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RESEARCH

The value of APRI and FIB-4 scores in detection of liver fibrosis of patients with chronic hepatitis C

Kronik hepatit C'li hastaların karaciğer fibrozisini göstermede APRI ve FIB-4 skorlamalarının değeri

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Abstract

Purpose: Infection with hepatitis C virus causes chronic liver damage, fibrosis and in later processes, cirrhosis and liver cancer. Currently, the use of biomarkers, instead of invasive procedures, is recommended to identify liver fibrosis. In this study, we aimed to evaluate the sensitivity and specificity of aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) and Fibrosis-4 Index (FIB-4) scoring for detection of "significant fibrosis" in chronic hepatitis C patients.

Materials and Methods: Liver biopsy results and blood test results of 50 patients, infected with chronic hepatitis C, were analyzed. APRI and FIB-4 scores were calculated. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and consistency for APRI and FIB-4 scorings were calculated using a fourfold table. The values of APRI and FIB-4, providing the best specificity and sensitivity in the diagnosis of significant fibrosis, was determined by ROC (receiver operator characteristics curve) analysis.

Results: The mean fibrosis stage of 30 patients with significant fibrosis was 2.83±0.74 and the mean patient age was 56.8±13. The sensitivity of APRI ≥ 1.5 to detect significant fibrosis was 16%, the specificity was 90%, PPV was 71% and NPV was 41%. A FIB-4 score of ≥3.25 had a sensitivity of 20%, a specificity of 95%, a PPV of 85% and a NPV of 44%.

Conclusion: APRI and FIB-4 have high specificity and PPV in demonstrating significant fibrosis, but have low sensitivity and NPV. The sensitivity of FIB-4 was higher compared to the APRI scoring. More research on this subject is needed, as well as revision of fibrosis scores and development of new fibrosis scores.

Keywords: APRI, AST, chronic hepatitis C, FIB-4, significant fibrosis

Öz

Amaç: Kronik hepatit C enfeksiyonu kronik karaciğer hasarına, inflamasyona, fibrozise ve ilerleyen süreçlerde siroz ve karaciğer kanserine sebep olmaktadır. Günümüzde, karaciğer fibrozunu tanımlamak için invaziv prosedürler yerine biyobelirteçlerin kullanılması tavsiye edilmektedir. Bu çalışmada, kronik hepatit C hastalarında "belirgin fibrozisi" saptamada aspartat aminotransferaz (AST) Trombosit Oranı İndeksi (APRI) ve Fibrozis-4 İndeksi (FIB-4) skorlamalarının duyarlılık ve özgüllükleri araştırılmıştır.

Gereç ve Yöntem: Kronik hepatit C ile enfekte 50 hastanın karaciğer biyopsi sonuçları ve kan sonuçları analiz edildi. APRI ve FIB-4 puanları hesaplandı. APRI ve FIB-4 skorlamaları için duyarlılık, özgüllük, pozitif prediktif değer (PPD), negatif prediktif değer (NPD) ve tutarlılığı dört gözlü tablo ile hesaplandı. APRI ve FIB-4'ün belirgin fibrozis tanısındaki en iyi spesifite ve sensitiviteye sahip değeri ROC (reciever operator characteristics curve) analizi ile belirlendi.

Bulgular: Belirgin fibrozu olan 30 hastanın ortalama fibrozis evresi 2,83±0,74 ve ortalama hasta yaşı 56,8±13 idi. APRI ≥ 1.5'in belirgin fibrozisi saptama duyarlılığı %16, özgüllüğü %90, PPD %71 ve NPD %41 idi. FIB-4 skorunun ≥3,25 olmasının duyarlılığı %20, özgüllüğü %95, PPD %85 ve NPD %44 olarak bulundu.

Sonuç: Belirgin fibrozisi saptamada APRI ve FIB-4'ün özgüllük ve PPD'si yüksek olmasına rağmen duyarlılığı ve NPD'si düşüktür. FIB-4 skorunun duyarlılığı APRI'den daha yüksektir. Bu konuda daha fazla araştırmaya, fibrozis skorlarının revize edilmesine ve yeni fibrozis skorları geliştirilmesine ihtiyaç vardır.

Anahtar kelimeler: APRI, AST, kronik hepatit C, FIB-4, belirgin fibrozis

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INTRODUCTION

Chronic hepatitis C (CHC) infection causes chronic liver damage, inflammation, fibrosis and in later stages, cirrhosis and liver cancer[1,2]. Fibrosis status is widely acknowledged as a critical prognostic factor for unfavorable hepatic outcomes and mortality in individuals afflicted with chronic hepatitis C virus (HCV) infection. Significant fibrosis indicates damage to the liver before it reaches the stage of cirrhosis[3]. Liver biopsy is still accepted as the gold standard method, since it shows the fibrosis in the liver parenchyma by direct imaging with histological examination. Since liver biopsy is an invasive procedure, it has contraindications and may yield complications. As in all invasive procedures, it requires hospitalization, its results may vary from physician to physician and the objectivity of results cannot be ensured[4].

All these reasons have triggered the search for non-invasive fibrosis detection methods. In addition to imaging methods, fibrosis detection studies, conducted by combining serum biomarkers with scoring systems, are available[5]. World Health Organization (WHO), American and European guidelines recommend ultrasonography and elastography, as well as non-invasive scores in determining fibrosis[6-8]. Some of the commonly used non-invasive scores are aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) and Fibrosis-4 Index (FIB-4). In these scores, AST, alanine aminotransferase (ALT) and platelet are used as serum biomarkers. These scores have limitations and the diagnostic criteria for cirrhosis are not clear. Non-invasive scores may vary depending on the etiology of liver fibrosis and additional comorbid diseases[9].

There are more than one systems for histological scoring of the liver damage in chronic viral hepatitis. METAVIR system is the most commonly used system in European guidelines[4,8,10]. In Turkey, modified Ishak hepatitis activity index (HAI) scoring system is the most commonly used system[11]. In this study, we aimed to evaluate the sensitivity and specificity of APRI and FIB-4 scoring for detecting "significant fibrosis" in 50 chronic hepatitis C patients with biopsy results, using the modified Ishak HAI scoring system.

MATERIALS AND METHODS

Sample

This study was designed retrospectively. The study was carried out in the infectious diseases clinic of İzmir Katip Çelebi University, Atatürk Training and Research Hospital, a clinic in a tertiary care hospital, following-up chronic hepatitis C cases and performing liver biopsy. In this center, chronic hepatitis C patients are followed-up regularly and their information is kept in the files. The files of these cases including demographic information, blood results and liver biopsy results were reviewed. Cases, who had been followed up with chronic hepatitis C between 2014 and 2018 and had liver biopsy results and liver function test and platelet results, were included in the study. Cases with "insufficient material" biopsy results, previously treated cases, patients, who were co-infected with chronic hepatitis B (CHB) and cases without liver function test or platelet results, were excluded from the study. Ethical approval of the study was obtained from İzmir Katip Çelebi University Non-Interventional Ethics Committee with the date of May 26, 2022 and number 0265.

Procedure

The biopsy samples were at least 25 mm in length and in pathology examination, a minimum of 10 portal areas were included in each sample. All liver tissue samples were analyzed by a pathologist. In order to evaluate the extent of hepatic fibrosis, grading of necro-inflammatory activity and staging of fibrosis were performed using the histologically modified Ishak HAI scoring system. Accordingly, fibrosis in some of the portal areas was graded as F1, fibrosis in most of the portal areas as F2, rare bridging fibrosis as F3, diffuse bridging fibrosis as F4, pre-cirrhotic liver as F5, and cirrhosis as F6[11]. Patients with a fibrosis score of F2 and above were considered as cases with "significant fibrosis". Hemogram, kidney function tests, liver function tests (AST, ALT) and coagulation tests were requested for the patients prior to the biopsy procedure. According to the data obtained, AST, ALT, platelet values were scanned and APRI and FIB-4 scores were accordingly calculated.

The APRI score was calculated as described by Wai, et al[12].

- APRI= [(patient's AST value / AST normal upper limit value)/patient's platelet value (10^9/L) x 100] and
- An APRI score of ≤ 0.5 was considered as absence of fibrosis and an APRI score of ≥ 1.5 was considered as an indicator of significant fibrosis.

The FIB-4 score was calculated as described by Sterling, et al[13].

- FIB-4 score = (age x AST)/platelet value x (ALT) ^{½} and
- A FIB-4 score of ≤ 1.5 was considered as an indicator for absence of fibrosis and a score of ≥ 3.25 was considered as an indicator of significant fibrosis.

Statistical analysis

All data was analyzed using the SPSS 22.0 Windows package program. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and consistency for APRI and FIB-4 scorings were calculated using a fourfold table. The value of APRI and FIB-4 with the best specificity and sensitivity in the diagnosis of significant fibrosis, was determined by ROC (receiver operator characteristics curve) analysis. AUC (area under the curve) was used for the value of APRI and FIB-4 in the diagnosis of significant fibrosis. p values less than 0.05 were considered significant, and all statistical analyses were conducted at the 95% confidence interval (CI).

Table 1. Comparison of patients by fibrosis levels

	Significant Fibrosis (F2-F4) ± SD	Without Significant Fibrosis (F0-F1) ± SD	p value
Age	56.8±13.8	45.8±15.9	**0.012**
AST (U/L)	44.5±52.5	56.4±90.4	0.558
ALT (U/L)	52.3±69.8	108±212.9	0.187
Platelet (10^3 x μL)	182±62.9	248±79.6	**0.002**
APRI	0.96±1.5	0.74±1	0.586
FIB-4	2.35±2.1	1.35±1.2	0.060

p<0.05 significance) T-Test. SD: Standard Deviation, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, APRI: Aspartate aminotransferase to Platelet Ratio Index, FIB-4: Fibrosis-4 Index.

RESULTS

Out of 62 cases of chronic HCV infection, who had biopsy results, three were excluded due to co-infection with chronic hepatitis B, five due to insufficient material in the biopsy results and four due to the absence of blood tests. A total of 50 patients were included in the study. Mean age of the patients was 52 ± 15 years and 58% (n=29) were male. Mean HAI necro-inflammatory score was 6.36±2.66 and fibrosis stage was 1.86±1.37. According to the biopsy results, while significant fibrosis was detected in 60% (n=30) of patients, it was not detected in 40% (n=20) of patients. Mean fibrosis stage of 30 patients with significant fibrosis, was 2.83±0.74 and the mean age for this group was 56.8±13. Mean fibrosis stage of 20 patients, without significant fibrosis, was 0.4±0.5 and mean age of this group was calculated as 45.8±15.9 (Table 1). Significant fibrosis in liver biopsy result was accepted as a reference and APRI score, FIB-4 score ratio, sensitivity, specificity and NPD were calculated. The sensitivity of an APRI score of ≥ 1.5 to detect significant fibrosis was 16%, its specificity was 90%, PPV was 71% and NPV was 41%. A FIB-4 score of ≥3.25 had a sensitivity of 20%, a specificity of 95%, a PPV of 85% and a NPV of 44% (Table 2). Advanced age was found to have significance in detection of significant fibrosis (p=0.012) (Table 1). In ROC analysis, it was found that the most favorable APRI score for detection of significant fibrosis, was 1.75 and on accepting this as the threshold value, sensitivity was 13% and specificity was 50%. It was observed that the most favorable FIB-4 score was 2.25 and on accepting this as the threshold value, sensitivity was 40% and specificity was 50% (APRI AUC;0.603, 95% CI 0.436-0.770, FIB-4 AUC;0.703 95% CI 0.555-0.850). ROC analysis is shown in Figure 1.

Table 2. Role of FIB-4 and APRI scores in prediction of significant fibrosis

	APRI ≥1.5	FIB-4≥3.25
Sensitivity	16%	20%
Specificity	90%	95%
Positive Predictive Value	71%	85%
Negative Predictive Value	41%	44%
Consistency	46%	50%

APRI: Aspartate aminotransferase to Platelet Ratio Index, FIB-4: Fibrosis-4 Index.

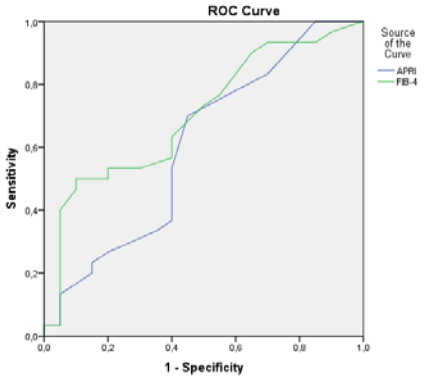

Figure 1. ROC analysis of APRI and FIB-4 values

APRI: Aspartate aminotransferase to Platelet Ratio Index, FIB-4: Fibrosis-4 Index, ROC Curve: Receiver Operator Characteristics Curve.

DISCUSSION

Due to the concerns of complications, such as cirrhosis and liver failure in patients, who do not receive treatment, in current treatment guidelines, emergency treatment is recommended in patients with chronic HCV infection, who have significant fibrosis. Patients with significant fibrosis must be followed-up regularly following treatment due to the risk of complications, such as cirrhosis. Therefore, detection of liver fibrosis prior to treatment is also important for addressing complications of chronic HCV infection[8].

Although liver biopsy is widely used, the limitations of this procedure have exacerbated the need for novel non-invasive methods, which can accurately demonstrate liver fibrosis. Therefore, indirect and direct indicators of fibrosis are being used in combination[4]. Also, there are patients, who are scared of the biopsy procedure and therefore in whom liver fibrosis cannot be detected. Non-invasive methods provide patient comfort while demonstrating liver fibrosis. In this study, we aimed to investigate the value of FIB-4 and APRI scoring systems, which can be easily applied in daily practice, in detection of significant fibrosis in patients with chronic HCV infection.

In their study, Sterling, et al., have found a threshold of ≥3.25 for FIB-4, a PPV of 65%, and a specificity of 97% for demonstration of significant fibrosis. However, the researchers have accepted fibrosis stage 4 and higher in the ISHAK scoring system as "significant fibrosis"[13]. In our study, a PPV value of 85% and a specificity value of 95% were achieved, when the same threshold value was calculated for F2 and over. Accordingly, it can be said that the PPV and specificity remains high even with a decrease in the fibrosis level.

Vallet-Pichard, et al., in their study on 847 patients with chronic HCV infection, have found NPV as 94.7%, sensitivity as 74.3% and specificity as 80.1% for demonstration of the absence of fibrosis, when the FIB-4 value was less than 1.45. When the FIB-4 value was greater than 3.25, the specificity for demonstration of fibrosis was 98.2%, the sensitivity was 37.6% and the PPD was 82.1%. This data is similar to the results of our study[14]. Similarly, in a study, conducted in Turkey in 2008 on 30 patients with chronic HCV infection and 39 patients with chronic hepatitis B (HBV) infection, a significant fibrosis of F2 and over was acknowledged using Knodell score. Consequently, the sensitivity and positive predictive values of non-invasive methods, used in demonstrating significant fibrosis, have been found to be low, while their specificity and negative predictive values have been found to be high. When the FIB-4 score was higher than 3.25, statistical data could not be obtained due to the low number of cases[15].

The APRI score has first been calculated by Wai, et al., in 2003 on 192 patients with chronic HCV infection. It has been stated that the APRI score was 51% for F3 and over and PPV was 81% for cirrhosis[12]. In our study, the PPV value was higher for F2 and above. We contemplated that the difference in the number of patients caused this result.

In a study in Turkey, the role of FIB-4 and APRI scores in detection of significant fibrosis in patients with chronic HCV infection has been compared with different methods (Fibro test, AP index). For FIB-4, the sensitivity for the cut-off value of 1.45 was 62% and the specificity was 67%, while for the cut-off value of 0.5 for APRI, the sensitivity was 71% and the specificity was 55%. In the study, it has been reported that APRI and FIB-4 scores gave similar results with different non-invasive methods in terms of detection of significant fibrosis[16].

Advanced age is a significant factor in detection of significant fibrosis. The sensitivity of FIB-4 is higher

than that of APRI scoring. A possible reason for this is the inclusion of age in the calculation of FIB-4 score. However, studies have shown that advanced age could be misleading in the prediction of fibrosis using FIB-4 index[17,18].

Many studies have reported that APRI and FIB-4 were important in the diagnosis of fibrosis and cirrhosis, but different threshold values, different sensitivity and specificity values have been reported. These results suggest that current non-invasive scores alone will not be sufficient to identify fibrosis.

The most important limitation of this study is that due to its retrospective design, the biopsies were not performed by the same specialist. Another limitation is that the blood tests used in scoring systems, may be affected by the current health condition of the patients.

In conclusion, APRI and FIB-4 have high specificity and PPV in demonstration of significant fibrosis, but have low sensitivity and NPV. Therefore, despite its potential disadvantages, biopsy still maintains its importance as the gold standard in demonstration of liver fibrosis. APRI and FIB-4 are useful in demonstration of significant fibrosis, but different threshold values and other causes of fibrosis must also be taken into account during evaluation. There is a need to develop new non-invasive scoring systems to predict fibrosis in chronic hepatitis C patients.

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