Research Article

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Diagnostic Performance of Non-invasive Fibrosis Indexes in Hepatitis B Related Fibrosis

Hepatit B İlişkili Fibrosiste Non-invaziv Fibrozis Göstergelerinin Tanısal Performansı

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ABSTRACT

Objectives: The aim of this study was to evaluate the diagnostic performance of non-invasive fibrosis markers [AST to platelet ratio (APRI), Fibrosis Index based on four factors (FIB-4) İndex, AST/platelet/GGT/Alpha-fetoprotein (AFP) Index (APGA), FI, Fibro-quotient (FibroQ), AST/ALT ratio (AAR), GGT/Platelet ratio (GPR), Platelet-age-phosphatase-AFP-AST (PAPAS) and S-Index] in chronic hepatitis b (CHB) patients.

Materials and Methods: Treatment naive CHB patients who underwent liver biopsy were screened. Four hundred seventeen patients were included in the study. Fibrosis stage was reevaluated according to ISHAK score. The diagnostic efficacy of non-invasive fibrosis indicators for significant fibrosis (≥F3) and cirrhosis (≥F5) was evaluated. The diagnostic performance of the non-invasive markers was defined as the AUROC value of ≥0.9 as excellent, 0.9> AUROC ≥0.8 as good, 0.8> AUROC ≥0.7 as moderate and AUROC <0.7 as poor.

Results: AUROC values of S-index, GPR, APRI, FIB-4 index, FibroQ and PAPAS for diagnosing significant fibrosis were 0.683, 0.667, 0.679, 0.679, 0.585, 0.606 respectively. AUROC values of S-Index, GPR, APGA and FIB-4 index, APRI, FibroQ, PAPAS, FI for diagnosing cirrhosis were 0.841, 0.833, 0.819, 0.802, 0.767, 0.700, 0.697, 0.620 respectively.

Conclusion: Diagnostic performance of S-Index for diagnosing cirrhosis and significant fibrosis was found superior to other indexes, but diagnostic performance of all these indexes was poor in predicting significant fibrosis. Diagnostic performance of S-Index, APGA, GPR, and FIB-4 index were good in determining cirrhosis.

Keywords: Hepatitis B, Liver fibrosis, non-invasive fibrosis indexes.

ÖZ

Amaç: Bu çalışmada kronik hepatit B (KHB) hastalarında non-invaziv fibrozis göstergelerinin [AST/trombosit oranı (APRI), dört faktöre dayalı fibrozis İndeksi (FIB-4), AST/platelet/GGT/alfa-fetoprotein (AFP) indeks (APGA), FI, fibro-quotient (FibroQ), AST / ALT oranı (AAR), GGT/trombosit oranı (GPR), Trombosit-Yaş-fosfataz-AFP-AST (PAPAS) ve S-index] tanısal performanslarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Karaciğer biyopsisi yapılan tedavi naiv KHB tanılı hastalar tarandı. Çalışmaya 417 hasta dahil edildi. Fibrozis evreleri ISHAK skoruna göre tekrar değerlendirildi. Non-invaziv göstergelerin anlamlı fibrozis (≥F3) ve siroz (≥F5) için diagnostik etkinliği değerlendirildi. Non-invaziv göstergelerin tanısal performansı AUROC değeri ≥0,9 ise mükemmel, 0,9> AUROC ≥0,8 ise iyi, 0,8> AUROC ≥0,7 ise orta ve AUROC <0,7 ise zayıf olarak tanımlandı.

Bulgular: S-index, GPR, APRI, FIB-4 Index, FibroQ and PAPAS skorlarının anlamlı fibrozis için AUROC değerleri sırası ile 0,683, 0,667, 0,679, 0,679, 0,585, 0,606 idi. Siroz tanısı için S-index, GPR, APGA and FIB-4 index, APRI, FibroQ, PAPAS, FI skorlarının AUROC değerleri sırası ile 0,841, 0,833, 0,819, 0,802, 0,767, 0,700, 0,697, 0,620 idi.

Sonuç: Siroz ve anlamlı fibrozis tanısı için S-indeksin tanısal performansı diğer göstergelerden üstün saptandı, fakat tüm göstergelerin anlamlı fibrozisi ön görmedeki tanısal performansları zayıf idi. S-index, APGA, GPR ve FIB-4 indeksin sirozu belirlemedeki tanısal performasları iyi idi.

Anahtar Kelimeler: Hepatit B, karaciğer fibrozisi, non-invaziv fibrosis göstergeleri

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Introduction

Hepatitis B virus (HBV) infection is one of the major causes of morbidity and mortality around the world. About 240 million people worldwide are known to have chronic HBV infection (1). The prevalence of chronic HBV infection in adult population in Turkey is 4%, also 40-45% of all patients with chronic hepatitis and cirrhosis have HBV infection (2).

To reduce the mortality associated with cirrhosis and hepatocellular carcinoma caused by HBV infection, it is important to start treatment in optimal time. Liver fibrosis grade is the most important indicator for timing of treatment. Also, it is a predictor of treatment response and prognosis (3,4,5). Liver biopsy is the gold standard for evaluating fibrosis. However, liver biopsy is an invasive procedure and it is not always accepted by patients and requires expert histopathological interpretation. There are also limitations of biopsy such as interobserver variability and sample variability (6). These drawbacks have led to conduction of studies on the evaluation of liver fibrosis by non-invasive methods. According to research in this field, it may be possible to diagnose fibrosis grade with using fibrosis biomarkers.

Direct fibrosis biomarkers (enzymatic indicators, collagen markers, glycoproteins and matrix-metalloproteinase indicators and glycosaminoglycans) reflect fibrogenic changes and extracellular matrix cycle at the cellular level in the liver. However, these indicators are not liver-specific, but also have disadvantages such as cost and availability difficulties in routine clinical practice (7). Indirect markers include gamma glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time, albumin and bilirubin levels, reflecting alteration in hepatic function. These markers are also useful in diagnosing, evaluating severity and assessing the prognosis of liver diseases (7).

Combination of different indirect fibrosis markers such as AST to platelet ratio (APRI), Fibrosis Index based on four factors (FIB-4), AST/platelet/GGT/Alpha-fetoprotein (AFP) Index (APGA), Fibrosis Index, Fibro-quotient (FibroQ), AST/ALT ratio (AAR), GGT/Platelet ratio (GPR), Platelet-age-phosphatase-AFP-AST (PAPAS) and S-index can improve sensitivity and specificity of these tests (7,8,9,10,11,12,13,14,15,16).

However, most of these scores have not been validated in independent data sets, therefore they cannot be used routinely in clinical practice (17). The aim of this study was to evaluate the diagnostic performance of APRI, FIB-4 Index, APGA, FI, FibroQ, AAR, GPR, PAPAS and S-index in chronic hepatitis B (CHB) patients.

Materials and Methods

A total of 466 consecutive treatment naive CHB patients who underwent liver biopsy between 2012 and 2017 were screened. Demographic, serologic and biochemical data performed within one month before the biopsy were recorded from file and computer database of patients. CHB defined as hepatitis B surface antigen positivity for more than six months.

Patients who have hepatitis C, delta virus, human immunodeficiency virus (HIV) infection, with a history of alcohol intake higher than 20 gr/day, accompanying autoimmune hepatitis, fewer than 6 portal areas on liver biopsy, and lack of any biochemical parameters used to calculate non-invasive markers were excluded.

Non-invasive fibrosis scores (APRI, FIB-4, APGA, FibroQ, FI, AAR, GPR, PAPAS, S-index) of patients were calculated. Methods for calculating non-invasive markers are shown in Table 1.

Liver biopsies of all patients were reevaluated by an experienced pathologist who was blinded to the clinical and laboratory findings. Fibrosis stage and histological activity were recorded according to ISHAK score. The diagnostic efficacy of non-invasive fibrosis indicators for significant fibrosis (≥F3) and cirrhosis (≥F5) was evaluated.

The diagnostic performance of the non-invasive markers was defined as the AUROC value of ≥0.9 as excellent, 0.9> AUROC ≥0.8 as good, 0.8> AUROC ≥0.7 as moderate and AUROC <0.7 as poor (18). This study was approved by the Local Ethical Committee of Ümraniye Training and Research Hospital (approval number: B10.1TKH.4.34.H.GP.0.01/34). İnformed consent of patients couldn't obtained due to retrospective design of study.

Statistical Analysis

Descriptive (mean, standard deviation, minimum, median, maximum) statistics were used to define continuous variables. The relationship between independent two categorical variables was evaluated by Fisher's exact test. The comparison of two

Table 1. Calculation methods of noninvasive fibrosis markers

APGA: Log (Index) = 1.441+0.1490 Log (GGT)+0, 3308.log (AST)-0, 5846.log (PLT)+0.1148 log (AFP+1)
FIB-4: Age (year) × AST ÷ PLT (10^3/L) × √ALT
FI: 8.0-0.01 × PLT (10^3/L) - Albumın (g/dL)
FibroQ: [10 x age x AST × INR] ÷ [PLT (10^3/L) × ALT]
S-index: 1000 × GGT (IU/L) ÷ [PLT (10^9/L) × Albumın^2 (g/dL)]
APRI: [AST/(ULN*) ÷ plt (10^3/L)] × 100
AAR: AST ÷ ALT
PAPAS: [Log (Index + 1) = 0.0255 + 0.0031 × age + 0.1483 × log (ALP) - 0.004 × log (AST) + 0.0908 × log (AFP + 1) - 0.028 × log (pLT 10^3/L]
Gpr: [GGT (IU/L)/(ULN**)] / [pLT (10^3/L)] × 100

APRI: Aspartate transaminase to-Platelet Ratio Index, FIB-4: Fibrosis Index based on four factors, AAR: Aspartate transaminase to- Alanin transaminase ratio, APGA Index: AST/Platelet/GGT/Alpha-fetoprotein Index, FibroQ: Fibro-quotient, PAPAS: Platelet-Age-phosphatase-alfa fetöprotein - aspartate transaminase, GPR: GGT Gama-glutamil transferaz to platelet ratio, FI: Fibrosis Index, ALP: Alkaline phosphatase, AST: Aspartat aminotransferaz, ALT: Alanin aminotransferaz, PLT: Platelet, ULN: Upper limits of normal, GGT: Gama glutamil transferase, AFP: Alfafeto protein, INR: İnternational normalized ratio, *ULN of ALT: 40 IU/mL, **ULN of GGT: 63 IU/mL

continuous variables who distributed not normally was evaluated by Mann-Whitney U test. Logistic regression analysis was performed to identify independent risk factors for significant fibrosis and cirrhosis. Diagnostic performance of non-invasive fibrozis markers were evaluated by receiver operating curve (ROC) analysis. Significance was set at a p-value of <0.05. The analyzes were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

Forty-nine patients who have at least one of the exclusion criteria were excluded from the study. Four hundred seventeen patients were included in the study. Flow chart the of study is shown in Figure 1.

1. Demographic Characteristics of Patients

One hundred and sixty-one (38.6%) of the patients were female and 256 (61.4%) were male. The mean age was 42.26±11.88 years. Two hundred and twenty-one (52.7%) of the patients had significant fibrosis, 80 (19.1%) had advanced fibrosis and 29 (6.9%) had cirrhosis. Demographic characteristics of the patients are shown in Table 2.

2. Risk Factors Associated with Fibrosis

2.1 Factors associated with significant fibrosis

Risk factors for significant fibrosis were determined as AST [p=0.014, odds ratio (OR): 1.026, 95% confidence interval (CI) Lower: 1.005-95% CI Upper: 1.048], GGT (p=0.001, OR: 1.022, 95% CI Lower: 1.008-95% CI Upper: 1.035), Albumin (p=0.009, OR: 0.456, 95% CI Lower: 0.252-95% CI Upper: 0.825) and PLT levels (p=0.001, OR: 0.994, 95% CI Lower: 0.990-95% CI Upper: 0.997). These findings are shown in Table 3.

2.2 Factors Associated with Cirrhosis

Risk factors for cirrhosis (F≥5) was determined as male gender (p=0.020, OR: 4.078, 95% CI Lower: 1.246-95% CI Upper: 13.348), GGT (p=0.031, OR: 1.013, 95% CI Lower: 1.001-95% CI Upper: 1.025) and AFP level (p=0.006, OR: 1.062, 95% CI Lower: 1.017-95% CI Upper: 1.109). These findings are shown in Table 3.

3. Diagnostic Performance of Non-invasive Markers

3.1 Significant fibrosis

Statistically significant difference was found between F≥3 and F <3 groups in terms of APGA, FIB-4 Index, FibroQ, S-index, APRI, PAPAS, GPR Index distributions (Mann-Whitney U, p<0.05). The mean values of these markers were higher in the patients with significant fibrosis. In the ROC analysis, S-index, GPR, APRI, FIB-4 Index, FibroQ and PAPAS scores showed poor diagnostic performance (AUROC <0.7). AUROC value S-index, GPR, APRI, FIB-4 index, FibroQ and PAPAS for diagnosing significant fibrosis were 0.683, 0.667, 0.679, 0.679, 0.585, 0.606 respectively. Cut off points, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), positive and negative likely ratios (LR) of these markers in diagnosing significant fibrosis are shown in Table 4. ROC analysis of non-invasive markers was shown in Figure 2. FI, APGA Index and AAR were not useful in the diagnosis of significant fibrosis.

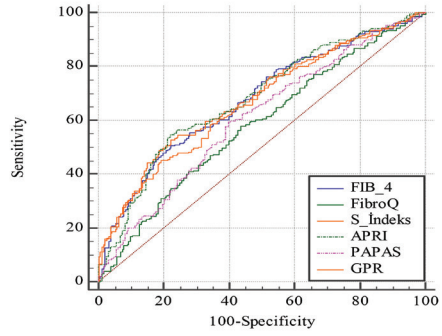

Figure 2. ROC analysis of non-invasive markers in prediction of significant fibrosis

FIB-4: Fibrosis Index based on four factors, FibroQ: Fibro-quotient, APRI: Aspartate transaminase to-Platelet Ratio Index, PAPAS: Platelet-Age-phosphatase-alfa fetöprotein - aspartate transaminase, GPR: GGT Gama-glutamil transferaz to platelet ratio, , ROC: Receiver operating characteristic

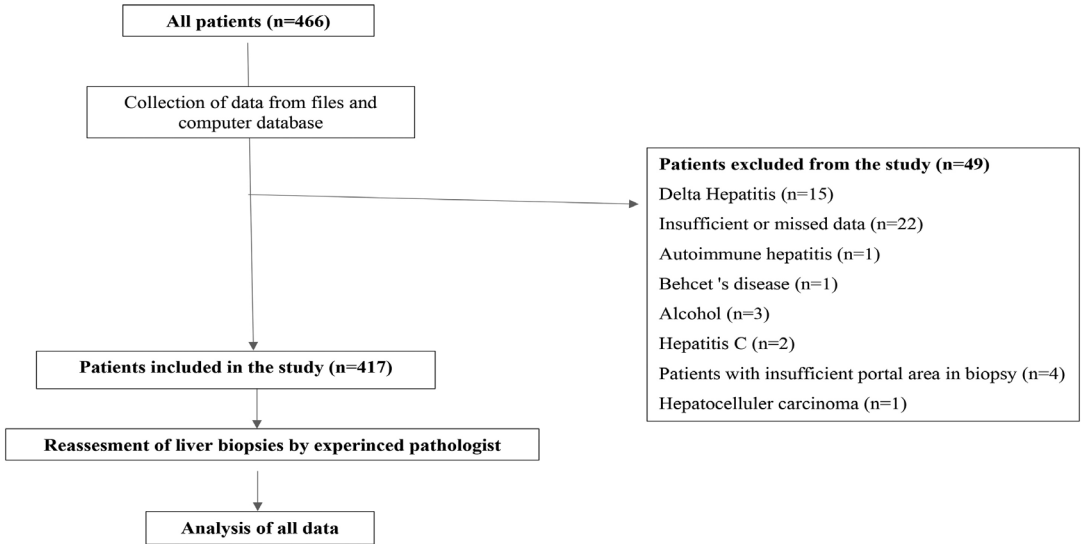

Figure 1. Flow chart the of the study

Table 2. Demographic and baseline characteristics of the patients (n=417)		
Parameters	**(n=417, (%) Mean ± SD**	**Median (min-max)**
Age	42.26±11.88	42 (18-73)
Sex		
Male	-	256 (61.4%)
Female	-	161 (38.6%)
	Mean ± SD	**Median (min-max)**
ALT (IU/L)	64.68±87.6	39 (6-862)
AST (IU/L)	43.04±49.55	30 (12-686)
GGT (IU/L)	32.72±27.95	24 (7-250)
ALP (IU/L)	78.17±24.17	74 (27-210)
Total Bilirubin (mg/dL)	0.87±1.29	0.7 (0.2-25)
Albumin (g/dL)	4.24±0.45	4.3 (0.2-7.8)
INR	1.07±0.11	1.06 (0.83-1.69)
AF (ng/mL)	4.11±6.32	2.85 (0,81-84.52)
PLT (10^3/L)	218.17±59.21	215 (76-550)
HBV DNA (IU/mL)	1.5±7.1 x107	1.2 $x10^5$ (3.1$x10^1$-9.2$x10^9$)
Liver Fibrosis (ISHAK)		
≥F2	-	387 (92.4%)
≥F3 (Significant fibrosis)	-	221 (52.7%)
≥F4 (Advance fibrosis)	-	80 (19.1%)
≥F5 (Cirrhosis)	-	29 (6.9%)
Anti-HBe positive	-	342 (82.5%)
NASH + CHB	-	15 (3.6%)
NAFLD + CHB	-	97 (23.3%)

ALP: Alkaline phosphatase, AST: Aspartat aminotransferase, ALT: Alanin aminotransferase, PLT: Platelet count, ULN: Upper limits of normal, GGT: Gama glutamil transferase, AFP: Alfafeto protein, INR: International normalized ratio, NAFLD: Non-alcholic fatty liver disease, NASH: Non-alcoholic steatohepatitis, CHB: Chronic hepatitis B infection

Table 3. Baseline Factors associated with significant fibrosis and cirrhosis in CHB patients				
Variables associated with significant fibrosis	**p**	**OR**	**95% CI Lower**	**95% CI Upper**
AST	**0.014**	1.026	1.005	1.048
GGT	**0.001**	1.022	1.008	1.035
Albumın	**0.009**	0.456	0.252	0.825
PLT	**0.001**	0.994	0.990	0.997
Variables associated with cirrhosis	**p**	OR	%95 CI Lower	%95 CI Upper
Male gender	**0.020**	4.078	1.246	13.348
GGT	**0.031**	1.013	1.001	1.025
AFP	**0.006**	1.062	1.017	1.109

(*Logistic regression analysis) AST: Aspartat aminotransferase, ALT: Alanin aminotransferase, PLT: Platelet count, GGT: Gama glutamil transferase, AFP: Alfafeto protein, INR: International normalized ratio, OR: Odds ratio, CI: Confidence interval

3.2 Cirrhosis

Statistically significant difference was found between the groups F≥5 and F<5 (cirrhosis vs non-cirrhosis) in terms of APGA, FIB-4, FI, FibroQ, S-index, APRI, PAPAS, GPR distributions (Mann-Whitney U, $p<0.05$). The mean values of these indicators were significantly higher in the cirrhosis group. The diagnostic performance of these indicators was evaluated by ROC analysis. Diagnostic performance of S-index (AUROC: 0.841), GPR (AUROC: 0.833), APGA (AUROC: 0.819) and FIB-4 Index (AUROC: 0.802) were good, APRI (AUROC: 0.767), FibroQ (AUROC: 0.700) were moderate and PAPAS (AUROC: 0.697), FI (AUROC: 0.620) were poor. Cut off points, sensitivity, specificity, PPV, NPV, positive and negative LR of these markers in diagnosing cirrhosis are shown in Table 5. ROC analysis of non-invasive markers are shown in Figure 3A, B.

Table 4. Diagnostic performance of non-invasive fibrosis markers in diagnosing significant fibrosis

İndexes	Diagnostic scan							ROC curve		p
	Cut off	Sensitivity	Specificity	PPV	NPV	LR +	LR-	Area	95% CI	
FIB-4	1.1087	50.68	77.95	72.3	58.2	2.5	0.64	0.679	0.628-0.730	**<0.001**
Lower	0.2893	99.55	0.51	53.1	50.0	1.0	0.88			
Upper	4.122	1.36	99.49	75.0	47.1	2.65	0.99			
FibroQ	1.6145	57.92	56.92	0.74	60.4	1.34	0.74	0.585	0.530-0.640	**0.002**
Lower	0.3235	99.55	1.03	53.1	50.0	1.0	0.88			
Upper	8.2984	0.45	99.49	50.0	46.7	0.88	1.0			
S-index	7.3051	52.94	77.84	73.1	59.2	2.39	0.60	0.683	0.632-0.733	**<0.001**
Lower	1.8469	99.55	2.58	53.8	83.3	1.03	0.13			
Upper	26.956	9.95	99.48	95.7	49.2	19.3	0.91			
APRI	0.4212	54.75	77.95	73.8	60.3	2.48	0.58	0.679	0.628-0.731	**<0.001**
Lower	0.1235	99.55	2.05	53.5	80.0	1.02	0.22			
Upper	1.9079	6.79	99.49	93.8	48.4	13.2	0.94			
PAPAS	0.417	59.36	60.31	62.8	56.8	1.50	0.67	0.606	0.551-0.660	**<0.001**
Lower	0.3171	99.54	0.52	53.0	50.0	1.00	0.89			
Upper	0.5337	1.83	99.48	80.0	47.3	3.54	0.99			
GPR	0.2454	45.25	80.61	72.5	56.6	2.33	0.69	0.667	0.616-0.718	**<0.001**
Lower	0.0669	99.55	3.57	53.8	87.5	1.03	0.13			
Upper	0.9081	7.24	99.49	94.1	48.7	14.2	0.93			

AUROC: Area under ROC curve, NPV: Negative predictive value, PPV: Positive predictive value, LR: Likelihood ratio, FibroQ: Fibro-quotient, FIB-4: Fibrosis index based on the four factors, GPR: GGT to Plateler Ratio, APRI: AST to Platelet ratio index, PAPAS: Platelet-Age-Phosphatase-Alfa Fetoprotein-Aspartate transaminase Index, CI: Confidence interval

Table 5. Diagnostic performance of non-invasive fibrosis markers in diagnosing cirrhosis

İndexes	Diagnostic scan							ROC Curve		p
	Cut off	Sensitivity	Specificity	PPV	NPV	LR +	LR-	Area	95% CI	
APGA	0.8886	86.21	65.12	15.6	98.4	2.47	0.21	0.819	0.751-0.888	**<0.001**
Lower	0.8058	96.55	39.02	10.6	99.3	1.58	0.088			
Upper	1.3507	3.45	99.74	50.0	93.2	13.3	0.97			
FIB-4	1.1095	86.21	66.67	16.2	98.5	2.59	0.21	0.802	0.730-0.874	**<0.001**
Lower	0.7178	96.55	32.04	9.6	99.2	0.11	9.6			
Upper	4.0348	3.45	98.97	20.0	93.2	3.34	0.98			
FI	10.34	62.07	65.37	11.8	95.8	0.58	11.8	0.620	0.504-0.736	**0.043**
Lower	8.83	96.55	5.68	7.1	95.5	1.02	0.64			
Upper	11.44	3.45	99.74	50.0	93.2	13.3	0.97			
FibroQ	1.6013	82.76	49.61	11.0	97.5	0.35	11.0	0.700	0.612-0.787	**<0.001**
Lower	0.9798	96.55	23.0	8.6	98.9	1.25	0.15			
Upper	7.7429	3.45	99.22	25.0	93.2	4.45	0.97			
S-İndex	7.9225	93.10	69.69	18.8	99.3	3.07	0.09	0.841	0.782-0.900	**<0.001**
Lower	4.9331	96.55	36.27	10.2	99.3	1.51	0.09			
Upper	74.8364	3.45	99.48	33.3	93.2	6.66	0.97			
APRI	0.4861	79.31	71.06	17.0	97.9	2.74	0.29	0.767	0.687-0.846	**<0.001**
Lower	0.2533	96.55	30.75	9.5	99.2	1.39	0.11			
Upper	3.3516	3.45	98.97	20.0	93.2	3.34	0.98			
PAPAS	0.4167	85.71	51.95	11.5	98.0	1.78	0.28	0.697	0.615-0.780	**<0.001**
Lower	0.3743	96.43	21.82	8.2	98.8	1.23	0.16			
Upper	0.5443	3.57	99.74	50.0	93.4	13.7	0.97			
GPR	0.2558	86.21	72.94	19.2	98.6	3.19	0.19	0.833	0.769-0.898	**<0.001**
Lower	0.1329	96.55	33.51	9.8	99.2	1.45	0.10			
Upper	1.8606	3.45	99.74	50.0	93.3	13.4	0.97			

AUROC: Area under ROC curve, NPV: Negative predictive value, PPV: Positive predictive value, LR: Likelihood ratio, APGA index: AST/Platelet/GGT/Alpha-fetoprotein Index, FI: Fibrosis Index, FibroQ: Fibro-quotient, FIB-4: Fibrosis index based on the four factors, GPR: GGT to Plateler Ratio, APRI: AST to Platelet ratio index, PAPAS: Platelet-age-phosphatase-alfa Fetoprotein-Aspartate Transaminase Index, CI: Confidence interval

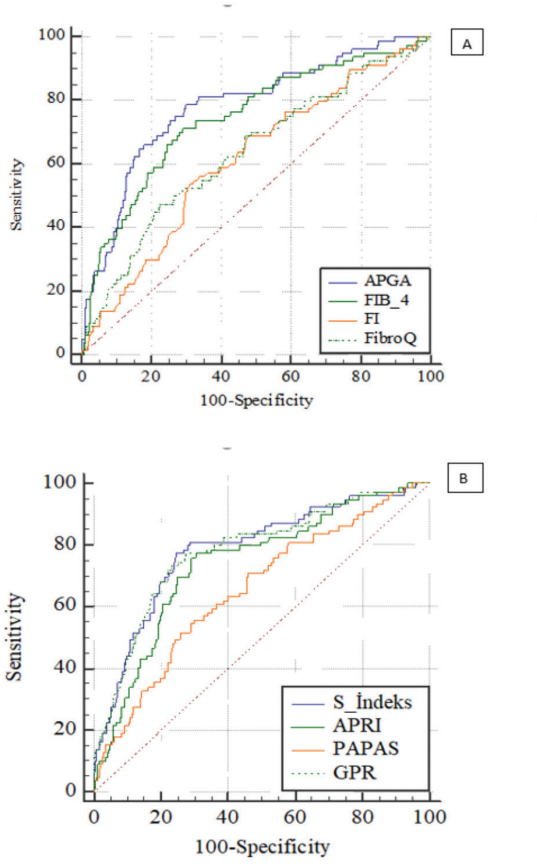

Figure 3. Receiver operating characteristic analysis of non invasive markers in the prediction of cirrhosis (A-B)

APGA Index: AST/Platelet/GGT/Alpha-fetoprotein Index, FIB-4: Fibrosis Index based on four factors, FI: Fibrosis Index, FibroQ: Fibro-quotient, APRI: Aspartate transaminase to-Platelet Ratio Index, PAPAS: Platelet-Age-phosphatase-alfa fetöprotein - aspartate transaminase, GPR: GGT Gama-glutamil transferaz to platelet ratio

Discussion

In the management of CHB, the grade of liver fibrosis is an important determinant of prognosis and timing of the treatment decision. Liver biopsy is the gold standard for detecting fibrosis, however the procedure is invasive, costly and not always repeatable. Furthermore, biopsy may not accurately reflect the stage of fibrosis due to heterogeneous distribution and a small sampling size (19). In addition, biopsy material should be evaluated by experienced pathologists (11). For this reason, studies are carried out to determine fibrosis grade by the non-invasive methods. In this study, the diagnostic performance of simple non-invasive fibrosis markers (APGA, FI, FIB-4, FibroQ, S-index, APRI, AAR and GPR) were evaluated.

We found that S-index, APRI, FIB-4 Index, GPR, PAPAS and FibroQ indicators can detect accurately significant fibrosis. In diagnosis of significant fibrosis, the AUROC value of the S-index was higher than the other non-invasive indicators, but the diagnostic performance of the S-index and others were poor (AUROC <0.700). PPV, AUROC and positive likelihood ratio values of S-index, APRI, FIB-4, GPR Index were found close to each other. If these tests are used at optimal cut-off points, 26-28% of patients can be diagnosed to have significant fibrosis as false positive.

In addition, we found that the AUROC value of the S-index in the diagnosis of cirrhosis was high (AUROC: 0.841), and the diagnostic performance was better than the other non-invasive indicators. Along with S-index, we also found that GPR (AUROC: 0.833), APGA (AUROC: 0.819) and FIB-4 (AUROC: 0.802) indexes had good diagnostic performance in detecting cirrhosis. If these tests are used for a value at or below the optimal cut-off point to exclusion of cirrhosis, %98-99 of patients will be determined correctly.

The APRI and FIB-4 Indexes are non-invasive fibrosis indicators used firstly in patients with HCV or HCV/HIV co-infection in the Western population. In 2015, a meta-analysis evaluated the diagnostic performance of APRI, FIB-4 Index in CHB, reported that AUROC values were found to be 0.740, 0.784 for significant fibrosis and 0.726, 0.844 for cirrhosis respectively (20). In 2015, the WHO recommended the use of the APRI score (APRI score >2 in adults) to assessing the presence of cirrhosis where source limited settings in CHB patients (21). However, in our study, diagnostic performance of APRI was not as good as S-index, GPR, APGA and FIB-4 for determining cirrhosis.

Zhou et al. (13) reported that S-index has good diagnostic performance in detecting significant fibrosis (AUROC: 0.812) and cirrhosis (AUROC: 0.890) (14). Also, Tag-Adeen et al. (22) confirmed this result (AUROC: 0.810) in diagnosing significant fibrosis and reported that the S-index was excellent in the diagnosis of cirrhosis (AUROC: 0.960), superior to the APRI, FIB-4 Index. In our study, the diagnostic performance of the S-index was not as good as the results reported by Zhou et al. (13) and Tag-Adeen et al. (22) These inconsistencies may be related to different demographic, viral characteristics of the study groups and ethnic differences. Also, in our study, liver fibrosis was evaluated with Ishak score but Zhou et al. (13) and Tag-Adeen et al. (22) used Scheuer's and Metavir scores, respectively. ISHAK score documents the minimal changes in fibrosis stage better than other classifications and evaluates fibrosis as 7 stages (23,24).

Lemoine et al. (16) reported that the diagnostic performance of GPR was superior to the APRI and FIB-4 Index in the diagnosis of significant fibrosis (AUROC: 0.720 and 0.730 in different cohorts) and cirrhosis (AUROC: 0.830 and 0.870) in CHB patients (17). However, in a recent meta- analysis it has been shown that, GPR has moderate diagnostic accuracy for predicting HBV-related significant fibrosis, severe fibrosis, and cirrhosis (AUROC values 0.733, 0.777, and 0.796, respectively) (25). Our study demonstrated that diagnostic performance of GPR was poor in significant fibrosis and good in cirrhosis. Different from our study, the use of elastography as a reference in the study of Lemoine et al. (16) may explain the inconsistency of results between studies.

Our study demonstrated that APGA, FI and AAR Idexes could't determinated the significant fibrosis, also AAR could't diagnosed the cirrhosis. In addition, FibroQ, PAPAS and FI scores were found to be weaker than other indexes to diagnosis of cirrhosis.

Study Limitations

Retrospective and single centre design are limitation of our study. İn adition, the distribution of most patients between fibrosis stage 2,3 might have negatively affect the diagnostic performance results of non-invasive tests.

Conclusion

We found that the diagnostic performance of S-index for diagnosing cirrhosis and significant fibrosis was superior to GPR APRI, FIB-4 Index, FibroQ, PAPAS, AAO, APGA and FI indices in patients with CHB. However, diagnostic performance of S-index, GPR, APRI, FIB-4, FibroQ, PAPAS indices were poor in predicting significant fibrosis (AUROC <0.700). Therefore, we believe that these indirect non-invasive fibrosis indicators have limited value for diagnosing significant fibrosis. The diagnostic performance of S-index, APGA, GPR, and FIB-4 Index were good for excluding cirrhosis. We think that these indexes can be used to excluding CHB related cirrhosis in source limited regions.

Ethics

Ethics Committee Approval: The ethics committee approval for the study was obtained from the Local Ethics Committee of Ümraniye Training and Research Hospital (approval number: B10.1TKH.4.34.H.GP0.01/34, date: 20/02/2019).

Informed Consent: Couldn't obtained due to retrospective design.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.K., R.K., Z.Ç., S.S., H.D., Gü.A., R.A., Concept: S.S., Design: S.S., Data Collection or Processing: S.S., R.A., Ş.Ç., K.K., Gü.A., Analysis or Interpretation: G.A., K.Ö., S.S., Literature Search: R.A., H.L.D., O.Ö., Writing: S.S.

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