

Noninvasive evaluation of significant liver fibrosis in chronic hepatitis B patients

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Abstract

Background & Aims: Chronic hepatitis B is still a major cause of morbidity and mortality worldwide. In recent years, there has been increasing research on inexpensive, noninvasive, reproducible methods for detecting fibrosis in the liver. In this study, we examined the efficacy of 15 different noninvasive fibrosis markers for predicting significant liver fibrosis in chronic hepatitis B patients.

Methods: Patients who underwent liver biopsy for chronic hepatitis B between 01.01.2010 and 01.01.2022 were retrospectively analysed. The study population was divided into two groups according to significant fibrosis ($F \geq 3$). Receiver operating characteristic analysis was performed to examine the diagnostic performance of these noninvasive fibrosis markers for the prediction of significant fibrosis. Multiple logistic regression analysis was used to create a model which predicts significant fibrosis better than the individual markers.

Results: In total, 234 chronic hepatitis B patients were enrolled in this study. Among the 15 noninvasive fibrosis markers, King's score was found to have the biggest AUC in predicting significant fibrosis ($F \geq 3$). Furthermore, a model containing King's score, GUCI and GPR has the ability of prediction of significant fibrosis better than every individual marker (cut-off of the model >0.3356 , $p < 0.0001$).

Conclusion: According to our study results, the model containing King's score, GUCI and GPR can be used to predict significant liver fibrosis in chronic hepatitis B patients followed-up in countries with limited sources. (*Acta gastroenterol. belg.*, 2024, 87, 388-392).

Keywords: Chronic hepatitis B, liver fibrosis, King's score, GUCI, GPR.

Introduction

Hepatitis B virus (HBV) is a DNA virus that can cause acute hepatitis, chronic hepatitis, cirrhosis and liver cancer. It is well known that two billion people in the world are infected with HBV, and 350 million people are being monitored for chronic HBV infection (1).

Fibrosis and related complications are the main causes of morbidity and mortality in chronic hepatitis B (CHB) patients (2). Therefore, the degree of liver fibrosis should be accurately determined. Biopsy and histopathological examination are the gold standard methods for determining fibrosis. However, due to the invasiveness and complications of this method, the number of studies on alternative methods has increased in recent years (3).

An ideal marker for staging and grading liver fibrosis should be noninvasive, liver specific, easy to administer, fast and accurate, easily reproducible, and usable for disease monitoring (4,5). Therefore, noninvasive methods such as direct and indirect serum marker detection, transient elastography and magnetic resonance elastography have gained importance (6).

Liver biopsy is invasive, expensive and not reproducible. Moreover, it cannot be performed in all health-care centers, it has several complications, and only a section of liver can be evaluated. Therefore, there is a need to determine the diagnostic performance of indirect serum markers that do not pose a risk to patients or clinicians. Hence, the aim of this study was to investigate the efficacy of 15 noninvasive fibrosis markers for predicting hepatic fibrosis in patients with CHB.

Materials and methods

We applied the STROBE criteria for this study.

Study population

The data of CHB patients who underwent liver biopsy at our institution between 01/01/2010 and 01/01/2022 were analysed retrospectively. Flow chart of the study was shown in Figure 1.

Demographic and laboratory data

Liver biopsy results of the study population were evaluated according to the Ishak scoring system, and the study population was divided into two groups according to significant fibrosis ($F \geq 3$). The numbers of patients with mild and significant fibrosis group were 157 and 77, respectively. Age, sex, comorbidities, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), total bilirubin, albumin, prothrombin time (PT), international normalized ratio (INR), mean platelet volume (MPV), red cell distribution width (RDW), neutrophil count, lymphocyte count, platelet count, hemoglobin, HBV-DNA, and hepatic fibrosis scores were recorded from the hospital database.

Noninvasive fibrosis markers

The 15 noninvasive fibrosis markers were measured as follows: **APRI** = $[(AST/AST \text{ upper limit of normal})/PLT \times 100]$, **API** = Age score + PLT score, Age $<30=0$; 30-

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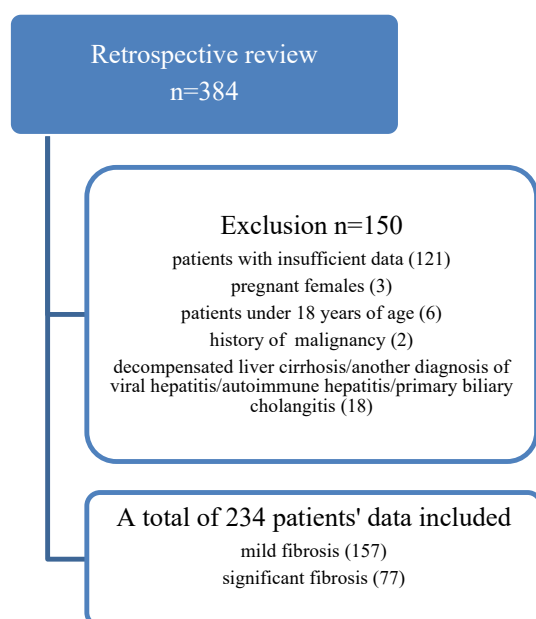


Figure 1. — Flow chart of the study.

39=1; 40-49=2; 50-59=3; 60-69=4; $\geq 70=5$. PLT: $\geq 225=0$; 200-224=1; 175-199=2; 150-174=3; 125-149=4; $<125=5$, **AAR**= AST/ALT, **King's Score**= (Age $\times$ AST $\times$ INR)/PLT, **FIB-4**= (Age $\times$ AST)/(PLT $\times$ ALT)^{1/2}, **NLR**= Neutrophil/Lymphocyte, **MLR**= MPV/Lymphocyte, **MPR**= MPV/PLT, **PLR**= PLT/Lymphocyte, **RPR**= RDW/PLT, **GPR**=[(GGT/upper limit of normal)/PLT $\times 100$], **GUCI**= (AST/AST ULN $\times$ INR $\times 100$)/PLT, **FIB-5**= (Albumin $\times 0.3$ + PLT $\times 0.05$) - (ALP $\times 0.014$ + AST/ALT $\times 6$ + 14), **BONACINI**= PLT + ALT/AST + INR, **GAR**= GGT/Albumin.

Statistical analysis

All the statistical analyses were performed with MedCalc software demo version 19.0.7 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2019). Continuous variables are presented as the mean $\pm$ standard deviation or median (interquartile range). The Kolmogorov-Smirnov test was used to determine the normality of the variables. Variables that met the normality assumption were analysed by an independent samples t test, and variables that did not meet the normality assumption were analysed by the Mann-Whitney U test. Categorical variables were compared by the chi-square test. Spearman's correlation analysis was used to show the possible correlation between noninvasive fibrosis markers and liver fibrosis scores. Receiver operating characteristic (ROC) analysis was performed to determine the efficacy of noninvasive fibrosis markers in predicting significant fibrosis. Youden's index has been used to determine cut-offs. Multiple logistic regression analysis was used to determine the independent predictors of significant liver fibrosis. The odds ratio (OR) and 95% confidence interval

(CI) were calculated for each independent variable. A p value less than 0.05 was considered to indicate statistical significance.

Ethical aspects

This study was conducted with the approval of the Bolu Abant Izzet Baysal University Faculty of Medicine Local Ethics Committee (date: 08/03/2022, decision number: 2022/39).

Results

In total, 234 CHB patients were enrolled in this study. Among these patients, 136 (58%) were male, and 98 (42%) were female. The mean age of the patients was 47.7 ± 11.6 years, and 57 (24%) had other comorbidities.

When the study population was divided into two groups according to significant fibrosis status ($F \geq 3$), no statistically significant differences were found between the two groups in terms of ALP, GGT, total bilirubin, albumin, PT, INR, MPV, RDW or lymphocytes ($p > 0.05$ for all). Significant differences were found between the groups in terms of ALT, AST, GGT, total bilirubin, neutrophils, HBV-DNA and platelets ($p < 0.05$ for all). Moreover, the mean ALT, AST, GGT, total bilirubin, HBV-DNA levels were significantly greater in patients with significant fibrosis, while the mean neutrophil and platelet counts were lower in patients with significant fibrosis. Comparisons of demographic and laboratory data of the study population according to fibrosis scores are presented in Table 1.

According to the ROC curve analysis for significant fibrosis ($F \geq 3$), among all the parameters, King's score had the largest area under the curve (AUC) for the prediction of significant fibrosis (AUC=0.751, $p < 0.001$). The AUCs of noninvasive fibrosis markers for significant fibrosis are presented in Table 2. The optimal cut-off point of King's score for significant fibrosis was >8.18 , with a sensitivity and specificity of 61.0% and 82.1%, respectively (Fig. 2).

Among the 15 noninvasive fibrosis markers investigated in our study, King's score showed the strongest correlation with liver fibrosis scores ($r=0.404$, $p < 0.0001$). AAR was the only marker that was negatively correlated with fibrosis scores ($r=-0.192$, $p=0.003$).

Multiple logistic regression analysis revealed that GPR (OR: 13.6685; 95% CI: 2.2643-82.5119; $p=0.0044$), GUCI (OR: 0.2452; 95% CI: 0.0838-0.7177; $p=0.0103$), and King's score (OR: 1.1329; 95% CI: 1.0486-1.2240; $p=0.0016$) were independent predictors of mortality. A model containing King's score, GUCI and GPR has the ability of prediction of significant fibrosis better than every individual marker (cut-off of the model >0.3356 , $p < 0.0001$).

Discussion

Among the 15 noninvasive fibrosis markers examined in our study, King's score was the unique noninvasive

Table 1. — Demographic and laboratory data of the study population according to fibrosis scores

Variable		Fibrosis <3 (n=157)	Fibrosis ≥3 (n=77)	p value
Age		46,8±12,2	49,6±10,0	0,087
Hemoglobin		14,4±1,4	14,5±1,5	0,481
Gender	Female	67	31	0,725
	Male	90	46	
Comorbidity	Yes	43	14	0,124
	No	114	63	
HBeAg	Positive	21	9	0,717
	Negative	136	68	
ALT		26,0 (17,0-46,0)	61,0 (25,0-129,5)	<0,0001
AST		24,0 (18,7-31,0)	38,0 (24,7-68,5)	<0,0001
ALP		70,0 (59,7-85,0)	72,0 (59,7-91,2)	0,494
GGT		20 (14-30)	28 (22-46)	<0,0001
T. Bilirubin		0,6 (0,5-0,8)	0,7 (0,5-1,0)	0,030
Albumin		43,0 (41,0-46,0)	43,0 (40,0-45,0)	0,325
INR		1,0 (0,9-1,0)	1,0 (0,9-1,0)	0,130
PTZ		12,2(11,4-13,0)	12,2 (11,7-13,0)	0,278
MPV		8,5 (7,6-9,4)	8,6 (7,6-9,7)	0,457
RDW		15,3 (13,9-16,3)	15,2 (14,0-16,1)	0,706
Neutrophil		3,7 (3,0-4,4)	3,3 (2,7-4,1)	0,022
Lymphocyte		2,2 (1,7-2,6)	2,0 (1,7-2,6)	0,542
HBV DNA		23270,0 (5429,0-888916,0)	1026000,0 (23205,0-7593700,0)	<0,0001
HAI		5,0 (3,0-6,0)	7,0 (5,0-10,0)	<0,0001
Platelet		230,0 (194,0-263,0)	205,0 (178,7-245,5)	0,006
APRI		0,2 (0,1-0,3)	0,5 (0,2-0,9)	<0,0001
FIB-4		0,8 (0,7-1,2)	1,3 (0,9-1,7)	<0,0001
NLR		1,7 (1,2-2,3)	1,5 (1,1-2,1)	0,086
MLR		3,8 (3,0-4,9)	4,0 (3,1-5,4)	0,388
MPR		0,0 (0,0-0,0)	0,0 (0,0-0,0)	0,008
RPR		0,0 (0,0-0,0)	0,0 (0,0-0,0)	0,020
PLR		103,8 (84,4-136,1)	101,6 (77,3-127,7)	0,186
AAR		0,8 (0,6-1,1)	0,7 (0,5-0,9)	0,007
API		3,0 (2,0-4,0)	3,0 (3,0-5,0)	0,006
GUCI		0,2 (0,1-0,3)	0,5 (0,3-0,9)	<0,0001
BONACINI		4,0 (3,0-5,0)	4,0 (3,0-5,0)	0,661
King's		4,9 (3,4-7,1)	10,4 (5,3-18,6)	<0,0001
GAR		4,4 (3,3-6,7)	6,3 (4,7-11,6)	<0,0001
GPR		0,1 (0,1-0,2)	0,2 (0,1-0,4)	<0,0001
FIB-5		3,8 (1,9-6,5)	4,1 (0,9-6,3)	0,448

fibrosis marker with the highest diagnostic power for predicting significant fibrosis ($F \geq 3$). Another important finding was that King's score had the strongest positive correlation with liver fibrosis scores.

King's score was first developed and used by Cross et al. in 2009 in a study involving patients with chronic hepatitis C (CHC) at King's College Hospital in the UK. They compared the efficacy of King's score with that of FIB-4, the AAR, the BONACINI, the API and the APRI in predicting significant fibrosis ($F \geq 3$) and cirrhosis ($F \geq 5$)

and suggested that King's score was the best noninvasive fibrosis marker for predicting every degree of fibrosis (7).

According to the formula (7), King's score is directly proportional to age, AST and the INR, whereas it is inversely proportional to platelet count. When we divided our study population into two groups according to significant fibrosis, statistically significant differences were found between the groups in terms of AST and platelet counts. AST levels were significantly greater and platelet counts were significantly lower in the significant

Table 2. — The area under the curve of the noninvasive markers for significant fibrosis

	AUC	SE	95% CI
AAR	0,608	0,0396	0,542 - 0,671
API	0,608	0,0374	0,543 - 0,671
APRI	0,748	0,0348	0,687 - 0,802
BONACINI	0,517	0,0415	0,451 - 0,583
FIB-4	0,697	0,0370	0,634 - 0,755
FIB-5	0,531	0,0414	0,464 - 0,596
GAR	0,701	0,0346	0,638 - 0,759
GPR	0,704	0,0365	0,641 - 0,762
GUCI	0,744	0,0349	0,683 - 0,799
King's	0,751	0,0342	0,690 - 0,805
MLR	0,535	0,0405	0,469 - 0,600
MPR	0,602	0,0375	0,536 - 0,665
NLR	0,569	0,0415	0,503 - 0,633
PLR	0,553	0,0408	0,487 - 0,618
RPR	0,592	0,0391	0,526 - 0,655

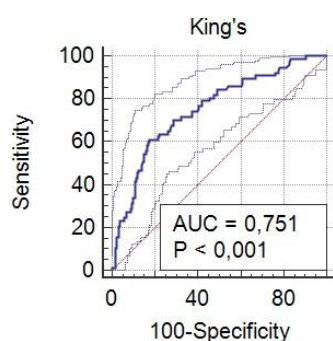


Figure 2. — ROC curve of King's score for predicting significant fibrosis.

fibrosis ($F \geq 3$) group. However, no significant differences were found in terms of age or INR. We believe that the lack of significant differences between the two groups in terms of age and INR was probably due to the low number of elderly patients (≥ 65 years; $n=17$) and cirrhotic patients ($F \geq 5$ patients; $n=8$) in our study cohort.

There are various studies in the literature supporting the use of King's score in CHB patients. In a similar study conducted by Çelik et al. among 539 CHB patients, 10 noninvasive fibrosis markers, including the APRI and FIB-4, were compared. As a result, King's score was found to be one of the two best predictors of significant fibrosis ($F \geq 3$) together with the APRI (8). In a meta-analysis conducted by Dong et al., King's score was compared with the APRI and FIB-4. In this meta-analysis, four studies (958 patients) were examined for significant fibrosis ($F \geq 3$), and as a result, it was suggested that King's score was better than the APRI and FIB-4 in predicting the degree of significant fibrosis (9). In a similar study, Liu et al. reported that King's score was better than the APRI and FIB-4 in predicting cirrhosis in CHB patients (10). In another study conducted by Ekin

et al., the efficacy of 9 noninvasive fibrosis markers, including the APRI and FIB-4, in predicting advanced fibrosis ($F \geq 4$) was compared, and the noninvasive fibrosis marker with the highest diagnostic power was found to be King's score (11).

In a meta-analysis published in 2015, the World Health Organization reported that the APRI and FIB-4 can be used to predict advanced liver fibrosis in CHB patients in regions with limited facilities (1). In our study, we showed that King's score can also be used in centers with limited facilities.

GUCI (Goteborg University Cirrhosis Index) is a noninvasive fibrosis marker developed by Islam et al. in Sweden in 2005. It was used to predict cirrhosis in 179 CHC patients and was reported to be superior to APRI (AUC= 0.850, sensitivity 80%, specificity 78%, positive predictive value 31%, negative predictive value 97%) (12). In our study, the GUCI marker was found to be the second best predictor of significant fibrosis ($F \geq 3$) in patients with CHB (AUC= 0.744, $p < 0,0001$). In a study conducted by Dong et al. in China in 2018, 30 different noninvasive fibrosis markers were compared and GUCI was found to be one of the three markers with the highest efficiency in predicting cirrhosis in treatment-experienced CHB patients (AUC= 0.807). In treatment-naïve patients, the efficiency of predicting cirrhosis was found to be lower (AUC= 0.730) (13). In a similar study conducted by Giada et al., GUCI was found to be useful for predicting cirrhosis in patients with CHB (AUC= 0.560, sensitivity 21%, specificity 91%, positive predictive value 73%, negative predictive value 83%) (14). In previous literature, most of the studies dealing with GUCI were conducted among patients with CHC and Non-Alcoholic Fatty Liver Disease and the number of studies including CHB patients is rather limited (13-16). So, we think that the results of our study are important.

GPR was firstly developed as a noninvasive marker by Lemoine et al. in 2016. In a multicenter study, the efficacy of GPR in predicting significant fibrosis ($F \geq 3$) and cirrhosis ($F \geq 5$) in patients with CHB was compared with APRI and FIB-4 and it was found to be superior to APRI and FIB-4 in both fibrosis grades (17). In another study conducted by Okdemir and Çakmak in 2022, the efficacy of GPR in predicting advanced fibrosis in patients with CHB was investigated and similarly, it was found that GPR predicted advanced fibrosis ($F \geq 4$) better than APRI and FIB-4 (18). In another study by Çelik et al., it was reported that FIB-4 predicted cirrhosis better than GPR, and the analysis result overlapped with our study (8). In our study, GPR was found to be the third best predictor of significant fibrosis ($F \geq 3$) (AUC= 0.704, $p < 0,0001$).

When we combine the best three markers in a model for the prediction of significant fibrosis, this model was found superior to every individual marker (cut-off of the model $> 0,3356$, $p < 0,0001$). So, we advocate the use of this model combining King's score, GUCI and GPR for the prediction of significant fibrosis.

The relatively small number of patients in our study is a limiting factor. In addition, the fact that our study was a single-center and retrospective study is another limiting factor. However, we think that our study is important because it is one of the few studies comparing numerous noninvasive fibrosis markers in CHB patients.

In conclusion, combination of King's score, GUCI and GPR was found to have the highest efficacy in predicting significant liver fibrosis in patients with CHB. Therefore, we believe that this model can be used to predict significant fibrosis in CHB patients living in countries with limited facilities.

Conflict of interest

No conflict of interest was declared by the authors.

Author contributions

K.H.D. and H.T.G. conceived and designed the study. K.H.D. collected data and performed the statistical analyses; H.T.G. revised the manuscript and analysed the data. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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