flora

RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2023;28(3):507-517 • doi: 10.5578/flora.20239722

Comparison of Invasive and Non-Invasive Liver Fibrosis Indicators in Chronic Hepatitis C Patients

Kronik Hepatit C Hastalarında İnvaziv ve Non-Invaziv Karaciğer Fibrozis Göstergelerinin Karşılaştırılması

Ahmet ŞAHİN[1](İD), Özlem AKAY[2](İD), Mehmet ÇELİK[3](İD), Ayşe Özlem METE[4](İD)

[1] Clinic of Infectious Diseases and Clinical Microbiology, Dr. Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye
[2] Department of Biostatistics, Gaziantep Islam, Science and Technology University Faculty of Medicine, Gaziantep, Türkiye
[3] Department of Infectious Diseases and Clinical Microbiology, Harran University Faculty of Medicine, Şanlıurfa, Türkiye
[4] Department of Infectious Diseases and Clinical Microbiology, Gaziantep University Faculty of Medicine, Gaziantep, Türkiye

Cite this article as: *Şahin A, Akay Ö, Çelik M, Mete AÖ. Comparison of invasive and non-invasive liver fibrosis indicators in chronic hepatitis C patients. FLORA 2023;28(3):507-517.*

ABSTRACT

Introduction: *Liver biopsy is a standard method used to determine the stage of liver fibrosis. Base formulations have been developed to replace liver biopsy.*

Materials and Methods: *All patients aged 18 years and older, who were diagnosed with chronic hepatitis C and underwent liver biopsy, and who presented to the outpatient clinic of infectious diseases and clinical microbiology at our hospital between January 2011 and January 2017, were included in the study. Liver biopsies of the patients were evaluated according to the modified Knodell (Ishak) fibrosis score. The patients were categorized into two groups based on their fibrosis scores: the low fibrosis group (F0, F1, F2) and the high fibrosis group (F3, F4, F5, F6). The diagnostic performance of non-invasive methods [modified fibrosis-4 index (mFIB-4), fibrosis-4 index (FIB-4), AST/platelet ratio (APRI), AST/ALT ratio (AAR), University of Gothenburg cirrhosis index (GUCI), King's score, FibroQ test and Lok index] in predicting these two groups were compared retrospectively.*

Results: *A total of 70 patients with chronic hepatitis C, comprising 40 women (57.1%) and 30 men (42.9%), who underwent liver biopsy and sought treatment at the outpatient clinic of infectious diseases and clinical microbiology between January 2011 and January 2017, were included in our study. The mean age of the patients was 50.47 ± 17 years. Based on liver biopsy results, there were 14 patients (20%) with a fibrosis score of 1, 25 patients (35.7%) with a score of 2, 20 patients (28.6%) with a score of 3, seven patients (10%) with a score of 4, and four patients (5.7%) with a score of 5. According to the Ishak score, there were 39 patients (55.7%) with low fibrosis and 31 patients (44.3%) with high fibrosis. The Area under the ROC Curve (AUROC), cut-off values, and p-values were compared to differentiate between patients with low fibrosis and those with high fibrosis. The highest AUROC value was found in the FIB-4 score, followed by the King's score. Analyzing the noninvasive tests yielded the following results: FIB-4 index: AUROC= 0.749 (95% CI= 0.636-0.863, cut-off= 1.1276, sensitivity= 71%, specificity= 69.2%, p= 0.000); King's score: AUROC= 0.733 (95% CI= 0.617-0.849, cut-off= 7.9069, sensitivity= 64.5%, specificity= 64.1%, p= 0.001); FibroQ index: AUROC= 0.668 (95% CI= 0.543-0.794, cut-off= 1.5981, sensitivity= 58.1%, specificity= 59%, p= 0.016); mFIB-4 index: AUROC= 0.647 (95% CI= 0.519-0.775, cut-off= 1.7118, sensitivity= 58.1%, specificity= 59%, p= 0.036); GUCI index: AUROC= 0.651 (95% CI= 0.522-0.780, cut-off= 0.4173, sensitivity= 61.3%, specificity= 61.5%, p= 0.031); APRI index: AUROC= 0.644 (95% CI= 0.515-0.774, cut-off= 0.4135, sensitivity= 61.3%, specificity= 59%, p= 0.039).*

Conclusion: *In our study, we found that FIB-4 and King›s score can be used more safely than others in differentiating between low and high fibrosis.*

Key Words: *Hepatitis C virus; Fibrosis; Biopsy*

Received/Geliş Tarihi: 22/07/2023 - Accepted/Kabul Ediliş Tarihi: 23/08/2023

Available Online Date: 20.09.2023

ÖZ

Kronik Hepatit C Hastalarında İnvaziv ve Non-Invaziv Karaciğer Fibrozis Göstergelerinin Karşılaştırılması

Ahmet ŞAHİN[1], Özlem AKAY[2], Mehmet ÇELİK[3], Ayşe Özlem METE[4]

[1] Dr. Ersin Arslan Eğitim ve Araştırma Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, Gaziantep, Türkiye
[2] Gaziantep İslam Bilim ve Teknoloji Üniversitesi Tıp Fakültesi, Biyoistatik Anabilim Dalı, Gaziantep, Türkiye
[3] Harran Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Şanlıurfa, Türkiye
[4] Gaziantep Üniversitesi Tıp Fakültesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Gaziantep, Türkiye

Giriş: *Karaciğer biyopsisi karaciğerin fibrozis evresini göstermek için kullanılan altın standart bir yöntemdir. Karaciğer biyopsisinin yerine kullanılabilecek baz formülasyonlar geliştirilmiştir.*

Materyal ve Metod: *Çalışmaya Ocak 2011-Ocak 2017 tarihleri arasında hastanemiz infeksiyon hastalıkları ve klinik mikrobiyoloji polikliniğine başvuran kronik hepatit C tanısı almış, karaciğer biyopsisi yapılan 18 yaş ve üzeri tüm hastalar dahil edildi. Hastaların karaciğer biyopsileri modifiye Knodell (Ishak) fibrozis skoruna göre değerlendirildi. Hastalar fibrozis skoruna göre hafif fibrozis (F0, 1, 2) ve şiddetli fibrozis (F3, 4, 5, 6) olanlar şeklinde iki gruba ayrıldı. Non-invaziv yöntemlerin [modifiye fibrozis-4 indeksi (mFIB-4), fibrozis-4 indeksi (FIB-4), AST/platelet oranı (APRI), AST/ALT oranı (AAR), Göteborg Üniversitesi siroz indeksi (GUCI), King's skoru, FibroQ testi ve Lok indeksi] bu iki grubu öngörmedeki tanısal performansı retrospektif olarak karşılaştırıldı.*

Bulgular: *Çalışmamıza Ocak 2011-Ocak 2017 tarihleri arasında infeksiyon hastalıkları ve klinik mikrobiyoloji polikliniğine başvuran kronik hepatit C'li karaciğer biyopsisi yapılmış 40'ı (%57.1) kadın, 30'u (%42.9) erkek toplam 70 hasta dahil edildi. Hastaların yaş ortalaması 50.47 ± 17 yıl idi. Karaciğer biyopsisine göre fibrozis skoru bir olan hasta sayısı 14 (%20), iki olan hasta sayısı 25 (%35.7), üç olan hasta sayısı 20 (%28.6), dört olan hasta sayısı yedi (%10), beş olan hasta sayısı ise dört (%5.7) idi. Ishak skoruna göre hafif fibrozisli hasta sayısı 39 (%55.7) iken şiddetli fibrozisli hasta sayısı 31 (%44.3) idi. Hastalarda hafif fibrozis ve şiddetli fibrozisi ayırt etmek için eğri altında kalan alan (AUROC), cut-off ve p değerleri karşılaştırıldı. En yüksek AUROC değeri FIB-4 skorunda, sonra ise King's skorunda tespit edildi. Non-invaziv testler incelendiğinde, FIB-4 indeksi için AUROC= 0.749 (%95 CI= 0.636-0.863, cut-off= 1.1276, duyarlılık %71, özgüllük %69.2, p= 0.000); King's skoru için AUROC= 0.733 (%95 CI= 0.617-0.849, cut-off= 7.9069, duyarlılık %64.5, özgüllük %64.1, p= 0.001); FibroQ indeksi için AUROC= 0.668 (%95 CI= 0.543-0.794, cut-off= 1.5981, duyarlılık %58.1, özgüllük %59, p= 0.016); mFIB-4 indeksi için AUROC= 0.647 (%95 CI= 0.519-0.775, cut-off= 1.7118, duyarlılık %58.1, özgüllük %59, p= 0.036); GUCI indeksi için AUROC= 0.651 (%95 CI= 0.522-0.780, cut-off= 0.4173, duyarlılık %61.3, özgüllük %61.5 p= 0.031) ve APRI indeksi için AUROC= 0.644 (%95 CI= 0.515-0.774, cut-off= 0.4135, duyarlılık %61.3, özgüllük %59 p= 0.039) saptandı.*

Sonuç: *Çalışmamızda FIB-4 ve King's skorunun hafif ve şiddetli fibrozis ayrımında diğerlerine göre daha güvenle kullanılabileceğini tespit ettik.*

Anahtar Kelimeler: *Hepatit C virüsü; Fibrozis; Biyopsi*

INTRODUCTION

The hepatitis C virus (HCV) is estimated to affect 58 million people worldwide. While the seroprevalence of HCV varies across different regions, it typically ranges between 0.5% and 1.4%[1]. The effect of HCV in the liver ranges from minimal inflammation to severe fibrosis, and it is associated with cirrhosis and hepatocellular carcinoma (HCC) in the long term[2]. Bridging fibrosis is known to be a major risk factor for cirrhosis. Accurately determining the degree of liver fibrosis determines the type and duration of antiviral therapy that the patient will receive, and also provides information about the prognosis of the disease[3].

Liver biopsy is used as a "gold standard" method in the diagnosis of chronic hepatitis C (CHC) disease and the staging of fibrosis[4,5]. However, the drawbacks of biopsy include its invasive nature, the potential for complications (such as bleeding and pain), the possibility of sampling errors, and discrepancies in interpretation among pathologists[6]. As a non-invasive method, Fibroscan can be used to estimate the stage of fibrosis by measuring liver stiffness[7]. However, it is seldom utilized in our country, and certain drawbacks associated with it include its high cost and the need for specialized expertise. Several methods have been developed to predict liver fibrosis in chronic hepatitis, utilizing formulations

that combine patients' age with specific laboratory parameters. Some of the non-invasive methods used in chronic hepatitis C are Modified fibrosis-4 index (mFIB-4)[8], fibrosis-4 index (FIB-4)[9], Aspartate aminotransferase to platelets ratio (APRI)[10], Aspartate aminotransferase-alanine aminotransferase ratio (AAR)[11], Goteborg University Cirrhosis Index (GUCI)[12], King's score[13], Fibro-quotient (FibroQ)[14], and Lok index[15].

In our study, we aimed to compare liver biopsy, which is an invasive method for detecting liver fibrosis, and non-invasive methods (mFIB-4, FIB-4, APRI, AAR, GUCI, King's score, FibroQ, and Lok index).

MATERIALS and METHODS

All patients aged 18 years and older, who were diagnosed with chronic hepatitis C and underwent liver biopsy, and who presented to the outpatient clinic of infectious diseases and clinical microbiology at our hospital between January 2011 and January 2017, were included in the study. Patients under the age of 18 and patients who did not undergo liver biopsy for any reason were excluded from the study. Liver biopsies of the patients were evaluated according to the modified Knodell (Ishak) fibrosis score[16]. Fibrosis scoring is shown in the table (Table 1). The patients were categorized into two groups based on their fibrosis scores: the low fibrosis group (F0, F1, F2) and the high fibrosis group (F3, F4, F5, F6). We employed the Ishak scoring system as an invasive method in our study. Nevertheless, numerous other studies have utilized the METAVIR scoring system. The correlation between Ishak and METAVIR scoring is as follows: Ishak F0 corresponds to METAVIR F0, Ishak F1-2 corresponds to METAVIR F1, Ishak F3 corresponds to METAVIR F2, Ishak F4-5 corresponds to METAVIR F3, and Ishak F6 corresponds to METAVIR F4[17]. The comparisons of F0-2/F3-6 in Ishak scoring and F0-1/F2-4 in METAVIR were examined for the distinguishing of low/high fibrosis. We used mFIB-4, FIB-4, APRI, AAR, GUCI, King's score, FibroQ, and Lok index as non-invasive methods. Plasma HCV RNA levels were determined by a real-time PCR assay, using the Bosphore HCV Quantification Kit V2 (Anatolia Geneworks, Türkiye) with a detection limit of 25 IU/mL. This study adheres to medical ethics standards, and it has received approval (Approval No. 237.25.14, dated 30.05.2023) from the Ethics Committee.

Patients were categorized into two groups based on their fibrosis severity: low fibrosis and high fibrosis. This categorization was determined according to the modified Knodell (Ishak) fibrosis score obtained from liver biopsy results. The diagnostic performance of non-invasive methods (mFIB-4, FIB-4, APRI, AAR, GUCI, King's score, FibroQ, and Lok index) in predicting these two groups was compared retrospectively.

Statistical Analysis

Descriptive statistics of the variables used in the study are given as frequency and percentage values for categorical variables, and mean, median, minimum, and maximum values for quantitative variables. The patients were divided into two groups: low fibrosis [those with scores of 0, 1, and 2 after liver biopsy according to the Modified Knodell (Ishak) score] and high fibrosis (those with scores of 3, 4, 5, and 6). The conformity

Table 1. Modified Knodell score (Ishak), fibrosis score

Architectural changes	Score
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas, with occasional portal to portal bridging	3
Fibrous expansion of portal areas with marked bridging (portal to portal) as well as portal to central	4
Marked bridging (portal to portal and/or portal to central) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6

Table 2. Non-invasive liver fibrosis tests

mFIB-4	10 x Age (years) x AST (U/L)/PLT (10^9/L) x ALT (U/L),
FIB-4	Age (years) × AST (U/L)/[PLT (10^9/L) × ALT (U/L)1/2]
APRI	AST/upper limit of normal for AST (U/L) x 100/PLT (10^9/L)
AAR	AST (U/L) / ALT (U/L)
GUCI	[AST/ upper limit of normal for AST (U/L)] x INR x 100/ PLT (10^9/L)
King's score	Age (years) x AST (U/L) x INR/PLT (10^9/L)
FibroQ	[10 x Age (years) x AST (U/L) x INR]/[PLT 10^9/L) x ALT (U/L)]
Lok index	-5.56–0.0089 x PLT (10^9/L) + 1.26 x AST/ALT + 5.27 x INR

mFIB-4: Modified fibrosis-4 index, FIB-4: Fibrosis-4 index, APRI: Aspartate aminotransferase to platelets ratio, AAR: Aspartate amino-transferase-alanine aminotransferase ratio, GUCI: Goteborg University Cirrhosis Index, FibroQ: Fibro-quotient, PLT: Platelet count.

of the measurements of liver fibrosis scores obtained to normal distribution was examined with the Kolmogorov-Smirnov test. While age, PLT, and AAR variables were in accordance with normal distribution, it was observed that other variables did not comply with normal distribution ($p> 0.05$). Independent samples, t-test, and Mann-Whitney U test were used to compare variables according to fibrosis status. The analysis results are given as mean ± standard deviation for the variable conforming to the normal distribution, and the median (min-max) analysis results for the variables not conforming to the normal distribution. Receiver operating characteristic (ROC) curves were constructed to assess the discriminatory capacity of each variable. These curves were utilized to identify optimal sensitivity and specificity values, along with corresponding cut-off points for the variables in question. Sensitivity, specificity, standard error (SE) estimates, and areas under the ROC curves (AUROC) and the corresponding 95% confidence intervals (CI) were calculated to evaluate the diagnostic performance of non-invasive liver fibrosis tests. Statistical analysis was performed using the IBM SPSS 25.0 version (IBM SPSS, Chicago, IL). A significance level of $p< 0.05$ was adopted.

RESULTS

A total of 70 patients with chronic hepatitis C, comprising 40 female (57.1%) and 30 male (42.9%), who underwent liver biopsy and sought treatment at the outpatient clinic of infectious diseases and clinical microbiology between January 2011 and January 2017, were included in our study. The mean age of the patients was 50.47 ± 17 years. Based on liver biopsy results, there were 14 patients (20%) with a fibrosis score of 1, 25 patients (35.7%) with a score of 2, 20 patients (28.6%) with a score of 3, seven patients (10%) with a score of 4, and four patients (5.7%) with a score of 5. We did not have any patients with a fibrosis score of 0 or 6. The median HCV-RNA level was 913000 IU/mL (2600-17000000) (Table 3). According to the Ishak score, the number of patients with low fibrosis was 39 (55.7%), while the number of patients with high fibrosis was 31 (44.3%). INR, mFIB-4, FIB-4, APRI, GUCI, King's score, and FibroQ values showed a statistically significant difference in patients with low and high fibrosis ($p< 0.05$, all). It was noted that these values exhibit an increase in patients with high fibrosis. Table 4 shows that there was no statistically significant difference observed between the groups in terms of age, PLT, AAR, ALT, AST, and Lok index test values.

ROC curves for non-invasive liver fibrosis tests (mFIB-4, FIB-4, APRI, GUCI, King's score, and FibroQ) are given in Figure 1. The cut-off values, sensitivity, specificity, SE estimates, and AUROC, the corresponding 95% confidence

Table 3. Descriptive statistics

	(n, %) or Median (Min-Max)	Mean (Standard Deviation)
Fibrosis score		
1	14 (20%)	
2	25 (35.7%)	
3	20 (28.6%)	
4	7 (10%)	
5	4 (5.7%)	
Gender		
Male	30 (42.9%)	
Female	40 (57.1%)	
Age	51 (17-80)	50.47 ± 17.002
PLT, x109/L	239 (90-462)	246.0 ± 68.567
ALT, U/L	47.5 (9-392)	78.62 ± 84.386
AST, U/L	34.5 (14-350)	53.61 ± 56.334
HCV RNA, IU/mL	913000 (2600-1700000)	
INR	1 (0.81-2.30)	1.028 ± 0.173
mFIB-4	1.65 (0.28-9.27	2.072 ± 1.682
FIB-4	1.11 (0.19-6.43)	1.35 ± 0.982
ARPI	0.41 (0.10-3.88)	0.66 ± 0.663
GUCI	0.41 (0.10-8.91)	0.74 ± 1.140
King's score	7.86 (1.30-165.37)	12.81 ± 21.11
FibroQ	1.55 (0.28-10.02)	2.16 ± 1.816
Lok index	0.20 (0.03-1.12)	0.16 ± 0.212
AAR	0.82 (0.30-2.07)	0.85 ± 0.363

intervals (CI), and p values of the non-invasive liver fibrosis tests are given. Lok index and AAR scores were not statistically significant in detecting low/high fibrosis of the patients (p= 0.103, p= 0.306, respectively) (Table 5).

AUROC, cut-off, and p values were compared to distinguish patients with low fibrosis from those with high fibrosis. The highest AUROC value was found in the FIB-4 score, followed by the King's score. Analyzing the non-invasive tests yielded the following results: AUROC= 0.749 (95% CI= 0.636-0.863, cut-off= 1.1276, sensitivity 71%, specificity 69.2%, p= 0.000) for the FIB-4 index; AUROC= 0.733 (95% CI= 0.617-0.849, cut-off= 7.9069, sensitivity 64.5%, specificity 64.1%, p= 0.001) for the King's score; AUROC= 0.668 (95% CI= 0.543-0.794, cut-off= 1.5981, sensitivity 58.1%, specificity 59%, p= 0.016) for the FibroQ index; AUROC= 0.647 (95% CI= 0.519-0.775, cut-off= 1.7118, sensitivity 58.1%, specificity 59%, p= 0.036) for the mFIB-4 index; AUROC= 0.651 (95% CI= 0.522-0.780, cut-off= 0.4173, sensitivity 61.3%, specificity 61.5% p= 0.031) for the GUCI index; and AUROC= 0.644 (95% CI= 0.515-0.774, cut-off= 0.4135, sensitivity 61.3%, specificity 59% p= 0.039) for the APRI index (Table 5).

In our study, we found that the AUC (Area Under the Curve) value of FIB-4 and King's scores, evaluated in patients with CHC for distinguishing between low and high fibrosis, was consistently above 0.7. This suggests that these scores can be considered safer and more reliable options compared to other methods for achieving this objective.

Table 4. Demographics, laboratory results, and the results of non-invasive models of the groups

	Low Fibrosis (n= 39) F(0-1-2)	High Fibrosis (n= 31) F(3-4-5-6)	p value
Age	45.871 ± 16.97	56.258 ± 15.41	0.436 η
PLT	251.025 ± 56.66	239.83 ± 8169	0.080 η
ALT	46 (9-392)	49 (11-346)	0.408 Ψ
AST	31 (14-132)	40 (15-350)	0.078 Ψ
INR	1 (0.81-1.15)	1.02 (0.89-2.30)	0.042* Ψ
FIB-4	0.85 (0.19-2.82)	1.44 (0.60-6.43)	0.000* Ψ
King's score	5.17 (1.30-33.47)	10.28 (3.11-165.37)	0.001* Ψ
FibroQ	1.36 (0.28-7.21)	1.81 (0.79-10.02)	0.016 * Ψ
mFIB-4	1.36 (0.28-7.21)	1.79 (0.71-9.27)	0.036* Ψ
GUCI	0.33 (0.10-2.20)	0.55 (0.16-8.91)	0.031* Ψ
ARPI	0.36 (0.10-1.91)	0.53 (0.13-3.88)	0.039* Ψ
Lok index	0.16 (0.03-1.12)	0.29 (0.05-1.00)	0.103 Ψ
AAR	0.835 ± 0.41	0.882 ± 0.28	0.177 η

*p< 0.05, η: t-test Ψ: Mann-Whitney U test.

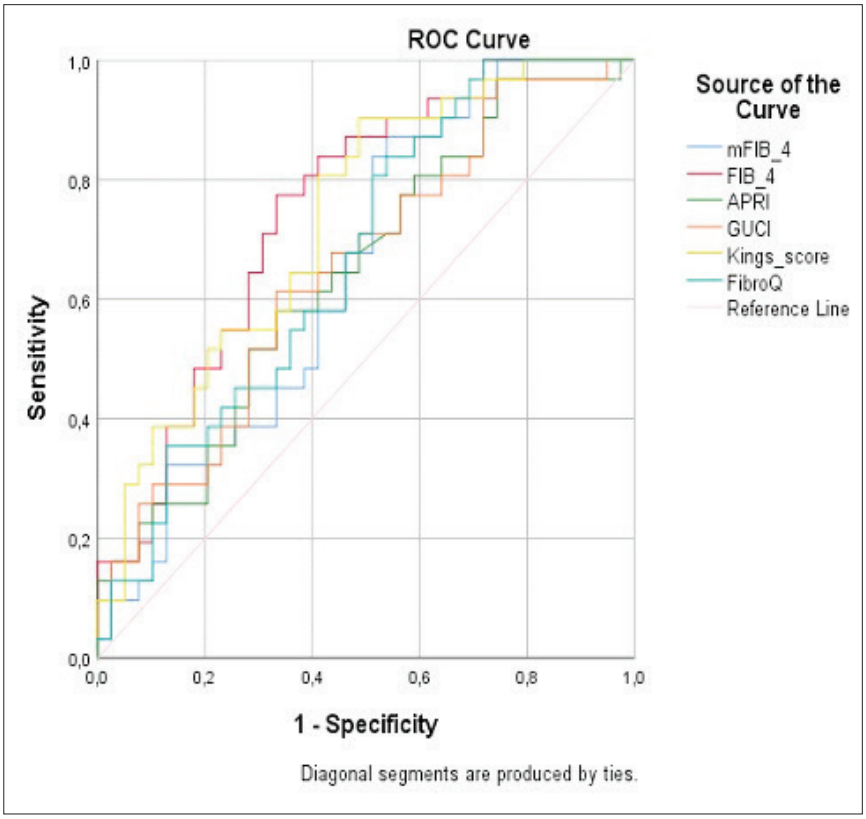

Figure 1. Receiver operating characteristic (ROC) curves of the six non-invasive tests for prediction of significant fibrosis (F3-4-5-6) versus insignificant fibrosis (F0-1-2).

Table 5. The sensitivity, specificity, PPV, NPV, and AUC of different scoring systems

Score	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC (SE)	95% CI		p value
							Lower Limit	Upper Limit	
mFIB-4	1.7118	0.581	0.590	59.9%	58.0%	0.647 (0.065)	0.519	0.775	0.036*
FIB-4	1.1276	0.710	0.692	69.2%	70.9%	0.749 (0.058)	0.636	0.863	0.000*
GUCI	0.4173	0.613	0.615	61.5%	61.2%	0.651 (0.066)	0.522	0.780	0.031*
King's score	7.9069	0.645	0.641	64.1%	64.5%	0.733 (0.059)	0.617	0.849	0.001*
FibroQ	1.5981	0.581	0.590	58.9%	58.0%	0.668 (0.064)	0.543	0.794	0.016*
APRI	0.4135	0.613	0.590	58.9%	61.2%	0.644 (0.066)	0.515	0.774	0.039*
Lok index	0.210	0.613	0.641	64.1%	61.2%	0.614 (0.070)	0.477	0.751	0.103
AAR	0.8203	0.548	0.538	53.8%	54.8%	0.572 (0.069)	0.437	0.706	0.306

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, SE: Standard error, CI: Confidence interval. *p< 0.05.

DISCUSSION

Today, many direct or indirect methods are used to determine the degree of liver fibrosis. The ideal non-invasive method should be inexpensive, accessible, easy, fast, and reliable[18]. In our study, we compared the diagnostic performance of eight different non-invasive models with liver biopsy in predicting the degree of fibrosis in patients with CHC. In two of the eight models (FIB-4 and King's score), the AUC value was found to be above 0.7 in distinguishing between low fibrosis and high fibrosis (0.749 and 0.733, respectively). In our study, it was determined that these two scores were especially useful for differentiating between low fibrosis and high fibrosis.

There are some studies associating the FIB-4 index with the degree of fibrosis[19,20]. In a study where 120 patients with CHC were evaluated with Ishak score, the AUROC was found to be 0.68 (95% CI, SE= 0.06, cut-off= 1.38, sensitivity 67%, specificity 61%, p= 0.007) for distinguishing between low/high fibrosis[21]. In Wang et al.'s study, which assessed 1284 liver biopsies based on the METAVIR scoring system, the AUROC was determined to be 0.7793 for distinguishing between F0-1 and F2-4 fibrosis stages[8]. In the cohort study comprising 2372 HCV patients, the AUROC was established as 0.83 for discriminating between F0-2 and F3-4 fibrosis stages. As the degree of fibrosis increases, the AUROC also increases[22]. In a multi-center study by Eminler et al., where liver biopsies of 1029 patients with HCV were evaluated based on the METAVIR scoring system, the AUROC was found to be 0.796 for the detection of advanced fibrosis[23]. In a study where 500 CHC patients were included in Egypt, the AUROC was found to be 0.76 for distinguishing between F0-1 and F2-4[24]. In another study performed to detect advanced fibrosis (F0-2/F3-4), the AUROC was 0.85 and the cut-off was 1.45[25]. The data from our study are compatible with the available literature.

As defined by Cross et al., King's score could be used to detect both advanced fibrosis and cirrhosis. In a study where 923 patients who underwent liver biopsy for CHC were evaluated using the Ishak score, the AUROC was found to be 0.79 (95% CI, SE= 0.026, 0.75-0.83, p< 0.0001) for distinguishing between low/high fibrosis, and 0.91 in cirrhosis patients[13]. In a study where 81 HCV patients were evaluated using the METAVIR scoring system, the AUROC was 0.643 for distinguishing between low/high fibrosis and 0.871 in cirrhotic patients. In both studies, King's score increased as the degree of fibrosis increased[26]. In the study by Eminler et al., where they evaluated liver biopsy according to Ishak scoring, the AUROC was 0.783 and the cut-off was 13.08 for distinguishing between low/high fibrosis[25]. In our study, the

AUROC and cut-off values were 0.733 and 7.9, respectively (p= 001). Despite variations attributed to the patient count, our study's outcomes are in alignment with existing data in the literature.

In our study, the AUROC for the FibroQ index was determined to be 0.668. The identified cut-off point for distinguishing between low and high fibrosis was 1.59. In the study by Gökcan et al., where 120 patients with CHC were included, the AUROC was 0.54 (95% CI, SE= 0.07, p= 0.525) for distinguishing between low/high fibrosis based on Ishak scoring[21]. In a different study, it was employed for predicting HCC, yielding an AUROC of 0.743 (95% CI= 0.720-0.766, cut-off= 5.01, sensitivity 70.1%, specificity 69.1%, p= 0.0001)[27]. In Wang et al.'s study utilizing the METAVIR scoring system, an AUROC of 0.7496 was identified for distinguishing between low and high fibrosis stages[8]. Studies indicate that the elevation of the FibroQ test results can be utilized for predicting both liver fibrosis and HCC.

The modified FIB-4 (mFIB-4) can serve as a fibrosis marker similar to the FIB-4 index. In a study encompassing 1284 patients with CHC using the METAVIR scoring, the AUROC was established at 0.7368 for distinguishing between low and high fibrosis stages. Additionally, as a cirrhosis marker, the AUROC was determined as 0.84080. In the same study, the cut-off value was found to be 2.36[8]. The cut-off value in our study was 1.71, while the AUROC was 0.647. We believe that the observed differences could be attributed to the patient sample size. However, we hold the opinion that further investigations are warranted to comprehensively assess the applicability and effectiveness of the mFIB-4 marker.

In a study employing the GUCI index, the AUROC was calculated as 0.72 for distinguishing between low and high fibrosis stages based on Ishak fibrosis scoring[21]. In a study by Kandemir et al., where 68 HCV-infected patients were evaluated based on METAVIR scoring, the difference between F0-2 and F3-4 was found to be statistically significant[28]. Studies have been conducted utilizing the GUCI index to identify cirrhotic patients. In a study conducted in Egypt based on the METAVIR scoring system, the AUROC, cut-off value, sensitivity, and specificity were determined as 0.783, 1.56, 60%, and 85.5%, respectively, for distinguishing between fibrosis stages F0-3 and F4 (p< 0.001)[29]. In our study, the AUROC, cut-off, sensitivity, and specificity were found to be 0.651, 0.41, 61.3%, and 61.5%, respectively, for distinguishing between F0-2 and F3-6 based on Ishak scoring (p= 0.031).

There are many studies conducted with the APRI scoring. In a study in which 150 HCV-infected patients were evaluated according to METAVIR, the AUROC, cut-off, sensitivity, and specificity for distinguishing F0-1 and F2-4 were found to be 0.766, 0.52, 70%, and 81%, respectively (p< 0.0001)[25]. In the systematic review, the AUROC was reported as 0.76 for detecting fibrosis stage F≥ 2 according to the METAVIR scoring system. However, for the detection of cirrhosis, the AUROC was higher at 0.82. In the same study, the cut-off was one, the sensitivity was 93.3%, and the specificity was 69% for the detection of cirrhosis[30]. In a study by Gökcan et al., the AUROC was found to be 0.72[21]. In a study conducted in Egypt to determine the distinction between F0-2 and F3-4 in 182 patients, the cut-off, sensitivity, and specificity values were found to be 0.7, 73%, and 82%, respectively[31].

According to the definition by Lok et al., the Lok index exhibited an AUROC of 0.79 for the detection of cirrhosis. In their study involving 1141 HCV-infected patients, they determined a cut-off of 0.2 to rule out cirrhosis and a cut-off of 0.5 to diagnose cirrhosis[32]. In a study by Sirli et al. using the METAVIR scoring system, the AUROC was found to be 0.701 (95% CI, SE= 0.0627, 0.619-0.774, cut-off= 0.17, p< 0.0001)[25]. In a study where 143 patients with CHC were evaluated based on Ishak scoring, the AUROC value was found to be 0.763 for distinguishing between low/high fibrosis[33]. In our study, the AUROC was found to be 0.614 (95% CI, SE= 0.070, 0.477-0.-0.751, cut-off= 0.21, p= 0.103). Although not statistically significant, similar cut-off values were present.

AAR is accepted as one of the parameters indicating fibrosis in people with liver disease[34].

Especially AAR≥ 1 has been associated with cirrhosis[35]. In the study where 1284 HCV-infected patients were evaluated according to METAVIR scoring, the AUROC was found to be 0.7741 for distinguishing between F0-1 and F2-4[8]. In another study, the cut-off was ≥1, the sensitivity was 29.6%, and the specificity was 85.3% for the determination of cirrhosis[36]. Similarly, in a study by Lackner et al., the AUROC was found to be 0.8 for the detection of advanced fibrosis[37]. The data from our study were compatible with the available literature.

CONCLUSION

In conclusion, our study revealed that FIB-4 and the King's score exhibited greater effectiveness in identifying advanced fibrosis in comparison to other noninvasive methods. Nevertheless, it's important to acknowledge the limitations of our study, including its single-center nature and retrospective design. We propose that until serum biomarkers or imaging techniques capable of replacing liver biopsy are established, certain non-invasive tests can aid in determining liver fibrosis stages. However, it's crucial to recognize that when utilizing these tests, adjustments to cut-off values and sensitivity/specificity might be necessary based on the specific fibrosis stage being predicted.

ETHICS COMMITTEE APPROVAL

This study was approved by the Gaziantep Islam, Science and Technology University Non-Invazive Clinical Research Ethics Committee (Decision no: 237.25.14, Date: 30.05.2023).

CONFLICT of INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: All of authors

Analysis/Interpretation: AŞ, ÖA

Data Collection or Processing: AŞ, MÇ

Writing: AŞ, AÖM

Review and Correction: ÖA, MÇ, AÖM

Final Approval: All of authors

REFERENCES

1. *Polaris Observatory HCV Collaborators. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: A modelling study. Lancet Gastroenterol Hepatol 2022;7:396-415. https://doi.org/10.1016/S2468-1253(21)00472-6*
2. *Massard J, Ratziu V, Thabut D, Moussalli J, Lebray P, Benhamou Y, et al. Natural history and predictors of disease severity in chronic hepatitis C. J Hepatol 2006;44:19-24. https://doi.org/10.1016/j.jhep.2005.11.009*
3. *Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: A systematic review. Ann Intern Med 2013;158:807-20. https://doi.org/10.7326/0003-4819-158-11-201306040-00005*
4. *Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004;39:1147-71. https://doi.org/10.1002/hep.20119*
5. *Loko MA, Bani-Sadr F, Valantin MA, Lascoux-Combe C, Fontaine H, Bonnard P, et al. Antiretroviral therapy and sustained virological response to HCV therapy are associated with slower liver fibrosis progression in HIV-HCV-coinfected patients: Study from the ANRS CO 13 HEPAVIH cohort. Antivir Ther 2012;17:1335-43. https://doi.org/10.3851/IMP2419*
6. *Trivedi HD, Patwardhan VR, Malik R. Chronic hepatitis C infection - Noninvasive assessment of liver fibrosis in the era of direct acting antivirals. Dig Liver Dis 2019;51:183-9. https://doi.org/10.1016/j.dld.2018.11.016*
7. *Masuzaki R, Tateishi R, Yoshida H, Arano T, Uchino K, Enooku K, et al. Assessment of disease progression in patients with transfusion-associated chronic hepatitis C using transient elastography. World J Gastroenterol 2012;18:1385-90. https://doi.org/10.3748/wjg.v18.i12.1385*
8. *Wang HW, Peng CY, Lai HC, Su WP, Lin CH, Chuang PH, et al. New noninvasive index for predicting liver fibrosis in Asian patients with chronic viral hepatitis. Sci Rep 2017;7:3259. https://doi.org/10.1038/s41598-017-03589-w*
9. *Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-25. https://doi.org/10.1002/hep.21178*
10. *Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-26. https://doi.org/10.1053/jhep.2003.50346*
11. *Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology 1988;95:734-9. https://doi.org/10.1016/S0016-5085(88)80022-2*

12. *Islam S, Antonsson L, Westin J, Lagging M. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. Scand J Gastroenterol 2005;40:867-72. https://doi.org/10.1080/00365520510015674*

13. *Cross TJ, Rizzi P, Berry PA, Bruce M, Portmann B, Harrison PM. King's Score: An accurate marker of cirrhosis in chronic hepatitis C. Eur J Gastroenterol Hepatol 2009;21:730-8. https://doi.org/10.1097/MEG.0b013e32830dfcb3*

14. *Hsieh YY, Tung SY, Lee IL, Lee K, Shen CH, Wei KL, et al. FibroQ: An easy and useful noninvasive test for predicting liver fibrosis in patients with chronic viral hepatitis. Chang Gung Med J 2009;32:614-22.*

15. *Deng H, Qi X, Guo X. Diagnostic accuracy of APRI, AAR, FIB-4, FI, King, Lok, Forns, and FibroIndex Scores in predicting the presence of esophageal varices in liver cirrhosis: A systematic review and meta-analysis. Medicine (Baltimore) 2015;94:e1795. https://doi.org/10.1097/MD.0000000000001795*

16. *Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696-9. https://doi.org/10.1016/0168-8278(95)80226-6*

17. *Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24:289-93. https://doi.org/10.1002/hep.510240201*

18. *Duarte-Rojo A, Altamirano JT, Feld JJ. Noninvasive markers of fibrosis: Key concepts for improving accuracy in daily clinical practice. Ann Hepatol 2012;11:426-39. https://doi.org/10.1016/S1665-2681(19)31456-5*

19. *Schmid P, Bregenzer A, Huber M, Rauch A, Jochum W, Müllhaupt B, et al. Progression of liver fibrosis in HIV/HCV Co-Infection: A comparison between non-invasive assessment methods and liver biopsy. PLoS One 2015;10:e0138838. https://doi.org/10.1371/journal.pone.0138838*

20. *Sripongpun P, Tangkijvanich P, Chotiyaputta W, Charatcharoenwitthaya P, Chaiteerakij R, Treeprasertsuk S, et al. Evaluation of aspartate aminotransferase to platelet ratio index and fibrosis 4 scores for hepatic fibrosis assessment compared with transient elastography in chronic hepatitis C patients. JGH Open 2020;4:69-74. https://doi.org/10.1002/jgh3.12219*

21. *Gökcan H, Kuzu UB, Öztaş E, Saygılı F, Öztuna D, Suna N, et al. The predictive value of noninvasive serum markers of liver fibrosis in patients with chronic hepatitis C. Turk J Gastroenterol 2016;27:156-64. https://doi.org/10.5152/tjg.2015.150449*

22. *Holmberg SD, Lu M, Rupp LB, Lamerato LE, Moorman AC, Vijayadeva V, et al. Noninvasive serum fibrosis markers for screening and staging chronic hepatitis C virus patients in a large US cohort. Clin Infect Dis 2013;57:240-6. https://doi.org/10.1093/cid/cit245*

23. *Itakura J, Kurosaki M, Setoyama H, Simakami T, Oza N, Korenaga M, et al. Applicability of APRI and FIB-4 as a transition indicator of liver fibrosis in patients with chronic viral hepatitis. J Gastroenterol 2021;56:470-8. https://doi.org/10.1007/s00535-021-01782-3*

24. *Bonnard P, Elsharkawy A, Zalata K, Delarocque-Astagneau E, Biard L, Le Fouler L, et al. Comparison of liver biopsy and noninvasive techniques for liver fibrosis assessment in patients infected with HCV-genotype 4 in Egypt. J Viral Hepat 2015;22:245-53. https://doi.org/10.1111/jvh.12285*

25. *Sirli R, Sporea I, Bota S, Popescu A, Cornianu M. A comparative study of non-invasive methods for fibrosis assessment in chronic HCV infection. Hepat Mon 2010;10:88-94.*

26. *Abd El hafez A, Elesawy B, Dorgham L, El Askary A, Dahlawi H. King's Score, FI, FibroIndex and Lok Index Predict METAVIR Stage of Fibrosis among Chronic HCV Mono-infected Patients. Int J Curr Med Appl Sci 2017;15:31-8.*

27. *Abdelaziz AO, Nabil MM, Omran DA, Abdelmaksoud AH, Asem N, Shousha HI, et al. Hepatocellular Carcinoma Multidisciplinary Clinic-Cairo University (HMC-CU) score: A new simple score for diagnosis of HCC. Arab J Gastroenterol 2020;21:102-5. https://doi.org/10.1016/j.ajg.2020.04.001*

28. *Kandemir Ö, Polat G, Saraçoğlu GV, Taşdelen B. The predictive role of AST level, prothrombin time, and platelet count in the detection of liver fibrosis in patients with chronic hepatitis C. Turkish J Med Sci 2009. https://doi.org/10.3906/sag-0902-11*

29. *Fouad SA, Esmat S, Omran D, Rashid L, Kobaisi MH. Noninvasive assessment of hepatic fibrosis in Egyptian patients with chronic hepatitis C virus infection. World J Gastroenterol 2012;18:2988-94. https://doi.org/10.3748/wjg.v18.i23.2988*

30. *Shaheen AA, Myers RP. Diagnostic accuracy of the aspartate aminotransferase-to-platelet ratio index for the prediction of hepatitis C-related fibrosis: A systematic review. Hepatology 2007;46:912-21. https://doi.org/10.1002/hep.21835*

31. *Yosry A, Fouad R, Alem SA, Elsharkawy A, El-Sayed M, Asem N, et al. FibroScan, APRI, FIB4, and GUCI: Role in prediction of fibrosis and response to therapy in Egyptian patients with HCV infection. Arab J Gastroenterol 2016;17:78-83. https://doi.org/10.1016/j.ajg.2016.05.002*

32. *Lok AS, Ghany MG, Goodman ZD, Wright EC, Everson GT, Sterling RK, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: Results of the HALT-C cohort. Hepatology 2005;42:282-92. https://doi.org/10.1002/hep.20772*

33. *Eminler AT, Ayyildiz T, Irak K, Kiyici M, Gurel S, Dolar E, et al. AST/ALT ratio is not useful in predicting the degree of fibrosis in chronic viral hepatitis patients. Eur J Gastroenterol Hepatol 2015;27:1361-6. https://doi.org/10.1097/MEG.0000000000000468*

34. *Giannini E, Risso D, Botta F, Chiarbonello B, Fasoli A, Malfatti 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;163:218-24. https://doi.org/10.1001/archinte.163.2.218*

35. *Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. Am J Gastroenterol 1998;93:44-8. https://doi.org/10.1111/j.1572-0241.1998.044_c.x*

36. *Elesawy BH, Abd El Hafez A, Dorgham LS, El-Askary A. Limited reliability of five non-invasive biomarkers in predicting hepatic fibrosis in chronic HCV mono-infected patients opposed to METAVIR scoring. Pathol Res Pract 2014;210:922-8. https://doi.org/10.1016/j.prp.2014.07.005*

37. *Lackner C, Struber G, Liegl B, Leibl S, Ofner P, Bankuti C, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Hepatology 2005;41:1376-82. https://doi.org/10.1002/hep.20717*

Address for Correspondence/Yazışma Adresi

Dr. Ahmet ŞAHİN

Clinic of Infectious Diseases and Clinical Microbiology, Dr. Ersin Arslan Training and Research Hospital, Gaziantep-Türkiye

E-posta: ahmet27sahin@hotmail.com