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Klinik Araştırma

Predictive ability of non-invasive scoring systems in the measurement of hepatic inflammatory threshold values determined by the National Health System for the treatment chronic hepatitis B

Ulusal Sağlık Sisteminin kronik hepatit B tedavisi için belirlediği karaciğer inflamasyon eşiklerinin ölçümünde invaziv olmayan skorlama sistemlerinin öngörme yeteneği

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ABSTRACT

Objective: In Turkey chronic hepatitis B therapy can be initiated only in the presence of hepatic inflammation score equal or above 6/18 and/or fibrosis score equal or above 2/6 based on National Health Systems histologic active disease cutoffs (HADc determined by histologic examintion of liver biopsy specimens. Non- invasive hepatic scoring system may be useful to predict HAD. The aim of this study was to evaluate the predictive ability of non-invasive scores to foresee HAD for the treatment of patients with chronic hepatitis B (CHB).
Method: In this retrospective study, we analyzed data from 132 CHB patients who had been subjected to liver biopsy. Previously described noninvasive scoring models APRI, Hui's model, Age/platelet ratio, Forn's index, FIB-4 index and AST/ALT ratio were evaluated for the predictive ability to foresee cut-off values of HAD.
Results: Hepatic inflamation and/or fibrosis higher than HAD cut-off values were detected in 83 patients (63%). The areas under the curve (AUCs) values of noninvasive test data used to predict HAD were statistically significant for FIB4 index (0.66), APRI (0.75), 0.73 for the HBV DNA level (0.73) and alanine aminotransferase (ALT ;0.68) as indicated in parentheses (for all p <0.05). The ability of the AST - to - platelet ratio (APRI) to predict cutoffs was greater than that of the other measures. At APRI cut- off value of 0.5, the specificity and positive predictive value were 89.8 and 91.2%, respectively. Fifty-two (91.2%) patients out of 57 with APRI scores above 0.5 had higher HADc values above the cut-off value (as assessed by liver biopsy) in 52 (91.2%).
Conclusions: The APRI score may be a useful noninvasive marker predicting National Health System HADc for treatment of CHB patients.

Key words: Chronic hepatitis B, prediction, hepatic inflammatory activity, liver fibrosis, noninvasive scores

ÖZ

Amaç: Türkiye'de hepatit B tedavisi yalnızca, Ulusal Sağlık Sisteminin histolojik aktif hastalık (HAH) olarak belirlediği eşik değerler olan 6/18'ya eşit veya yüksek karaciğer inflamasyonu ve/veya 2/6'ye eşit ta da yüksek fibrozis varlığında başlanabilir. İnvaziv olmayan skorlama sistemleri bu eşik değerleri belirlemede yardımcı olabilir. Bu çalışmanın amacı, invaziv olmayan skorların kronik B hepatiti (KBH) tedavisi için belirlenmiş HAH eşik değerleri öngörme yeteneklerini araştırmaktı.
Yöntem: Bu retrospektif çalışmada, KHB nedeniyle karaciğer biopsisi yapılmış 132 hastanın verileri analiz edildi. Daha önce tanımlanmış invaziv olmayan skorlama modelleri; APRI, HUi modeli, yaş/trombosit oranı, Forn'un indeksi, FIB-4 indeksi ve AST/ALT oranı HAH eşik değerlerini öngörme yeteneği yönünden incelendi.
Bulgular: Hastaların 83'ünde (%63) HAH eşik değerlerin üzerinde inflamasyon ve/veya fibrozis saptandı. Histolojik aktif hastalık eşik değerlerini öngörme için invaziv olmayan testlerin elde edilen eğri altında kalan değerleri FIB-4 indeksi için 0,66, APRI indeksi için 0,75, HBV DNA için 0,73 ve ALT için 0,68 idi, bu değerler istatistiksel olarak anlamlıydı (p<0,05). APRI skorunun öngörme kapasitesi diğer test ve parametrelerden daha büyüktü. APRI skorunun eşik değeri 0,5 olduğunda özgüllük ve pozitif öngörme değeri sırasıyla %89,8 ve %91,2 saptandı. APRI skoru 0,5 üzerinde bulunan 57 hastanın 52'sinde (%91,2) karaciğer biyopsisinde HAH eşik değeri üzerinde saptandı.
Sonuç: APRI skoru Ulusal Sağlık Siteminin KHB hastaların tedavisi için belirlediği HAH eşik değerleri öngörmede faydalı bir gösterge olabilir.

Anahtar kelimeler: Kronik hepatit B, öngörme, karaciğer inflamasyon aktivitesi, karaciğer fibrozisi, invaziv olmayan skorlar

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INTRODUCTION

Chronic hepatitis B (CHB) virus infections cause liver fibrosis, which often progresses to liver cirrhosis combined with hepatocellular carcinoma. Major international guidelines suggest that patients should be considered for treatment when HBV DNA levels exceed 2.000 IU/ml, serum ALT levels rise above the upper limit of normal (ULN), and the extent of liver disease (as assessed by liver biopsy) features moderate-to-severe active necroinflammation and/or at least a moderate degree of fibrosis, using a standardized scoring system. However, HBeAg-positive and HBeAg-negative patients with ALT levels above twice the ULN, and serum HBV DNA levels above 20.000 IU/ml, may commence treatment even without liver biopsy data. In such patients, liver biopsy may provide additional useful information, but the results usually do not affect treatment decisions [1,2]. In Turkey, the National Health Insurance System requires demonstration of histopathogic activity by liver biopsy in that histological activity scores ≥6 (of a maximum of 18) and/or fibrosis scores ≥2 (of a maximum of 6) must be recorded prior to initiation of CHB therapy, associated with governmental policy on drug use [3]. This is not optional but mandatory. The aim of the present study was to evaluate noninvasive scores (measured using routine laboratory test data and standardized measures) to predict National Health System histologic active disease cutoffs (HADc) for the treatment of patients with CHB and provide predictive information to the clinicians before liver biopsy.

MATERIAL and METHODS

In this retrospective study, we analyzed data from CHB patients who were treated and subjected to liver biopsy in a Training and Research Hospital from 2009 to 2011. In total, 132 patients who signed an informed consent form were included in the study. The study was approved by the local ethics committee.

Diagnosis of chronic hepatitis B

Chronic hepatitis B disease was diagnosed based on HBsAg positivity for 6 months, and biopsy was indicated when the alanine aminotransferase (ALT) value was within or higher than the upper limit of normal (normal ALT, 0-40 IU/L) and the serum titer of HBV DNA was greater than 10,000 copies/mL. HBV DNA was quantified by RT-PCR assay using the artus HBV RG PCR Kit® with the Qiagen Rotor-Gene Q 6000™ instrument. The analytic lower detection limit of the assay was 3.8 IU/mL (constant: 8.2 to conversion copy: 31.4, p=0.05).

Histological grading and staging

Liver biopsy samples were evaluated histopathologically using modified necroinflamation and fibrosis score system [4-6]. Patients who had been previously treated, who had decompensated cirrhosis, who were co-infected with hepatitis B and hepatitis C and/or delta hepatitis, and/or who yielded insufficient biopsy material, were not included in the study.

Noninvasive tests

(a) APRI score (aspartate aminotransferase (AST) - to - platelet ratios) was calculated as described by Wai et al [7,8].
APRI = [(AST value / normal upper limit of AST) / platelet count (10^9/L) x 100]
An APRI score ≤0.5 indicated the absence of fibrosis, whereas an APRI score >1.5 indicated marked fibrosis.

(b) AST/ALT ratio (AAR) was calculated by dividing serum AST levels by ALT values. A ratio ≥1 was considered to reflect marked fibrosis [9].

(c) FIB - 4 index was calculated using: (age x AST level) / platelet count x (ALT) ½, where an FIB-4 score ≥1.5 indicated no fibrosis and ≥3.25 indicated marked fibrosis [10].

(d) Age-platelet indices (AP) were calculated by dividing age (in years) by platelet count. The AP index values were as follows according to different age groups: 0 for ≤ 30 years, 1 for 31-40 years, 2 for 41-50 years, 3 for 51-60 years, 4 for

61-70 years, and 5 for 71 years or older. Platelet counts were graded as follows:0 for ≥ 225.000/mL or more, 1 for 200-224,000/mL, 2 for 175-199,000/mL, 3 for 150-174.000/mL, 4 for 125–149.000/mL and 5 for ≤ 124,000/mL, and the sum of both scores were the AP scores. A score of 6 or more indicated marked fibrosis [11].

(e) Forn's index (FI) was calculated using the equation: FI=7.811-3.131 x ln (platelet count) (109/L)+0.781 x ln (GGT) + 3.467 x ln (age) (years) - 0.014 x cholesterol level). An FI score of 4.2 or less indicated the absence of fibrosis and scores of 6.9 or greater were indicative of marked fibrosis [12].

(f) Hui's model (HM) score was calculated using the equation: HM = [3.148+0.167 x Body Mass Index (BMI) (kg/m_2) + 0.088 x bilirubin (μM) - 0.151 x albumin (g/L) - 0.019 x platelet count (10^9/L)]/1 + [3.148 + 0.167xBMI (kg/m_2) + 0.088 x bilirubin (μM)-0.151 x albumin (g/L) - 0.019 x platelet count (10^9/L)]. The higher cut-off (0.15) value was indicative of mild fibrosis, and the low cut-off value of 0.5 suggested marked fibrosis [13]. All noninvasive test levels and score cut-off values were taken from original publications on the various topics.

According to the major international guidelines; in patients that have HBV DNA above 20000 IU/ml (or~100.000 copies/ml) and ALT above 2 x ULN, liver biopsy is optional for initiation of therapy. Because of this statement these HBV DNA and ALT cut- offs were also investigated for prediction of HADc [1,2].

Statistical analysis

All data were analyzed using SPSS version 15.0 for Windows. Chi-squared and Student's t-tests were used to compare qualitative and quantitative variables, respectively. Receiver operating characteristic (ROC) curves were plotted to assess the accuracies of each score in terms of treatment indications, and areas under curves (AUCs) were estimated. An AUC value of 1 was accepted as characteristic of an ideal test, whereas an AUC of 0.5 or less was deemed to show that the test was of no diagnostic value. Spearman correlation testing was also performed, and a P value of <0.05 was considered to reflect statistical significance.

RESULTS

A total of 132 patients with CHB were included in the study. Of these, 93 (70.5%) were male and 39 (29.5%) female. Mean patient age was 39.1±12.1 years (range 17-67 years). Overall, 22 patients (16.7%) were HBeAg-positive and 120 (83.3%) antiHBe positive. Besides, 82 (62.1%) patients exhibited inflammatory activity higher or equal than 6/18 and 38 (28.8%) fibrosis higher or equal than 2/6 by modified histopathologic scoring. A total of 83 patients (62.9%) exhibited HAD scores higher than HADc.

A total of 83 patients (62.9%) met the treatment criteria and 49 (37.1%) did not. Both groups were compared in terms of mean age, gender, BMI, platelet count, AST, ALT, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), and albumin levels, HBV DNA titer; and HBeAg-positivity. Mean platelet count (P=0.014), AST (P=0.000), ALT (P=0.000), and GGT levels (P=0.000) differed signi-

Tablo 1. Demographic characteristics of patients.

	Patients with Lower than HADc N=49	Patients with higher than HADc N=83	P
Male (n)	32	61	0.32
Mean age (years) ± standard deviation	38.2±11.8	39.7±12.3	0.49
Body mass index (BMI) (kg/m^2)	25.9±4.6	25.8 ± 3.8	0.8
Platelet count	221,410±54,640	196,050±57,160	0.014
AST	31.1±11.8	49±27.6	0.000
ALT	44.45±23.7	76.9±57.8	0.000
GGT	21.5±8.6	33.8±22.3	0.000
ALP	76.4±24.9	82.9±27.6	0.18
Total bilirubin	0.78±0.6	0.78±0.38	0.9
Albumin	4.5±0.3	4.44±0.33	0.36
HBV-DNA	102,524,588± 624,806,575	243,855,426± 706,216,038	0,25
HBeAg-positive (n)	5	17	0.13

AST: Aminotransferease
ALT: Alanine aminotransfrease
GGT: Gama-glutamyl transferase
ALP: Alkaline phosphatase

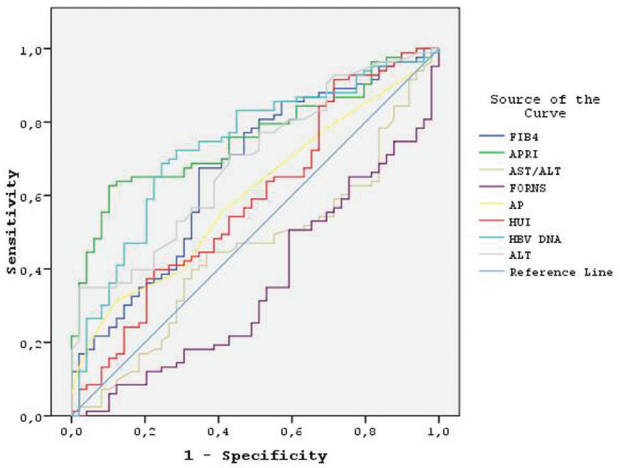

Figure 1. ROC curves in the predicting HAD.

Tablo 2. AUCs of noninvasive tests and scoring systems in terms of treatment indications (HAD).

Test result Variable (s)	Area[1]	Std Error[2]	Asymptotic Significance	Asmptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
FIB4 score	.668	.049	.001	.572	.764
APRI score	.758	.041	.000	.677	.838
AST/ALT ratio	.451	.051	.351	.350	.552
Forn's index	.358	.049	.007	.261	.455
AP index	.601	.049	.054	.504	.697
Hui's model	.586	.052	.101	.484	.688
HBV DNA	.734	.045	.000	.645	.823
ALT	.689	.046	.000	.599	.780

[1]Null hypothesis true area=0.5
[2]Under the nonparametric assumption
APRI: AST - to - platelet ratio
AP index: Age-platelet index

Tablo 3. Utilities of ALT level, HBV DNA titer, [ALT 2xULN - HBV DNA level > 100,000 copies/mL] index, APRI score, and FIB-4 index in determining HAD status.

	Patients with than HADc n=49 (%)	Patients with or higher than HADc n=83 (%)	Sensitivity %	Specificity %	PPV %	NPV %
ALT level						
ALT ULN-2 x ULN	44 (33.3%)	54 (40.9%)	34.9	89.8	85,9	44.9
ALT >2 x ULN	5 (3.7%)	29 (21.9%)				
HBV DNA titer						
<100,000	27 (20.4%)	16 (12.1%)	80.7	55.1	75.3	62.8
>100,000	22 (16.6%)	67 (50.7%)				
[ALT 2xULN and HBV DNA > 100,000 copies/mL]						
<100,000	46 (34.8%)	56 (42.4%)	32.5	93.8	90	45.1
>100,000	3 (2.2%)	27 (20.4%)				
APRI score						
≤0.5	44 (33.3%)	31 (23.4%)	62.7	89.8	91.2	58.7
>0.5	5 (3.7%)	52 (39.4%)				
≤1.5	49 (37.1%)	77 (58.3%)	7.2	100	100	38.9
>1.5	0	6 (4.5%)				
FIB-4 index						
≤1.45	42 (31.8%)	61 (46.2%)	26.5	85.7	75.9	40.8
>1.45	7 (5.3%)	22 (16.6%)				
<3.25	49 (37.1%)	79 (59.8%)	4.8	100	100	50.6
≥3.25	0	4 (3%)				

[3]Rates refer to the total number of patients
ULN: Upper limit of normal
APRI: AST - to - platelet ratio
ALT: Alanine aminotransfrease
PPV: Positive predictive value
NPV: Negative predictive value

Tablo 4. Validity of APRI>0.5, and ALT >2x ULN and HBV DNA >100,000 copies/mL, in predicting HAD status.

	APRI > 0.5		ALT > 2x ULN and HBV-DNA > 100,000 copies/mL	
		Confidence interval		Confidence interval
Sensitivity	62.65%	95% CI: 51.34% to 73.03%	32.53%	95% CI: 22.65 % to 43.70%
Specificity	89.80%	95% CI: 77.76% to 96.56%	93.88%	95% CI: 83.11 % to 98.65%
Positive predictive value	91.23%	95% CI: 80.69% to 97.06%	90.00%	95% CI: 73.44 % to 97.77%
Negative predictive value	58.67%	95% CI: 46.70% to 69.92%	45.10%	95% CI: 35.23 % to 55.26%

ULN: Upper limit of normal
APRI: AST - to - platelet ratio
ALT: Alanine aminotransfrease

ficantly between two groups of patients. Table 1 lists the demographic and laboratory characteristics of all patients.

Figure 1 and Table 2 present test values and the AUCs of inflammation and fibrosis predictive cut-off values . All of the APRI, FIB4 scores, and HBV DNA and ALT levels, were significant in this regard (all P values <0.05).

Table 3 illustrates the sensitivity, specificity, positive (PPV) and negative predictive values (NPV) of ALT levels, HBV DNA titers, ALT/HBV DNA, APRI scores and FIB-4 index at previously described cut-off levels.

Sensitivities of HBV DNA titers and APRI scores at level of 0.5 higher than the other test values and scores were 80.7 and 62.7% respectively. ALT levels, HBV DNA titers, ALT/HBV DNA, APRI score and FIB-4 index have higher specificities except HBV DNA titers. Although specificities of APRI at a level 1.5 and FIB-4 at 3.25 were 100%, this cut-off values provide information about small proportion of patients (6 and 4 patients respectively).

Furthermore PPV of APRI at level of 0,5 was found to be 91.2 percent. Using this APRI cut-off value, 52 of 57 (91.2%) patients could have been identified above HADc. APRI at 0.5 level was more useful and accurate than the other test values and scores.

The validities in terms of prediction of equal or higher HADc were in the order APRI > 0.5, ALT > 2 x ULN and HBVDNA > 100,000 copy / mL; Table 4 lists these data.

DISCUSSION

The ability to determine the stage of liver inflammation and fibrosis in patients with viral hepatitis B is essential to assess disease progression and prognosis, particularly when determining whether or not initiate antiviral treatment. Currently, liver biopsy remains the gold standard for assessing the histological outcomes of liver disease [1,2]. However, this procedure is costly and is associated with a small risk of complications caused by sampling error and the invasive nature of the procedure. The procedure always requires hospitalization for 6-18 h, increasing the possibility of complications [14]. In Turkey, the National Health Insurance System requires that histological activity scores ≥6 (of a maximum of 18) and/or fibrosis scores ≥2 (of a maximum of 6) must be measured prior to initiation of CHB therapy in compliance with governmental policy on drug use [3]. We evaluated the utility of several noninvasive methods involving routine biochemical testing to define HADc in patients with CHB.

Major international guidelines suggest that HBeAg-positive and HBeAg-negative patients with ALT levels above twice the ULN and serum HBV DNA titers above 20.000 IU/ml should commence treatment even in the absence of liver biopsy data [1,2]. In such patients, liver biopsy may provide additional useful information, but the results usually do not affect treatment decisions [1,2]. In our present study, the ALT 2 x ULN-HBV DNA level >100.000 copy/mL afforded high specificity and PPV, confirming the veracity of the guidelines but with lower sensitivity. Although combination of this parameters are main criteria of follow up of CHB, those tests didn't provide reliable information to the clinicians. Furthermore, APRI scores at a level of 0.5 predicted HAD status in 52 of 132 patients. However, the formula [ALT 2 x ULN - HBVDNA level] suggested by major international guidelines assessed 27 of 132 patients to be of HAD status.

Mohamadnejad et al. [16] described 115 inactive HBsAg carriers in whom ALT values were normal at least 6 months prior to the study. Of these patients, 63.5% had HAI scores ≥4, with serum HBV DNA titers of 2-8.6 log10 copies/mL, and a significant relationship was evident between HBV DNA level and HAI scores (p<0.05). Zacharakis et al. [17] found that HBV-DNA titers were significantly associated with the extent of liver fibrosis in those with HBeAg-negative hepatitis B infections. Mommeja-Marin et al. [18] described a correlation between viral load and histological grade, but Martinot-Peignoux et al. [15] found no such association between serum HBV DNA

titer and any of total histological score, stage, or grade. Shao et al. [19] evaluated HbeAg-positive and -negative patients with CHB and found that HBV DNA levels were not correlated with the severity of liver histology. In our study HBV DNA titers alone were found to have high sensitivity but specificity of test was much lower (55%) than that of others test and scores.

Wai et al. [7] introduced the APRI index to evaluate chronic hepatitis C patients. This index has been evaluated in several studies using cohorts of patients with hepatitis C, and yielded good diagnostic performance and reproducibility, particularly for patients with cirrhosis (AUCs ranged from 0.77-0.94), [14,20-22]. The utility of the APRI index in evaluating other forms of chronic liver disease remains uncertain. Wai et al. [7] determined the AUCs of the AST level, the AST/alanine ALT ratio, and the AST/platelet index ratio (the APRI), in CHB patients. Platelet count was the only factor associated with significant fibrosis and cirrhosis upon multivariate analysis, but the AUCs were modest, at levels of 0.63 and 0.73 respectively. Wai et al. [7] concluded that no simple and readily assessable marker can adequately predict cirrhosis in patients with CHB. Güzelbulut et al. [23] evaluated the diagnostic accuracy of the APRI index used to predict significant fibrosis and cirrhosis in CHB patients. They used AUCs of APRI scores to predict significant fibrosis and cirrhosis which were 0.779 and 0.781, respectively. Using cut-off values of ≤ 0.5 and >1.5, significant fibrosis was excluded with a negative predictive value of 91.30%, sensitivity of 87.69%, positive predictive value of 59.52% and a specificity of 90.81%, in 53.60% of the patients. Using cut-off values of ≤1 and >2, cirrhosis was excluded with a negative predictive value of 92.09% sensitivity of 64.10%, positive predictive value of 33.33 % and a specificity of 91.47% in 81.6 0% of patients. Güzelbulut et al. [23] concluded that the AST - platelet ratio index might serve as a useful noninvasive marker excluding both significant fibrosis and cirrhosis in CHB patients. However, this ratio failed to accurately predict either significant fibrosis or cirrhosis in a study conducted by Chrysanthos et al. [9] In the present study, APRI scores exhibited high specificity and PPV. The principal difference between previous research and our study is that we sought to predict not only fibrosis but also necroinflammatory activity in the liver. Thus, the HAD considered not only fibrosis but also necroinflammation. In our 83 patients with liver histology scores above the HADc, 82 (98.9%) patients had necroinflammation above ≥6/18 and 38 (45.8%) patients had fibrosis above ≥2/6. Thus, the predictive ability was more closely related to necroinflammation status than the extent of fibrosis. So in our study AUC of our APRI score was higher than those studies (0,758) and APRI at 0,5 level had high specificity (89,8%) and PPV (91,2%). Therefore, APRI scores may be useful to predict the HAD status of CHB patients.

In conclusion, APRI may be an accurate noninvasive marker predicting National Health System HADc guiding treatment decisions in patients with CHB.

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