Research Article

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# *Follow-up, Treatment and Non-invasive Scoring Systems in Chronic Hepatitis B: A Retrospective Observational Study*

## Kronik Hepatit B'de Takip, Tedavi ve Non-invaziv Skorlama Sistemleri: Retrospektif Gözlemsel Bir Çalışma

Ahmet Doğan[1], Yakup Gezer[2]

[1]*Fatsa State Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Ordu, Turkey*
[2]*Konya City Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Konya, Turkey*

**ABSTRACT**

**Objectives:** Chronic hepatitis B (CHB) may present with many clinical signs. This study evaluates the CHB cases followed in our center in terms of ELISA, treatment, and non-invasive scoring systems.

**Materials and Methods:** Four hundred CHB cases were retrospectively analyzed. ELISA and treatment status were recorded at the time of diagnosis and at the last admission. Fibrosis-4 (FIB-4) and aspartate aminotransferase - platelet ratio index (APRI) scores were calculated for the cases who underwent biopsy and received treatment (n=40) and for treatment-naive cases without biopsy (n=135). The cut-off values of FIB-4 and APRI were calculated in the groups. The obtained results were compared with the significance of fibrosis markers. The number of patients was determined as a percentage according to the cut-off value calculated for fibrosis ≥2 in FIB-4 and APRI scores in patients who did not undergo biopsy.

**Results:** Of the 400 patients, 52.5% were male. The mean age of the cases was 19.0-84.0 (49±12.7). Hepatitis B surface antigen negativity (p=0.012) developed in nine cases (2.25%) and hepatitis B virus-DNA negativity increased from 7.8% to 63.2% (p=0.001). Of the treatment-naive cases, 36.9% based on the FIB-4 score and 16.3% based on the APRI score were F ≥2. When biopsy was compared with FIB-4 and APRI, the positive predictive value of FIB-4 and APRI scores (87% and 95%, respectively) were found to predict low fibrosis (F ≤1), and negative predictive value NPV (94.7% and 95.8%, respectively) was found to predict advanced fibrosis (F ≥4).

**Conclusion:** The FIB-4 and APRI scores can guide some treatment-naive cases in terms of performing a biopsy and initiating treatment if necessary.

**Keywords:** APRI, chronic hepatitis B, FIB-4, treatment

**ÖZ**

**Amaç:** Kronik hepatit B (KHB) birçok klinik bulgu ile ortaya çıkabilir. Bu çalışmada merkezimizde takip edilen KHB olgularının ELISA, tedavi ve non-invaziv skorlama sistemleri açısından değerlendirilmesi amaçlanmıştır.

**Gereç ve Yöntemler:** Dört yüz KHB olgusu retrospektif olarak incelendi. Tanı anında ve son başvuruda ELİSA ve tedavi durumu kaydedildi. Biyopsi yapılan ve tedavi alan olgular (n=40) ve biyopsi yapılmayan tedavisiz olgular (n=135) için fibrozis-4 FIB-4 ve aspartat aminotransferaz - trombosit oranı indeksi (APRİ) skorları hesaplandı. Gruplarda FIB-4 ve APRİ cut-off değerleri hesaplandı. Elde edilen sonuçlar fibrozis belirteçlerinin anlamlılığı ile karşılaştırılmıştır. Biyopsi yapılmayan hastalarda FIB-4 ve APRİ skorlarında fibrozis ≥2 için hesaplanan cut-off değerine göre hasta sayısı, yüzde olarak belirlendi.

**Bulgular:** Dört yüz hastanın %52,5'i erkekti. Olguların yaş ortalaması 19,0-84,0 (49±12,7) idi. Dokuz olguda (%2,25) hepatit B yüzey antijeni negatifliği (p=0,012) gelişti ve HBV-DNA negatifliği %7,8'den %63,2'ye (p=0,001) yükseldi. Tedavi almayan olguların FIB-4 skoruna göre %36,9'u ve APRİ skoruna göre %16,3'ü F ≥2 idi. Biyopsi FIB-4 ve APRİ ile karşılaştırıldığında, FIB-4 ve APRİ skorlarının pozitif öngörme değerinin (sırasıyla; %87 ve %95) düşük fibrozu (F ≤1), negatif öngörme değerinin (sırasıyla; %94,7 ve %95,8) ise ileri fibrozu (F ≥4) öngördüğü tespit edildi.

**Sonuç:** FIB-4 ve APRİ skorları, tedaviye yanıtsız olguların bir kısmına biyopsi yapılması ve gerekirse tedaviye başlanması açısından rehberlik edebilir.

**Anahtar Kelimeler:** APRİ, kronik hepatit B, FIB-4, tedavi

**Address for Correspondence:** Ahmet Doğan MD, Fatsa State Hospital, Clinic of Infectious Diseases and Clinical Microbiology, Ordu, Turkey
**E-mail:** uzdrahmetdogan@gmail.com **ORCID ID:** orcid.org/0000-0001-5110-4027 **Received:** 01.11.2022 **Accepted:** 05.06.2023

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## Introduction

The World Health Organization reported in 2019, there were approximately 300 million cases of chronic hepatitis B (CHB) and 1.5 million new cases per year were added to this number. The most important causes of mortality in CHB cases are cirrhosis and hepatocellular cancer (HCC). In 2019, mortality was reported as approximately 820,000 (1). Treatment can be evaluated according to clinical and laboratory findings, family history, the presence of cirrhosis, and HCC. Antiviral treatments that prevent fibrosis in the liver and suppress hepatitis B virus (HBV)-DNA should be used for hepatitis B surface antigen (HBsAg) to become negative and hepatitis B surface antibody (anti-HBs) positivity to develop (2). Recently, low-level virema (LLV) has been reported as a persistent or intermittent elevation of detectable HBV-DNA (<2000 IU/mL, borderline 10 IU/mL) despite 12 months of HBV treatment. Oral antivirals such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alaninamide fumarate (TAF) have been reported to play an active role for treating CHB. Cases of LLV have been reported despite long-term effective oral antiviral treatments (3). Because biopsy is painful, invasive, costly and error prone, scoring systems and some biomarkers have been developed, which can be an alternative to biopsy in cases with advanced fibrosis. The fibrosis-4 (FIB-4) index, one of these scoring systems, is a reliable index with a high positive predictive value (PPV) in cases with advanced fibrosis. In cases with a high FIB-4 score, the FIB-4 score may be predictive of liver-related morbidity and mortality (4). Non-invasive scoring systems such as FIB-4 and aspartate aminotransferase (AST) - platelet ratio index (APRI) increase their importance day by day in estimating cases with a high risk of fibrosis and morbidity (5). The American Association for the Study of Liver Diseases recommends the FIB-4 index as an alternative to biopsy for hepatitis B to determine the severity of the disease, to detect cases that need antiviral therapy, and to determine the duration of treatment (6). The development of HBsAg negativity is a rare condition in CHB. The development of HB Ag negativity is less common in childhood CHBs than in adults. Although the development of HBsAg negativity also reduces the progression to HCC, there are cases that develop cirrhosis and HCC despite HBsAg negativity (7,8).

## Materials and Methods

### Study Design And Patients

Patients who applied to the ınfectious diseases outpatient clinic of our center due to chronic HBV infection between November 1, 2021 and September 19, 2022 were retrospectively included in the study. The data were obtained by scanning our hospital's automation system "Fonet Web HBYS". Demographic data, treatment status, laboratory values, radiological findings, accompanying factors, and histopathological findings were recorded. Fibrosis staging according to liver biopsy results was performed using the modified Ishak histological activity index (F 0-6). Biopsy patients (n=40) were analyzed in three different groups. The first group (F ≤1, F ≥2), the second group (F ≤2, F ≥3) and the third group (F ≤3, F ≥4) were divided into two groups: low and advanced fibrosis. In addition, in treatment-nave patients (n=135) who did not undergo biopsy, cases with F ≥2 were evaluated using non-invasive score markers.

### Non-invasive Fibrosis Scoring Calculation

The FIB-4 score was calculated using the following formula. A score of <1.45 predicts the absence of fibrosis, and a score >3.25 predicts a significant fibrosis (9,10). The APRI was calculated according to the formula below. A score of 0.5 predicts the absence of fibrosis, >1.5 predicts significant fibrosis (F 3-4) and ≥2 (F 5-6) predicts advanced fibrosis (11,12). The FIB-4 and APRI scores of the untreated cases and the cases with a known biopsy date were calculated and recorded. For FIB-4 score calculation, age [(years) x AST (U/L(]/[PLT ($10^9$/L)] x [alanine aminotransferase (ALT) (U/L) ($^{(1/2)}$)] formulation and APRI score calculation, APRI= 100* [(AST/AST Upper Limit of Normal)/(platelet/1,000)] were used.

### Ethics Committee Approval

Ethical approval was sought from the Ordu University Ethics Committee Unit (Black Sea Region/Ordu/Turkey) and permission was obtained with the decision of the ethics committee (approval number: 2022/220, date: 14/10/2022).

### Statistical Analysis

For statistical analysis, we entered the data obtained in our study into the SPSS 25.0 (IBM New York, USA) software using descriptive statistical methods in data analysis. The Kolmogorov-Smirnov Z-test determined whether the data showed a normal distribution. Median (minimum-maximum) was calculated for nonnormally distributed variables, and the mean and standard deviation (SD) were calculated for normally distributed variables. Student's t-test was used to compare two numerical categories with normal distribution and the Mann-Whitney U test without normal distribution. Pearson's chi-square test and Fisher's exact test were used for qualitative categorical data comparisons. The McNemar test was used to compare the bilateral nonparametric values before and after treatment. The Pearson correlation test was used for correlating normally distributed data and the Spearman correlation test was used for correlating nonnormally distributed data. The cut-off values of non-invasive fibrosis markers in the determined fibrosis groups were calculated using receiver operating characteristic (ROC) curve analysis. The cut-off values for each parameter were determined according to the Youden index. Sensitivity, specificity, PPV, and negative predictive value (NPV) were determined according to these cut-off values. The obtained results were compared with the significance of fibrosis markers. The number of patients who did not undergo biopsy was determined as a percentage according to the cut-off value calculated for FIB-4 and APRI scores F ≥2. The significance level for all results was evaluated with $p<0.05$.

## Results

### Demography

A total of 400 patients, 210 (52.5%) males and 190 (47.5%) females, were included in the study. The mean age of the cases was 19-84 (49±12.7). Eleven (2.8%) of them were newly diagnosed. Eight (2%) of the cases followed up under treatment were LLV, two (0.5%) cases voluntarily, and two (0.5%) cases discontinued the treatment due to pregnancy. Biopsy did not meet the treatment criteria in two (0.5%) cases and biopsy could not be performed in seven (1.8%) cases due to contraindications. Hepatomegaly and steatosis were detected in 52 (13%) cases and coarsening and granulation in the parenchyma were detected in 29 (7.25%) cases in liver ultrasonography performed during the initial diagnosis.

### ELISA

When the ELISA studied at the time of diagnosis and at the last control were compared, HBsAg negativity (p=0.012) developed in nine cases (2.3%) and anti-HBs positivity (p=0.064) developed in eight cases (2%). While data were missing for hepatitis B e antigen (HBeAg) and hepatitis B e antibody (anti-HBe), HBV-DNA negativity increased from 7.8% to 63.2% (p=0.001) (Table 1).

### Treatment

Regarding the treatment status of the cases, approximately one-third of them did not need treatment, and the initial treatment of one-third was revised later, usually due to side effects. Of the cases, 135 (33.8%) were followed without treatment, 24 (6%) received prophylaxis, and the other 241 (60.2%) were treated. The date of biopsy could be determined in only 40 (10%) cases. While TDF was the most preferred treatment in the initial treatment, maintenance treatment was most frequently revised to TAF (Table 2).

The patients who received and did not receive treatment were compared in two groups by calculating the mean ± SD values in terms of sex, age and ELISA. While there was a significant difference between the two groups in terms of HBeAg (p=0.001) and anti-HBe (p=0.001), no difference was observed in terms of sex (p=0.506) and anti-HBs (p=1.000). The mean age was higher in the treated group (p=0.001). In addition, non-invasive scoring in the group that did not receive treatment, i.e., no/low expected fibrosis, was lower than that in the group that had received treatment. FIB-4 (p=0.001) and APRI (p=0.001) (Table 3).

Cases that were biopsied and reported according to the ISHAK scoring system were divided into two groups as low fibrosis (F ≤2) and advanced fibrosis (F ≥3) compared with age, laboratory, and ELISA direction. The AST value was found to be significantly higher in the advanced fibrosis group (p=0.034). There was no significant difference between other parameters (p>0.05). Other parameters data are given in Table 4.

Correlations were investigated between age (p=0.219), serum AST (p=0.015), ALT (p=0.199), platelet (p=0.589), APRI (p=0.047), and FIB-4 (p=0.171) scores and fibrosis levels in the patients. A positive and significant correlation was found between fibrosis and AST values and APRI score.

### Relationship between scoring and fibrosis

The histological activity index and non-invasive scoring systems were compared according to the ISHAK scoring of the biopsy cases. The area under the curve was determined by performing ROC analysis for FIB-4 and APRI (Figure 1).

Because of ROC curve analysis, the best cut-off point was determined for detecting advanced fibrosis. Sensitivity, specificity, PPV and NPV were calculated. Table 5 shows the performance of non-invasive fibrosis scores according to cut-off values. Because of ROC curve analysis, the best cut-off value in detecting advanced fibrosis (F ≥3) of the FIB-4 score was taken as ≥1.340, sensitivity was 61.1%, specificity was 63.2%, PPV was 61.1%, and NPV was 63.2%. The best cut-off value for detecting advanced fibrosis (F ≥3) for the APRI score was ≥0.398, sensitivity was 72.2%, specificity was 73.7%, PPV was 72.2%, and NPV

**Table 1.** ELISA status of cases first and last study

| ELISA | | At the first diagnosis (n=400), (%) | At the last check (n=400), (%) | p-value |
|---|---|---|---|---|
| HBsAg | Pozitive | 387 (96.8) | 378 (94.5) | **0.012** |
| | Negative | 13 (3.2) | 22 (5.5) | |
| Anti-HBs | Pozitive | 12 (3) | 20 (5) | 0.064 |
| | Negative | 388 (97) | 380 (95) | |
| HBeAg | Pozitive | 55 (13.8) | 29 (7.2) | **0.001** |
| | Negative | 304 (76) | 304 (75.3) | |
| | No data | 41 (10.2) | 77 (17.5) | |
| Anti-HBe | Pozitive | 294 (73.5) | 282 (70.5) | 0.078 |
| | Negative | 64 (16) | 49 (12.3) | |
| | No data | 42 (10.5) | 69 (17.2) | |
| HBV-DNA | Pozitive | 327 (81.8) | 115 (28.7) | **0.001** |
| | Negative | 31(7.8) | 253 (63.2) | |
| | No data | 42 (10.4) | 32 (8.1) | |

HBsAg: Hepatitis B surface antigen, anti-HBs: Hepatitis B surface antibody, HBeAg: Hepatitis B e antigen Anti-HBe: Hepatitis B e antibody, HBV: Hepatitis B virus

**Table 2.** Treatment status

| **Treatment status** | | **(n=400)** | **(%)** |
|---|---|---|---|
| Initial treatment | Untreated | 135 | 33.8 |
| | TDF | 169 | 42.3 |
| | TAF | 10 | 2.5 |
| | ETV | 64 | 16 |
| | Lamivudine | 13 | 3.3 |
| | Telbivudine | 4 | 1 |
| | ETV + TDF | 1 | 0.3 |
| | TDF + lamivudine | 4 | 1 |
| Treatment change | Yes | 99 | 24.8 |
| | No | 166 | 75.3 |
| Reason for treatment change | Side effect | 78 | 19 |
| | No response | 20 | 4 |
| | Pregnancy | 1 | 0.3 |
| Maintenance treatments after the change | TDF | 12 | 3 |
| | TAF | 59 | 14.8 |
| | ETV | 26 | 6.5 |
| | ETV + TDF | 1 | 0.3 |
| | TAF + lamivudine | 1 | 0.3 |
| Prophylaxis | Yes | 24 | 6 |
| | No | 376 | 94 |

TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide fumarate, ETV: Entecavir

**Table 3.** Comparison of ELISA and fibrosis scores by treatment status

| **Parameters** | | **Untreated (n=135), (%)** | **Receiving treatment (n=241), (%)** | **p** |
|---|---|---|---|---|
| Gender | Male | 68 (50.4) | 130 (54) | 0.506 |
| | Female | 67 (49.6) | 111 (46) | |
| Age | Mean ± SD | 45.26±12.3 | 51.18±12.63 | **0.001** |
| HBsAg | Pozitive | 135 (100) | 241 (100) | - |
| | Negative | 0 (0) | 0 (0) | |
| Anti-HBs | Pozitive | 1 (0.7) | 2 (0.8) | 1.000 |
| | Negative | 134 (99.3) | 239 (99.2) | |
| HBeAg | Pozitive | 5 (3.7) | 50 (20.7) | 0.001 |
| | Negative | 101 (74.8) | 182 (75.5) | |
| Anti-HBe | Pozitive | 3 (2.2) | 56 (23.3) | 0.001 |
| | Negative | 102 (75.5) | 175 (72.6) | |
| FIB-4 | Mean ± SD | 1.02±0.76 | 2.28±1.98 | **0.001** |
| APRI | Mean ± SD | 0.28±0.33 | 1.10±1.20 | **0.001** |

HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, HBeAg: Hepatitis B e antigen, Anti-HBe: Hepatitis B e antibody, FIB-4: Fibrosis-4, APRI: Aspartate aminotransferase - platelet ratio index, SD: Standard deviation

was 73.7%. FIB-4 and APRI scores had a high PPV (87%, 95%) in the prediction of low fibrosis (F 1) and a high NPV (94.7%, 95.8%) in the prediction of advanced fibrosis (F ≥4).

In cases without biopsy and followed up without treatment (n=135), F ≥2 cases were estimated using non-invasive score markers. The cut-off was 1.03 for FIB-4 and 0.358 for APRI. F ≥2 was found in 36.9% of the patients according to the FIB-4 score and 16.3% according to the APRI score.

## Discussion

FIB-4 and APRI are widely used models to detect fibrosis among NASH patients. A meta-analysis of 13 studies investigated the ability of FIB-4, NFS, and APRI scores to predict liver-related events in NASH patients. While FIB-4 and NFS were safer than APRI in predicting mortality, all three markers were found to be inconsistent in predicting the change in fibrosis stage (13). In another study that included 1,038 patients from four studies,

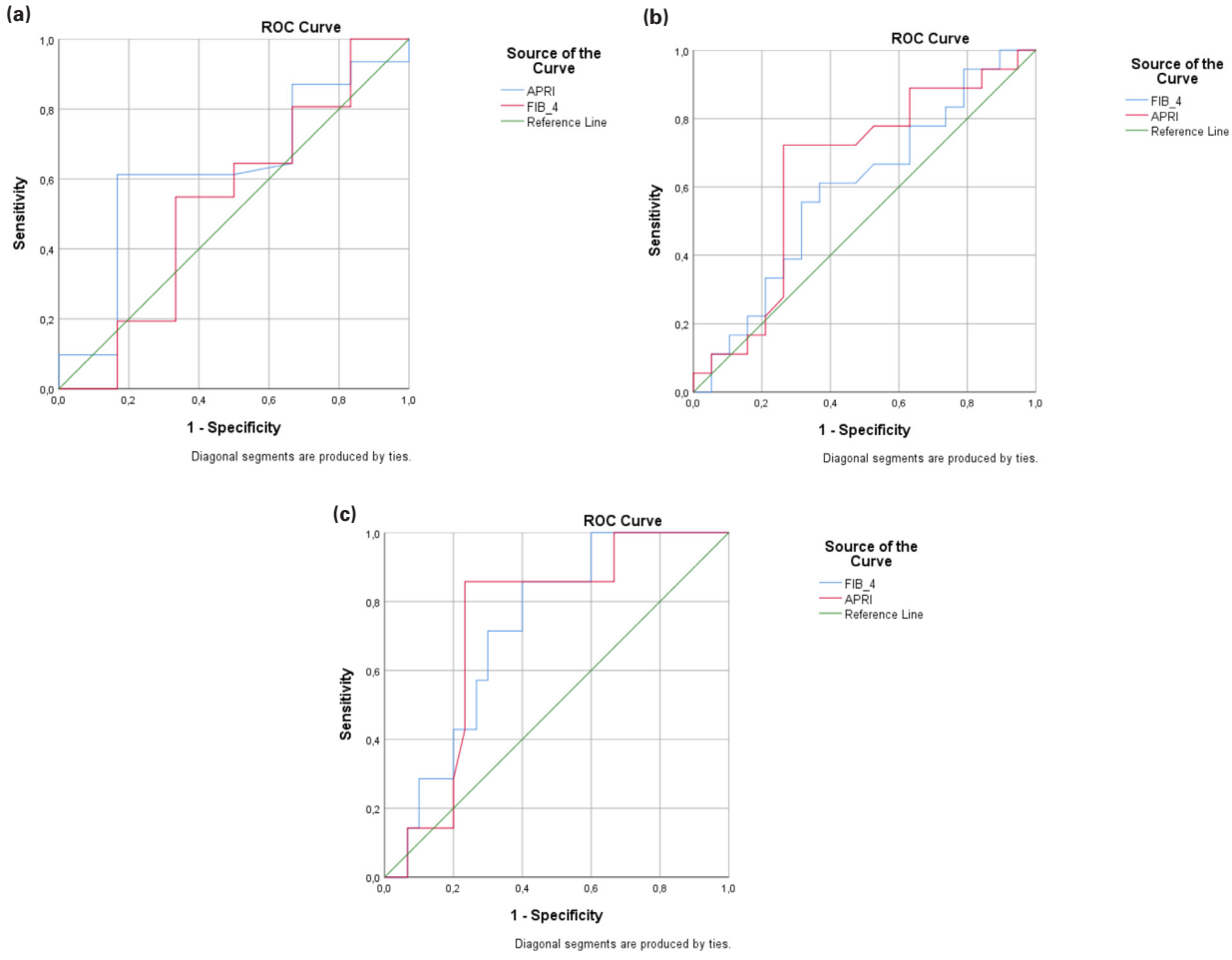


**Figure 1.** (a) ROC curves for non-invasive models in the diagnosis of fibrosis ≥2. (b) ROC curves for non-invasive models in the diagnosis of fibrosis ≥3. (c) ROC curves for non-invasive models in the diagnosis of fibrosis ≥4

ROC: Receiver operating characteristic

**Table 4.** Comparison of demographics, laboratory and histological characteristics of patients with low and advanced fibrosis

| **Parameters, (n)** | **Low fibrosis (F ≤2)** | **Advanced fibrosis (F ≥3)** | **p** |
|---|---|---|---|
| Gender (female/male) (91/101) | 49/52 | 42/49 | 0.744 |
| Age* | 49.13±13.60 | 50.64±12.16 | 0.421 |
| AST† | 23 (14-3030) | 30 (11-813) | **0.034** |
| ALT† | 29 (5-1525) | 32 (8-1215) | 0.410 |
| AFP† | 2.14 (0.1-37) | 2.74 (0-20) | 0.092 |
| HBV-DNA† | $1.2x10^6$±(101-$5.1x10^9$) | $0.3x10^6$±(20-$12x10^9$) | 0.180 |
| PLT* | 198.21±39.63 | 208.06±43.47 | 0.476 |
| FIB-4† | 1.14 (0.37-7.83) | 1.58 (0.51-7.78) | 0.598 |
| APRI† | 0.34 (0.15-3.83) | 0.64 (0.18-5.32) | 0.248 |
| HBsAg (pozitive/negative), (192/0) | 101/0 | 91/0 | - |
| Anti-HBs (pozitive/negative), (89/103) | 0/101 | 89/2 | - |
| HBeAg (pozitive/negative), (38/147) | 21/78 | 17/69 | 0.808 |
| Anti-HBe (pozitive/negative), (142/43) | 73/26 | 69/17 | 0.297 |

*Mean ± standard deviation, †Median (minimum-maximum), AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alpha fetoprotein, HBV: Hepatitis B virus, PLT: Platelet, FIB-4: Fibrosis-4, APRI: Aspartate aminotransferase - platelet ratio index, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, HBeAg: Hepatitis B e antigen, Anti-HBe: Hepatitis B e antibody

| Table 5. The performance of non-invasive fibrosis scores by cut-off values | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Fibrosis** | **Index** | **Cut-off** | **AUROC, (95%)** | **p** | **Sensitivity (%)** | **Specificity, (%)** | **PPV, (%)** | **NPV, (%)** |
| F≥2 | FIB-4 | 1.03 | 0.532 (0.243-0.822) | 0.805 | 64.5 | 50 | 87 | 21.4 |
| | APRI | 0.358 | 0.626 (0.382-0.871) | 0.333 | 61.3 | 83.3 | 95 | 29.4 |
| F≥3 | FIB-4 | 1.340 | 0.592 (0.406-0.778) | 0.338 | 61.1 | 63.2 | 61.1 | 63.2 |
| | APRI | 0.398 | 0.649 (0.464-0.835) | 0.121 | 72.2 | 73.7 | 72.2 | 73.7 |
| F≥4 | FIB-4 | 1.340 | 0.724 (0.549-0.899) | 0.068 | 85.7 | 60 | 33.3 | 94.7 |
| | APRI | 0.398 | 0.736 (0.556-0.916) | 0.055 | 85.7 | 76.7 | 46.2 | 95.8 |

AUROC: Area under the ROC, PPV: Positive predictive value, NPV: Negative predictive value, FIB-4: Fibrosis-4, Aspartate aminotransferase - platelet ratio index

13% of the cases had fibrosis. The pooled sensitivity, specificity, and area under the ROC (AUROC) curve of the FIB-4 index with a 95% confidence interval (CI) were found to be 0.844 (0.772-0.901), 0.685 (0.654-0.716) and 0.8496±0.0680 when the cut-off value was 1.30. When the cut-off value was 3.25, the same parameters were calculated as 0.38 (0.30-0.47), 0.96 (0.95-0.98) and 0.8445±0.0981. When the cut-off was -1,455, the pooled sensitivity and specificity with 95% CI were 0.77 (0.69-0.84), 0.70 (0.67-0.73) and 0.8355±0.0667 when the cut-off was 0.676, 0.27 (0.19-0.35) and 0.98 (0.96-0.98), respectively, and the AUROC was 0.647±0.2208. The cut-off value of 1.30 for the FIB-4 index has a better prognostic diagnostic yield than 3.25 (14). In another study, the FIB-4 index was compared with 138 cases with liver biopsy and 372 cases with FibroTest. When the FIB-4 cut-off value was ≤1.45 and the liver biopsy size was ≥20 mm, NPV was 86%, sensitivity 71.1%, and specificity 73.1% in differentiating moderate fibrosis F 0-2 from severe fibrosis F 3-4. In the study, the FIB-4 index was more useful in determining fibrosis than the APRI score and showed an 89% correlation with the FibroTest ($\kappa$=0.27, p<0.001). The FIB-4 index is an easy, inexpensive and accurate method to exclude fibrosis in CHB patients (15). In another similar study, the distinction between mild/absent fibrosis (F 0-1) and severe fibrosis (F 2-4) was evaluated using APRI, FIB-4, and AST/ALT ratios. AUROCs were calculated as 0.81 (0.76-0.87) for APRI, 0.81 (0.75-0.86) for FIB-4, and 0.56 (0.49-0.64) for AST/ALT. APRI and FIB-4 are useful in differentiating severe fibrosis from mild/absent fibrosis and in the treatment follow-up of fibrosis (16). Our ROC curve analysis showed that when the FIB-4 score was taken as ≥1.340 for the detection of advanced fibrosis (F ≥3), the sensitivity was 61.1%, specificity 63.2%, PPV 61.1%, and NPV 63.2%. When the cut-off of APRI score was ≥0.398 in the detection of advanced fibrosis (F ≥3), sensitivity was 72.2%, specificity 73.7%, PPV 72.2%, and NPV 73.7%. The PPV (87%, 95%) of FIB-4 and APRI scores in predicting low fibrosis (F ≤1) and NPV (94.7%, 95.8%) in predicting advanced fibrosis (F ≥4) were found to be high. Our study yielded similar results to other studies. These scores have been confirmed to be useful, especially in detecting advanced fibrosis. When examining the correlation between age, serum AST, ALT, platelet count, APRI, and FIB-4 scores and fibrosis levels in patients, a positive correlation was found between fibrosis and AST values (p=0.015) and APRI score (p=0.047). Various studies have been conducted on many non-invasive scoring systems. However, there is not yet a scoring system that can be an alternative to liver biopsy alone (17,18,19,20,21). In our study, unlike other studies, we tried to estimate the level of fibrosis in cases that did not undergo liver biopsy and did not receive treatment. When the cut-off was 1.03 for FIB-4 and 0.358 for APRI, 36.9% of the cases according to the FIB-4 score and 16.3% according to the APRI score were found to be F ≥2.

A spontaneous loss of HBsAg occurs in approximately 0.5% of CHB patients per year and most of them develop anti-HBs. In cases of untreated CHB (>18 years of age), the incidence of cirrhosis within five years is 8% to 20%, and the risk of HCC is 2% to 5%. The main goal of treatment is to provide a permanent virological response (22). ETV, tenofovir, and tenofovir alaninamide are the preferred high-barrier oral antivirals (23). The American guidelines recommend TAF for initial treatment in adults. Tenofovir alaninamide has fewer side effects on the kidney and bone than TDF. It is easily recommended except for patients with very low creatinine clearance (24). In our study, HBsAg negativity (p=0.012) developed in 2.3% of the cases, and anti-HBs positivity (p=0.064) developed in 2% of the cases at the last control. In addition, HBV-DNA negativity increased to 63.2% (p=0.001). In the initial treatment of our cases, oral antiviral therapy with a high resistance barrier was initiated in more than 61%, in line with the literature recommendations. In 19% of the cases, treatment changes were made due to side effects. TAF, which has a low probability of side effects on bone and kidney, was preferred most frequently in the change of treatment. The mean age (p=0.001), FIB-4 (p=0.001), and APRI (p=0.001) scores were lower in the patients who did not receive treatment (n=135). Sex and efficacy of ELISA on treatment were not demonstrated. For people who have had hepatitis B virus infection in the past, the serum appears to clear HBsAg, while producing antibodies against the hepatitis B core antigen (HBcAb) detectable in their serum (25). In a study conducted in Turkey, patients with anti-HBc IgG positivity who were treated with biological agents were evaluated in terms of HBV reactivation. Reactivation was observed in only five (17.2%) of the 278 patients included in the evaluation (26). Our study found that 24 (6%) of the cases needed prophylaxis to prevent reactivation.

### Study Limitations

Of course, the study has some limitations. Firstly, it is a single-center study. Therefore, it cannot be expected to reflect the country in a generalized way. Secondly, it is limited to 400 cases. The fact that the number of the biopsied group was 40 may have affected homogeneity in statistical evaluation. The

retrospective design of the study makes it difficult to access the initial presentation information of patients with long-term follow-up. Multicenter, prospective studies including large numbers of cases will reflect the population more objectively.

## Conclusion

As a result, oral antivirals with high resistance barriers provided a high rate of HBV-DNA negativity. The need for treatment increased in the older age group. Particularly, due to the side effects of TDF on bone and kidneys, a treatment change is needed in one-third of cases. In line with the literature, our study found that FIB-4 and APRI scores alone are not an alternative to biopsy. However, reaching a few cases with a certain biopsy date is the weakness of the study. These scores have high NPV in differentiating advanced fibrosis. Unlike the literature, these scoring systems can be helpful in terms of biopsy in some treatment-naive cases. However, this needs to be supported by larger case series.

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### Ethics

**Ethics Committee Approval:** Ethical approval was sought from the Ordu University Ethics Committee Unit (Black Sea Region/Ordu/Turkey) and permission was obtained with the decision of the ethics committee (approval number: 2022/220, date: 14/10/2022).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: A.D., Concept: A.D., Y.G., Design: A.D., Y.G., Data Collection and Processing: A.D., Analysis or Interpretation: A.D., Y.G., Literature Search: A.D., Writing: A.D., Y.G.,

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