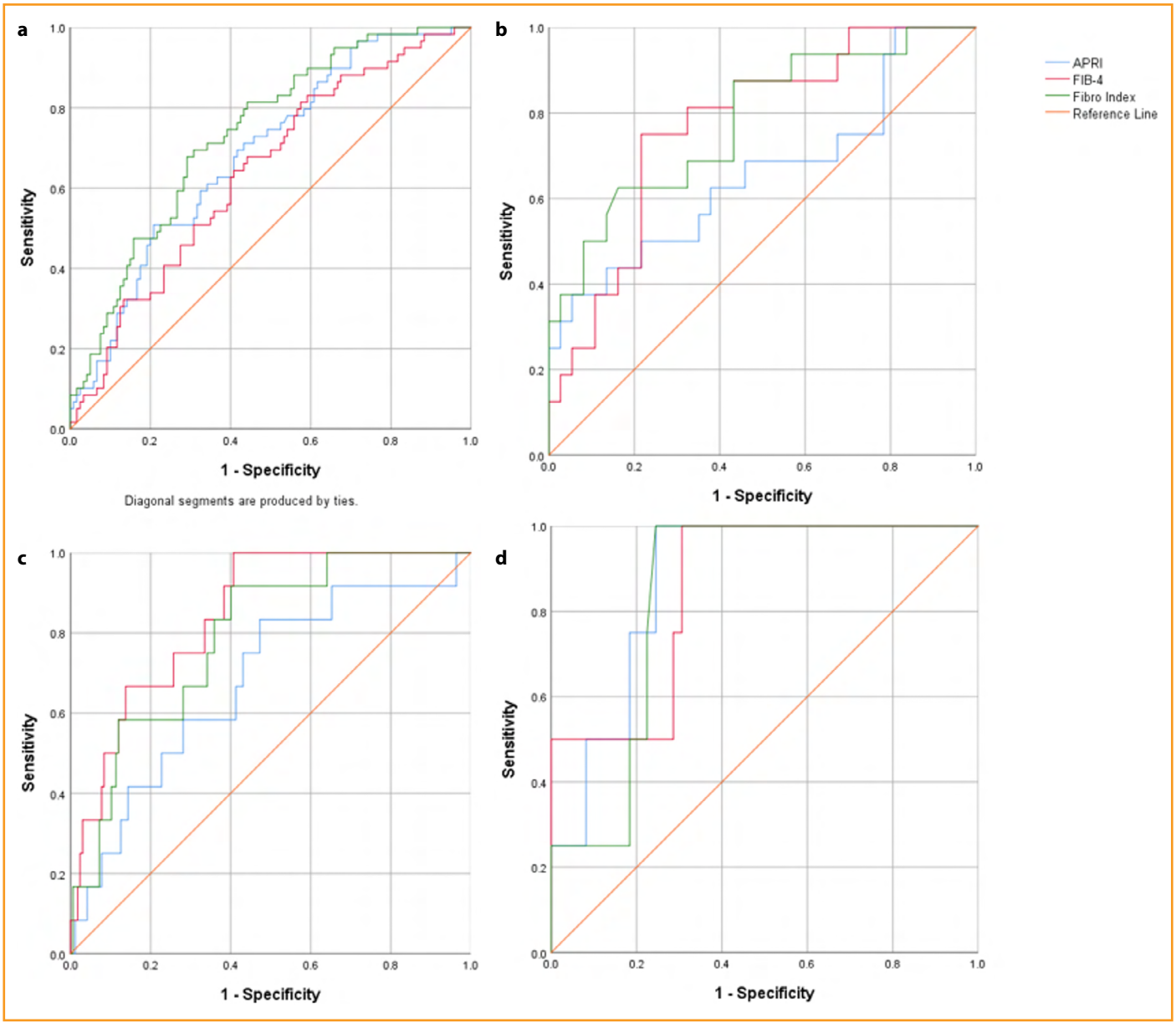

Figure 1. ROC curves of the non-invasive tests **(a)** Significant Fibrosis in CHB, **(b)** Significant Fibrosis in CHC, **(c)** Cirrhosis in CHB, **(d)** Cirrhosis in CHC).

Results

In this study, we collected data from 236 naïve CHB and CHC patients from our hospital registries. Patients were separated into two groups based on viral etiology: 77.5% (n=183) of patients had CHB, and 22.5% (n=53) had CHC. The proportion of men was 57.9% (n=136), while 42.1% (n=99) of patients were women.

ISHAK fibrosis stages were distributed as follows:

- F0: n=57 (24.2%)
- F1: n=59 (25%)
- F2: n=45 (19.1%)
- F3: n=35 (14.8%)
- F4: n=24 (10.2%)
- F5: n=10 (4.2%)
- F6: n=6 (2.5%)

The main demographic, laboratory, and histological features are summarized according to viral etiology in Table 1.

There was a significant correlation between fibrosis stages and non-invasive tests in the CHB group (APRI: r=0.267, FIB-4: r=0.333, Fibroindex: r=0.440, p<0.001 for all tests).

For patients with chronic hepatitis B, non-invasive tests demonstrated varying levels of diagnostic accuracy for fibrosis and cirrhosis.

- APRI index:
  - AUROC=0.684 (95% CI: 0.604-0.764) for significant fibrosis
  - Optimal cut-off=0.860
  - Sensitivity=50.85%, Specificity=77.42%
  - AUROC=0.659 (95% CI: 0.486-0.832) for cirrhosis
  - Sensitivity=83.33%, Specificity=51.46%
- FIB-4 index:
  - AUROC=0.640 (95% CI: 0.556-0.724) for significant fibrosis
  - Sensitivity=64.41%, Specificity=58.87%
  - AUROC=0.770 (95% CI: 0.637-0.904) for cirrhosis
  - Sensitivity=100.00%, Specificity=59.06%
- Fibroindex:
  - Highest AUROC for significant fibrosis at 0.735 (95% CI: 0.660-0.809)
  - Optimal cut-off=2.162
  - Sensitivity=69.49%, Specificity=69.17%
  - AUROC=0.780 (95% CI: 0.641-0.920) for cirrhosis
  - Sensitivity=91.67%, Specificity=59.88%. (Fig. 1).

In the CHC group, a significant correlation was observed between fibrosis stages and non-invasive test results (APRI: r=0.442, FIB-4: r=0.510, Fibroindex: r=0.508, p<0.001 for all tests).

Table 2. AUROCs, cut-offs, sensitivities, and specificities of APRI, FIB-4 and Fibroindex

	AUROC %95 CI	Optimal Cut-off	Sensitivity	Specificity	p
Chronic Hepatitis B					
APRI					
Significant Fibrosis	0.684 (0.604-0.764)	0.860	50.85%	77.42%	0.001
Cirrhosis	0.659 (0.486-0.832)	0.578	83.33%	51.46%	0.041
FIB4					
Significant Fibrosis	0.640 (0.556-0.724)	0.123	64.41%	58.87%	0.002
Cirrhosis	0.770 (0.637-0.904)	0.135	100.00%	59.06%	<0.001
Fibroindex					
Significant Fibrosis	0.735 (0.660-0.809)	2.162	69.49%	69.17%	<0.001
Cirrhosis	0.780 (0.641-0.920)	2.162	91.67%	59.88%	<0.001
Chronic Hepatitis C					
APRI					
Significant Fibrosis	0.680 (0.521-0.839)	1.308	37.50%	94.59%	<0.001
Cirrhosis	0.872 (0.754-0.991)	0.938	100.00%	75.51%	<0.001
FIB4					
Significant Fibrosis	0.844 (0.755-0.933)	0.226	75.00%	78.38%	<0.001
Cirrhosis	0.852 (0.690-1.000)	0.228	100.00%	69.39%	<0.001
Fibroindex					
Significant Fibrosis	0.790 (0.677-0.903)	2.495	62.50%	83.78%	<0.001
Cirrhosis	0.837 (0.708-0.966)	2.495	100.00%	75.51%	<0.001

- APRI index:
  - AUROC=0.680 (95% CI: 0.521-0.839) for significant fibrosis
  - Cut-off=1.308
  - Sensitivity=37.50%, Specificity=94.59%
  - AUROC=0.872 (95% CI: 0.754-0.991) for cirrhosis
  - Sensitivity=100.00%, Specificity=75.51%
- FIB-4 index:
  - AUROC=0.844 (95% CI: 0.755-0.933) for significant fibrosis
  - Cut-off=0.226
  - Sensitivity=75.00%, Specificity=78.38%
  - AUROC=0.852 (95% CI: 0.690-1.000) for cirrhosis
  - Sensitivity=100.00%, Specificity=69.39%
- Fibroindex:
  - AUROC=0.790 (95% CI: 0.677-0.903) for significant fibrosis
  - Sensitivity=62.50%, Specificity=83.78%
  - AUROC=0.837 (95% CI: 0.708-0.966) for cirrhosis
  - Sensitivity=100.00%, Specificity=75.51%. (Fig. 1).

Calculations were performed for both groups, CHB and CHC. AUROCs, cut-offs, sensitivities, and specificities of APRI, FIB-4, and Fibroindex are summarized in Table 2.

Discussion

The accurate staging of liver fibrosis plays a pivotal role in guiding therapeutic choices and evaluating the prognosis of chronic HBV infection.[17] Hui et al.[18] found that age, platelet count, serum albumin, total bilirubin, ALP, AST, ALT, AFP, INR levels were significantly different between patients with significant fibrosis and those with no/mild fibrosis in CHB patients. In our study, age, platelet count, serum AST, globulin, and GGT levels were statistically different compared to fibrosis stages in CHB patients (Table 2).

There was a significant correlation between all non-invasive tests and fibrosis stages. The highest correlation (r=0.440) between non-invasive tests and fibrosis stage was observed with Fibroindex in the CHB group. FIB-4 had the best correlation (r=0.510) with fibrosis stages in the CHC group. In the CHC group, all non-invasive tests had better correlation coefficients compared to the CHB group. The correlation between fibrosis stage and APRI, FIB-4, and Fibroindex has been reported in many studies, although correlation coefficients differ between studies.[15,19–21]

In their study, Zhu et al.[17] assessed the power of a non-invasive score in CHB patients. Liver fibrosis was graded using the METAVIR (F0–F4) classification system. The AUROC of APRI was 0.81 for significant fibrosis (F2-F3) and 0.83 for cirrhosis (F4). The AUROCs of FIB-4 for the detection of fibrosis and cirrhosis were 0.86 and 0.77, respectively. Sensitivities of APRI and FIB-4 for significant fibrosis were 82% and 67.4%; specificities were 82% and 74%. For cirrhosis, sensitivities of APRI and FIB-4 were 75.9% and 69%, while specificities were 69.2% and 75.3%, respectively.[17] Lin et al.[22] calculated AUROCs for APRI and FIB-4 in CHB patients. AUROCs were 0.693 and 0.766 for significant fibrosis, and 0.692 and 0.873 for cirrhosis, respectively.

Another study from Türkiye reported AUROCs of APRI and FIB-4 for METAVIR ≥F2 as 0.662 and 0.687 (sensitivity: 73.2% and 70.7%; specificity: 59.4% and 62.5%).[23] Utilizing optimal cutoff levels of the FIB-4 index accurately ruled out significant fibrosis in 69.5% of cases and diagnosed the presence of cirrhosis in 84.4% of patients. Similarly, the identification of significant fibrosis and cirrhosis was achieved with an acceptable percentage. Different results between studies may reflect population variation.

Dinesen et al.[24] performed non-invasive tests on 96 CHB patients and compared them with percutaneous liver biopsy. Fibroindex>1.82 acquired 70.4% sensitivity and 91.3% specificity as an indicator of cirrhosis, and the AUROC was 0.845. In our study, the best cut-off for distinguishing cirrhosis from other fibrosis stages was 2.162, and with this cut-off value, Fibroindex had 91.6% sensitivity and 59.9% specificity.

Boursier et al.[25] also calculated APRI scores in CHC for severe fibrosis (>F2) and cirrhosis (F4). AUROCs were 0.822 and 0.841, with sensitivity values of 77.5% and 84.6%, and specificity values of 74.6% and 71.5%, respectively. These results were similar to those in our study.

Koda et al.[16] compared AUROCs of Fibroindex with APRI for severe fibrosis (F≥2). AUROCs were 0.78 vs. 0.83, and values for predicting F≥3 were 0.77 vs. 0.81, respectively. Ichino et al.[19] also found similar AUROCs to those in Koda's study; AUROCs were 0.82 and 0.85, respectively. Fibroindex did not perform as well in our study population as in the aforementioned studies.

Our study has several limitations. Firstly, being a retrospective study, liver biopsies were interpreted by various pathologists. Secondly, the diagnostic accuracy of most non-invasive biomarkers relied on a binary distinction between the absence or presence of significant fibrosis

and the categorization of non-cirrhosis versus cirrhosis. However, since fibrosis severity is multilevel, these biomarkers were unable to distinguish the early stage of cirrhosis.

Conclusion

In conclusion, the results of our study indicate that non-invasive tests have acceptable performance in detecting liver fibrosis or cirrhosis in CHB and CHC patients, particularly in those with advanced fibrosis.

Ethics Committee Approval: The study was approved by İzmir Katip Çelebi University Ethics Committee (No: 163, Date: 24/07/2014).

Peer-review: Externally peer-reviewed.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept – R.B.; Design – R.B., T.D.; Supervision – R.B., T.D., S.U.; Fundings – R.B.; Materials – R.B., S.Ö., Ü.S.S.; Data collection &/or processing – R.B., S.Ö., Ü.S.S.; Analysis and/or interpretation – R.B.; Literature search – R.B.; Writing – R.B.; Critical review – R.B., S.A.N.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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