Routinely evaluated clinical assays and laboratory tests [real test] and fibrosis stages of chronic hepatitis B and C

LIVER

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ABSTRACT

Background/Aims: To provide a new mathematical formula to predict liver fibrosis in patients with chronic viral hepatitis.

Materials and Methods: Patients with chronic hepatitis B and C who underwent liver biopsy at different centers were included in this study. Chronic hepatitis B was defined as immunopositivity for the hepatitis B surface antigen for at least 6 months, and chronic hepatitis C was defined as positivity for HCV RNA for at least 3 months. The histological features were evaluated by the histological activity index and fibrosis.

Results: In total, 1299 patients were included in the study. The distribution and the mean of the parameters of the patients were as follows: 1009 patients with chronic hepatitis B with a mean age of 45±13/years [emale/male (F/M)=47.5/52.5%] and 290 patients with hepatitis C with a mean age of 52±10.3/years [F/M=61/39%]. When the cut-off value of the REAL TEST formula "[(age x pT x AST)/(PLT/1000)]/100" in patients with hepatitis B was determined to be ≥1.37, it was found that it could predict fibrosis with 79% specificity, 78% sensitivity, 85% negative predictive value (NPV), and 70% positive predictive value (PPV) (area under the curve (AUC)=0.852, 95% CI:0.82-0.87). When the cut-off value of the REAL TEST formula in patients with hepatitis C was determined to be ≥1.99, it was found that it could predict significant fibrosis with 87% specificity, 90% sensitivity, 94.4% NPV, and 79.4% PPV (AUC:0.95, 95% CI:0.93-0.98)

Conclusion: The REAL TEST formula results correlated with the pathological findings and may be a useful method for the evaluation of patients with chronic hepatitis B and C.

Keywords: Chronic hepatitis, REAL TEST, routine laboratory tests, fibrosis

INTRODUCTION

Hepatitis B and C viruses, which are responsible for chronic viral hepatitis, are hepatotropic viruses that affect more than 600 million people worldwide (1,2). In individuals infected with these viruses, viral inflammation becomes a chronic inflammatory process. The process of fibrosis is also initiated, and because of longstanding repetition of the inflammation and the healing process, the progression of fibrosis leads to cirrhosis-described to be end-stage liver failure that is characterized by regenerative nodules in the liver-and hepatocellular carcinoma (3).

The most important factor that may cause hepatocellular carcinoma in patients with chronic hepatitis B (CHB) is advanced liver fibrosis (4). The progression of fibrosis can be prevented with medical treatments; therefore, it is important to detect it in the early phase and to de-

cide whether to initiate the treatment. The basic goal of the treatment is to prevent the development of fibrotic progression, end-stage liver failure, and hepatocellular carcinoma, and this may be possible via the suppression of viral triggers (e.g., HBV DNA, HbxAg), which are the basic sources of inflammation in the liver (1,5). When the current guidelines are considered, the predictive factors in the decision for treatment are pathological fibrosis/inflammation, viral load, and serum alanine aminotransferase levels (6,7). Although the gold standard method to describe the fibro-inflammatory process in the liver is a biopsy, the patchy distribution of hepatic fibrosis (3,8) provides a static section instead of dynamic formation. Additionally, the destruction of the liver is induced by the fibrotic process (9), and therefore, the application of a biopsy specimen, which is equal to 1/50,000 of the liver, as a representation of the entire liver might pose challenges. In addition, liver biopsy is an invasive procedure that cannot be easily repeated due to reasons such as the patient's refusal, an increase in the risk of complications, and low cost-effectiveness (10). Under or overestimation of the degree of hepatic fibrosis, inter and intra observer variability of 10%-20% and sampling errors are other limitations (11-13). Therefore, the tendency towards the use of noninvasive methods has increased in recent years. To date, many laboratory tests, scores, and indices have been recommended for patients with CHB (14,15). However, the outcomes of these studies yielded different results in different study populations (16). Therefore, cost-effective, easily accessible, noninvasive tests that evaluate hepatic fibrosis are needed. Although many formulas have been recommended, most of these involved patients with hepatitis C (17) and utilized scores and indices, such as levels of hyaluronic acid, apo A1, and alpha-2 macroglobulin (e.g., FibroTest, Fibrosure, etc.) that are generally uncommon parameters (18). The studies that involve the role of noninvasive markers for the evaluation of fibrosis in patients with CHB are not well documented (19).

In this study, we aimed to provide a new mathematical formula to predict fibrosis in patients with chronic hepatitis B, to investigate the diagnostic value of this formula in patients with hepatitis C and to evaluate the efficiency of the formula in determination of transition to cirrhosis.

MATERIALS AND METHODS

Patients

Patients with chronic hepatitis B, C, and cirrhosis who underwent a liver biopsy between 2006 and 2012 at 8 centers were included in this study. The centers were as follows: two centers from İstanbul province (Bezmialem Vakif University, İstanbul University İstanbul and Cerrahpaşa Medical Faculties Gastroenterology Departments), four centers from Konya province (Necmettin Erbakan University Meram Medical Faculty, Başkent University Medical Faculty, Selçuklu Medical Faculty, and Konya Education and Research Hospital Gastroenterology Departments), and one center from Eskisehir province (Eskişehir Osmangazi University

Medical Faculty Gastroenterology Department). Chronic hepatitis B was defined as immunopositivity for hepatitis B surface antigen for at least 6 months, and chronic hepatitis C was defined as positivity for HCV RNA for at least 3 months.

Exclusion criteria

The exclusion criteria were as follows: history of anti-viral drug usage before liver biopsy, alcohol consumption, presence of concomitant chronic viral infections (such as hepatitis C, delta hepatitis, and HIV), coexistence of autoimmune hepatitis, the presence of fewer than 10 portal fields in the biopsy specimen, suspicion of a malignant mass in the liver, acute hepatitis, positivity for anti-HBc IgM, severe heart failure, chronic obstructive pulmonary disease, the use of angiotensin-converting enzyme inhibitors, chronic infectious diseases such as tuberculosis and brucellosis, sarcoidosis, scleroderma, and history of systemic vasculitis.

Histopathological evaluation for grading and staging

Hepatobiliary sonography was performed prior to the biopsy in all of the patients who were included in the study. The liver biopsies of the patients included in the study were performed by an experienced hepatologist. Liver biopsies were performed with liver biopsy needles by the classical Menghini method. All biopsy specimens were evaluated by pathologists who were blinded with regard to the clinical and laboratory information of patients with CHB and CHC. Formalin-fixed or paraffin-embedded liver tissues were cut into 4-µm-thick sections with a microtome. One section was stained with hematoxylin and eosin for the assessment of hepatic inflammatory activity, and the other sections were stained with Gomori stain for the evaluation of hepatic fibrosis. Biopsy specimens that were ≥1.5 cm in length and that bore at least 10 portal fields were considered to be representative.

The histological features were evaluated using the histological activity index (HAI), which ranges from 0 to 18 points, and the fibrosis grade, which ranges on a scale of 0 to 4 points (0, no fibrosis; 1, mild fibrosis; 2, moderate fibrosis; 3, severe fibrosis; 4, cirrhosis) as described by Knodell et al. (20).

HBV DNA viral load assay and evaluation of other tests

Sera for the complement assay were collected from patients before treatment commenced. HBV DNA quantitation was performed with the COBAS TaqMan HBV Monitor test (Roche Molecular systems; CA 94588, USA) in accordance with the manufacturer's instructions. The dynamic interval for HBV DNA detection was 6 to 110,000,000 IU/mL. HBsAg, anti-HIV, anti-HCV, and anti-delta were assayed using the ETI-MAK-4, ETI-AB-HCVK-4, and ETI-AB-DELTAK-2 kits, respectively, with a TIMAX (DiaSorin, Italy) device. Anti-HBc IgG, anti-HBc IgM, and HBeAg tests were performed with a DiaSorin LIAISON system. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), albumin, C-reactive protein, erythrocyte sedimentation rate, complete blood count, urine analysis, and urinary protein quantification were measured in all patients.

Laboratory and serologic parameters

Biochemical, serologic, and PCR results of the patients at the time of the biopsy or 1 week before the biopsy were obtained from patient follow-up cards or from electronic digital system data. Following an assessment of age, gender, and whether they had previously received antiviral (i.e., anti-HIV, anti-HCV, and anti-HBV) treatment, the patients with naive hepatitis B or C infections were included in the study.

The values of alanine aminotransferase (ALT), aspartate amino-transferase (AST), prothrombin time (PT), international normalization ratio (INR), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), and hemogram parameters of white blood cell (WBC), hemoglobin, mean corpuscular volume (MCV), red cell distribution width (RDW), platelet, and mean platelet volume (MPV) were also evaluated. The upper limit of normal for transaminases was considered to be 40 IU/L. Additionally, the following serologic parameters were determined: hepatitis B surface and e antigens/antibodies (HBsAg, HBeAg, anti-HBeAg, anti-HBsAg), HBV DNA, HCV RNA, anti-HCV, anti-delta, and HDV RNA levels in cases of suspicion of occult hepatitis delta infection.

Statistical analysis

Scale variables were documented as mean±standard deviation (SD). To assess the diagnostic performance of each non-invasive index, receiver operating characteristic (ROC) curves were constructed, and the areas under the ROC curves (AUROCs) were calculated. Then, to evaluate the usefulness of the non-invasive method, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were determined from the ROC curves. The most discriminating cut-off values were assessed from the ROC curves to maximize the sum of sensitivity and specificity. We constructed a formula by evaluating the parameters we had previously used in the formula with binary logistic regression analysis. Then, we compared the derived formula with the other mathematical formulas by ROC analysis. The Hanley-McNeil test was used to compare the AUROCs between two non-invasive models. For the evaluation of the parameters that could be associated with fibrosis progression in patients with hepatitis B and hepatitis C, the appropriate correlative method (Pearson and Spearman) was used.

Statistical Package for Social Sciences (SPSS, Inc, Chicago, IL, USA) for Windows, release 12.0.0 standard version software and Stata® statistical software package, version 11 (StataCorp LP, College Station, TX) were used for statistical investigations. A p-value <0.05 was considered statistically significant.

RESULTS

Patients and baseline characteristics

In total, 1791 patients were included in the study. The distribution and mean ages of the patients were as follows: 1009 patients with chronic hepatitis B with a mean age of 45±13/ years [female/male (F/M)=47.5/52.5%] and 290 patients with hepatitis C with a mean age of 52±10.3/years [F/M=61/39%].

Among the patients with chronic viral hepatitis B, 130 patients (16%) were at fibrosis stage 0, 304 patients (29%) were at fibrosis stage 1, 247 patients (24%) were at fibrosis stage 2, 239 patients (23%) were at fibrosis stage 3, and 89 patients (8%) were at fibrosis stage 4. Among the patients with chronic hepatitis C, 40 patients (16%) were at fibrosis stage 0, 118 patients (40%) were at fibrosis stage 1, 34 patients (12%) were at fibrosis stage 2, 63 patients (22%) were at fibrosis stage 3, and 30 patients (10%) were at fibrosis stage 4.

The baseline characteristics of the study patients are shown in Table 1.

Correlative analysis of the parameters that might be associated with fibrosis

In patients with hepatitis B, while a significant correlation was observed between the fibrosis score and age (r=0.318, p<0.001), platelet number (r=-0.507, p<0.001), prothrombin time (r=0.473 and p<0.001), and AST levels (r=0.355 and p<0.001), a weak correlation was observed between the fi-

Table 1. Baseline characteristics of the patients with chronic hepatitis B and C

	CHB	CHC
Gender (F/M %)	47.5/ 52.5	61/39
Age/year	45±13	52±10
AST (IU/L)	64.7±61	77±60.9
ALT (IU/L)	81±84	90±77
GGT (IU/L)	51±70	71±68
AP (IU/L)	184±1698	146±83
Platelet count (x109)	252±177	253±997
Hb (g/dL)	14±1.7	13.45±1.81
MCV (fl)	85.5±6.7	84.8±7.2
MPV (fl)	9±1.75	9.55±1.59
RDW (%)	13.4±2.7	13.5±5.3
PT (sec)	13±1.6	12.2±1.5
INR	1.49±5.9	1.09±0.17
HBsAg (COI)	1914±1269	-
HBVDNA (x107)	8±24.07	-
HCVRNA (x107)	-	4.65±3.73
HAI	7.18±3.13	6.61±2.98
Fibrosis	1.85±1.175	1.73±1.24

ALT: alanine transaminase; AST: aspartate transaminase; GGT: gamma glutamyl transpeptidase; AP: alkaline phosphatase; Hb: hemoglobin; MCV: mean corpuscular volume; MPV: mean platelet volume; RDW: red cell distribution width; PT: prothrombin time; INR: international normalization ratio; HBsAg: hepatitis b surface antigen; HAI: histological activity index

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brosis score and age (r=0.157), hemoglobin (r=-0.78), MCV (r=0.037), RDW (r=-0.109), INR (r=0.136), ALT (r=0.217), ALP (r=-0.150), GGT (r=0.200), and HBsAg (r=0.236) values.

In cases of hepatitis C, while the fibrosis score demonstrated a correlation with platelet number (r=-0.348 and p<0.001), PT (r=0.478 and p<0.001), the level of AST (r=0.630 and p<0.001), the level of ALT (r=0.326 and p<0.001), and INR (r=0.309 and p<0.001) with high correlation coefficients, it demonstrated a weak correlation with the other parameters.

Comparison of the REAL TEST and models of regression formula

Patients with chronic hepatitis B

Patients with chronic hepatitis B were divided into two groups according to fibrosis stage: the early stage, with a fibrosis score between 0 to 2 points and the significant stage, with a fibrosis score between 3 and 4 points.

In the binary logistic regression analysis, the best r values for age, platelet count, PT, and AST parameters were obtained on a square linear curve. According to this, the mathematical formula obtained according to the recommended linear curve for the prediction of fibrosis was found as "[(age x 0.047) + (plt/1000000) + (PT x 0.54) + (AST x 0.016) - 9.8]." When the cut-off value for the prediction of fibrosis (fibrosis stage: 3 and 4) in patients with CHB was determined to be ≤-0.11, this formula predicted fibrosis with 54% specificity and 86% sensitivity [AUC=0.830 and 95% confidence interval: 0.801-0.860] (Figure 1). The difference between the AUC values obtained by the REAL TEST formula, explained in detail below, was significant in favor of the REAL TEST formula (p<0.001). When the cut-off value for the prediction of fibrosis was determined to be ≥1.37 by the REAL TEST "[(age x pT x AST)/(PLT/1000)]/100" formula, it was found that it could predict fibrosis with 79% specificity, 78% sensitivity, 85% negative predictive value (NPV), and 70% positive predictive value (PPV) (AUC=0.852, 95% CI:0.82-0.87) (Figure 1).

When the cut-off value for the prediction of fibrosis (fibrosis stage: 0 and 1) in patients with CHB was determined to be ≥0.64 by the REAL TEST formula, it was found that it could predict fibrosis with 56.94% specificity, 71.75% sensitivity, 16.14% NPV, and 94.58% PPV (AUC=0.7242, 95% CI:0.69-0.75) (Figure 2).

Models with different combinations of variables and the best cut-off values for the prediction of significant fibrosis in patients with chronic hepatitis B are documented in Table 2.

Patients with chronic hepatitis C

Patients with chronic hepatitis C were divided into two groups according to fibrosis stage: the early stage, with a fibrosis score between 0 to 2 points and the significant stage, with a fibrosis score between 3 and 4 points.
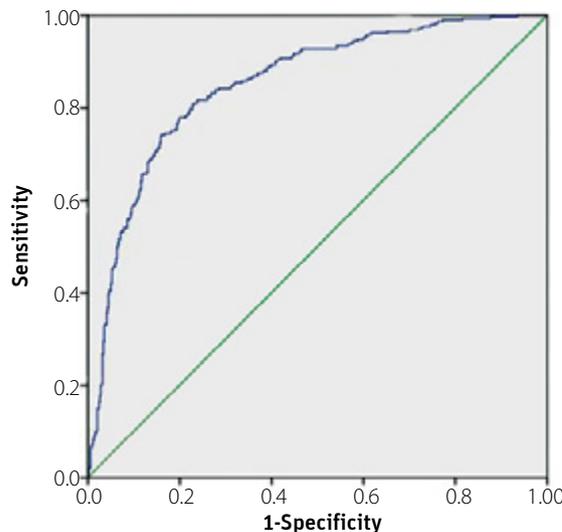

Figure 1. Cut-off value prediction for the REAL TEST formula by ROC analysis in patients with hepatitis B with significant fibrosis (fibrosis 3 and 4).
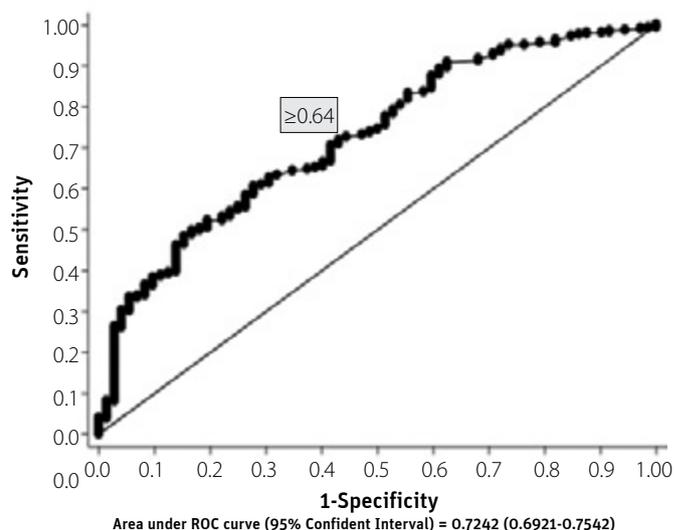

Figure 2. Cut-off value prediction for the REAL TEST formula by ROC analysis in patients with hepatitis B with mild fibrosis (fibrosis 0 and 1).

Table 2. Models with different combinations of variables and the best cut-off values for the prediction of significant fibrosis in patients with chronic hepatitis B

Variable Formula	AUC	CI
Regression Formula 1*	0.826	0.809-0.865
Regression Formula 2¥	0.830	0.801-0.860
PT-APRI£	0.837	0.8090.865
APRI≠	0.824	0.794-0.853
REAL TEST	0.852	0.820-0.870

AUC: area under the curve

*-1.64 + (AST X 10⁻³) + (PT X 0.267) - (PLT X 10⁶)

¥[(age x 0.047) + (plt/1,000,000) + (PT x 0.54) + (AST x 0.016) - 9.8]

£(AST X PT)/(PLT/1000)

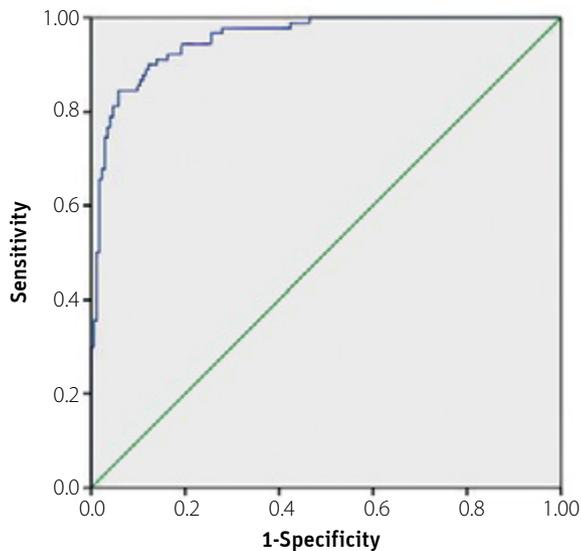≠((AST/ULN)/(PLT/1000)) X 100 (ULN= 40 U/L)

Figure 3. Cut-off value prediction for the REAL TEST formula by ROC analysis in patients with hepatitis C with significant fibrosis (fibrosis 3 and 4).

In the binary logistic regression analysis, the best r square values for age, platelet count, PT, and AST parameters were obtained on a square linear curve. According to this, the mathematical formula obtained according to the recommended linear curve for the prediction of fibrosis was found to be "[(age x 0.039) + (PT x 0.433) + (AST x 0.041) + (plt/100000) - 8.65]." By this mathematical formula, the AUC value was AUC=0.840 (95% confidence interval: 0.783-0.898). The difference between the AUC values obtained by the REAL TEST formula, explained in detail below, was significant in favor of the REAL TEST formula (p<0.001).

When the cut-off value of the REAL TEST formula in patients with hepatitis C and fibrosis stages 3 and 4 was determined to be ≥1.99, it was found that it could predict fibrosis with 87% specificity, 90% sensitivity, 94.4% NPV, and 79.4% PPV (AUC:0.95, 95% CI:0.93-0.98) (Figure 3).

DISCUSSION

It is a well-known issue that certain stages of fibrosis in cases of viral hepatitis are crucial for treatment decisions and prognosis determination. Patients with viral hepatitis who have severe fibrosis or cirrhosis should also be evaluated for hepatocellular carcinoma (21). Although a great number of noninvasive markers of fibrosis are recommended and have been shown to be useful for patients with CHC in recent years, they have not been sufficiently accepted for clinical use (22).

In this study, when the cut-off value for the REAL TEST formula for the prediction of significant fibrosis in patients with hepatitis B was determined to be ≥1.58, it was found that it could predict fibrosis with remarkable AUC values. The best AUC values in patients with CHB were reported by FibroTest and AST platelet ratio index (APRI) scores. In a meta-analysis performed by Poynard et al. (23), the AUC value from the FibroTest was reported to be

0.84. The APRI score is the most frequently studied formulation regarding routine laboratory tests (4,24). The APRI score, which was recommended for the first time for patients with CHC and yielded significant results in the prediction of significant fibrosis and cirrhosis, resulted in disappointing effects for patients with CHB. In a recent meta-analysis performed by Jin et al. (2) that evaluated the APRI score related to patients with CHB, the authors found that the summary receiver operating characteristic curves (SROC) for the prediction of significant fibrosis and cirrhosis were 0.79 and 0.75, respectively. The inadequacy of the APRI score for the prediction of significant fibrosis and cirrhosis according to this meta-analysis raises the importance of the scoring system that we derived. The frequent use of the Ishak scoring system in the handling of the stages of significant fibrosis and pre-cirrhosis in the two subgroups (porto-portal and porto-central) in previous studies may have played a role in the significant AUC values that we obtained. The prediction of significant fibrosis by the division of the fibrosis stages into two groups (i.e., early stage for fibrosis 0-2 and significant stage for fibrosis 3-5) instead of by separate stages begins in the initial study performed by Wai et al., and then appears in all of the studies in the literature (24). This subject suggests that intermediate stages do not cause significant laboratory changes. Additionally, in the studies that used scoring systems that did not divide the stages of fibrosis into subgroups apart from the Ishak scoring system (e.g., the Knodell and Metavir scoring systems), it has been reported that the APRI score gave the best AUC value and correlation coefficient in comparison studies with other scores in patients with CHB and CHC (3,22). Although some formulations with high AUC values between fibrosis stage and hyaluronic acid, apolipoprotein A1, and α2-macroglobulin in patients with CHB have been suggested in previous studies, these formulations are not extensively used. As the aforementioned markers of fibrosis are not routinely used and are not easily accessible, they are not cost-effective (19,4).

When the cut-off value of the REAL TEST formula in patients with hepatitis C was determined to be ≥2.01, it was found that it could predict significant fibrosis with 88.95% specificity and 92.22% sensitivity (AUC:0.9615, 95% CI:0.94-0.98). In this study, we determined significant AUC values between noninvasive tests in the literature regarding patients with hepatitis C. However, why different AUC values are obtained in patients with CHB and in patients with CHC despite the similarities in grades and stages is a matter of debate. Although patients with hepatitis B and C present with similar histopathological findings and are evaluated with the same scoring system, the observation of marked hepatosteatosis in patients with CHC (22) and the presence of inflammatory destruction and complementary activity suggest to us that different ultrastructural mechanisms may play a role (5,25).

In this study, we attempted to predict fibrosis using AST levels, age, platelet count, and prothrombin time. In fibrosis progression, the AST/ALT ratio increases in favor of AST. This finding

suggests that cellular damage occurs in cases of significant fibrosis in addition to cytoplasmic damage and mitochondrial damage. Consequently, an increase in mitochondrial AST occurs (26). The increase in the AST/ALT ratio in patients with cirrhosis can be explained by an associated decrease in AST clearance (27). Thrombocytopenia may occur in cases of significant fibrosis due to a decreased production of thrombopoietin in the liver, increased splenic platelet sequestration caused by increases in portal pressure, or a direct myelosuppressive effect of the virus (28,29). Many articles have reported the relationship between age and fibrosis. In particular, the age/platelet index (API) is a score that is based on the consideration of age. Advanced age was identified as a risk factor for severe liver disease (19). This condition is associated with increased fibrosis due to fibrogenesis with advancing age (30,31). We did not evaluate ALT and HBV DNA in the REAL TEST formulation. In addition to a weak correlation with the fibrosis score, ALT and HBV DNA levels showed fluctuations during the natural course of CHB disease (32). In a study performed by Zhang et al. (15), it was reported that the addition of hyaluronic acid to the APRI score in patients with CHB contributed to the meaningfulness of this diagnostic method. In this study, while APRI alone had a 41.3% PPV value and 84.7% specificity, by the addition of hyaluronic acid to this formula, these values increased to 93.7% and 98.9%, respectively. Additionally, in this current study, we obtained a more meaningful result with additions to the APRI score.

When this current study and the literature data are considered, it can be stated anecdotally that the division of the stages of fibrosis into two groups (i.e., early stage and advanced stage) may be more useful to ensure the compatibility between clinical and laboratory findings in cases of chronic viral hepatitis (33,34).

The most important limitation of this study is the retrospective design. Additionally, the other limitations are as follows: the adequacy of the biopsy material for the evaluation of the whole liver to achieve excellent formulation is controversial, as is the inter- and intraobserver variability of 20% between pathologists. Prospective studies in which the intraobserver variability during pathological evaluation is minimized and separate assessments are performed for each of the Ishak, Knodel, and Metavir scoring systems should be conducted for near-ideal formulation. We believe that the consideration of disease age instead of patient age in these studies will undoubtedly increase the significance. Additionally, the investigation of the applicability of this formulation for inactive carriers - the most intensive hepatitis group - will further increase the clinical benefit of this formulation.

According to the current guidelines, viral load and ALT levels are considered with respect to the decision to perform a biopsy (1,6), whereas these two parameters, on which the decision to perform a biopsy is based, are incompatible with significant fibrosis that is determined from the biopsy speci-

mens; in addition, they do not offer the opportunity for a pathological interpretation for all patients who require a liver biopsy (35). In this study, biopsies were also performed according to the guidelines that recommend a biopsy based on ALT level and viral load. Based on the results of the current study, more than 40% of both patients with CHB and those with CHC who have undergone liver biopsy according to the parameters in current guidelines, such as viral load and ALT levels, are in the mild fibrotic stages (stage 0-1). The incongruity with viral load could be attributed to the instability of HCV RNA load due to fluctuations, especially in patients with hepatitis C (36). Additionally, replication of HCV RNA in non-hepatocyte cells may contribute to this inconsistency (37). In this case, a biopsy in patients with high scores according to the models obtained from the noninvasive tests will be a more appropriate approach, and patients with more significant fibrosis will be identified earlier and effectively using the scores obtained with this formula.

With the selection of appropriate cut-off levels, the REAL TEST formula seems to be an effective procedure for the prediction of fibrosis. In addition, as the patient's age and routine laboratory tests are used, and no special equipment is essential to determine the test score, the REAL TEST formula is an easy and clinically applicable method which can be used extensively in daily clinical practice.

In conclusion, rather than an alternative method of liver biopsy, the evaluation of the REAL TEST formula may be a useful determinant for biopsy instead of viral load and transaminase values, which are inharmonious with fibrosis grades determined from biopsy specimens.

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