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ORIGINAL RESEARCH

Retrospective Evaluation of Non-Invasive Assessment Based on Routine Laboratory Markers for Assessing Advanced Liver Fibrosis in Chronic Hepatitis B Patients

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Background: At present, there is a lack of cheap, effective and convenient detection methods for hepatitis B-related liver fibrosis, especially in the developing area.

Aim: To evaluate the non-invasive methods for the significant and advanced fibrosis stage in chronic hepatitis B virus (HBV) patients in basic hospitals and to assess their diagnostic utility.

Methods: The study included 436 consecutive naive HBV individuals who had their livers biopsied. They were examined in one week using aspartate aminotransferase-to-aspartate aminotransferase ratio (AAR), age-platelet index (API), aspartate aminotransferase-to-platelet ratio index (APRI), fibrosis-4 (FIB-4), Forns, gamma-glutamyl transpeptidase-to-platelet ratio (GPR), S-index and transient elastography (TE). Scheuer scoring system was used to determine the histologic fibrosis grades (S0–S4). The diagnostic effectiveness was assessed using AUROCs and the DeLong test, both of which were based on statistical comparisons.

Results: For both substantial (≧S2) and advanced (≧S3) fibrosis phases, TE had good diagnostic performance in determining the hepatic fibrosis. Similar diagnostic performance was shown with Forns and S-index when it came to detecting fibrosis stages lower than S3. One model's diagnostic value was not significantly improved by combining serum models. Correlation coefficients between clinical features and fibrosis phases were greatest for Forns (r = 0.397), S-index (r = 0.382) and TE (r = 0.535) when compared to other variables.

Conclusion: This investigation showed that Forns and S-index may be helpful strategies for detecting advanced fibrosis in HBV patients admitted to community hospitals.

Keywords: hepatitis B virus, non-invasive, basic hospital, transient elastography, Forns, S-index

Introduction

Chronic hepatitis B virus (HBV) infections continue to be a global pandemic, with the majority of cases progressing to liver cirrhosis, hepatic failure or hepatocellular carcinoma.[1–3] Thus, HBV continues to be a significant public health concern.[4] Fibrosis of the liver is a typical complication of chronic hepatitis virus infection (CHV).[5] Although liver biopsy remains the gold standard for fibrosis grading, it has significant disadvantages, including sample bias and the possibility of serious consequences.[6] As a result, it is critical to investigate accurate, simple, and noninvasive approaches for

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evaluating liver fibrosis. Numerous imaging modalities and non-invasive models for the assessment of liver fibrosis have been developed.[7–9]

Transient elastography (TE), magnetic resonance (MR) elastography, shear wave elasticity imaging (SWEI), acoustic radiation force impulse imaging (ARFI), and supersonic shear wave imaging (SSI) have all been developed significantly during the last two decades.[10] TE is the most frequently used approach in everyday clinical practice and has been well validated in large patient cohorts.[11–13] There are a number of serum indicators that may be used to diagnose liver fibrosis, including forns, gamma-glutamyl transpeptidase to platelet ratio (GPR), liver fibrosis-4 (FIB-4), and the aspartate aminotransferase-to-platelet ratio index (APRI).[11] The predictive value of these blood indicators is currently debatable, which limits their widespread clinical use despite their accessibility benefits. Cirrhosis may easily occur if fibrosis of the liver is not treated in a timely manner. At accordance with the recommendations, patients in the fibrosis stage need medication intervention≧S2.[14] Studies in progress have showed that serum biomarker for S1 patients is of limited effectiveness,[15,16] and it still relies on pathological examination. Therefore, we conducted this research focusing on the fibrosis stage ≧S2 and ≧S3.

Because of the asymptomatic nature of liver fibrosis, it is essential to do routine screenings for the condition. More than a quarter of all patients might be saved from the onset of chronic disease by starting an early detection program at their primary care facilities. We expect to find many people who had no idea they had a persistent hepatitis infection. For example, hyaluronidase and laminin, type III procollagen peptide and type IV collagen levels,[17] as well as several novel indicators such as ceruloplasmin[18] and N-glycan[19] cannot be measured in many hospitals. Aspartate aminotransferase to aspartate aminotransferase ratio (AAR), age platelet index (API), APRI, FIB-4, Forns, GPR and S-index were among the non-invasive models we chose from the already existing pool. These seven non-invasive models are all based on the most common clinical parameters, such as age, platelet, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), cholesterol, and albumin (ALB), which can be obtained in blood routine and liver function tests. Non-invasive models that are comparable to TE in terms of diagnostic performance and are best suited for basic-level hospital promotion are our goal. Additionally, efforts are being made to better integrate the serological indications for use in diagnostics. Most investigations of non-invasive liver fibrosis detection currently have limited sample sizes and lack the ability to identify coupled hepatic fibrosis. We want to find the most accessible, most accurate noninvasive diagnostic technology available.

Methods

Patient Characteristics

Patients enrolled in this study, from Tianjin Second People's Hospital, China between April 2016 and December 2020, who were underwent a series of laboratory tests, liver biopsy and FibroScan. All of these patients were positive for serum hepatitis B surface antigen (HBsAg) for at least 6 months. The exclusion criteria were as follows: 1) age less than 18 years old; 2) co-infection with other hepatitis virus and HIV; 3) with hepatocellular carcinoma; 4) with drug-induced liver injury; 5) daily alcohol consumption >30g for men and >20g for women; 6) any type of positive autoantibody above 1:160; 7) immune suppressive treatment within 1 year. Before the research, all of the patients provided written informed consent. This study protocol was approved by the Ethics Committee of Tianjin Second People's Hospital and conducted in accordance with the Declaration of Helsinki.

Clinical and Laboratory Data Collection

Laboratory data such as ALT, AST, GGT, alkaline phosphatase (ALP), total bilirubin (TBIL), ALB, glucose (GLU), cholesterol (CHO), triglyceride (TG), hemoglobin (HGB), mean corpuscular volume (MCV) and Platelet (PLT) were measured and the demographic information, including age, sex and history of previous diseases were evaluated before clinical therapy. The APRI index was calculated as follows: AST (IU/L)/(upper limit of normal range (40 IU/L)) × 100/platelet count (10^9/L); FIB-4 score: age (year) × AST (U/L)/(platelet count (10^9/L) × (ALT (U/L)$^{1/2}$); Forns score was calculated as: 7.811–3.131 × ln (platelet count (10^9/L)) + 0.781 × ln (GGT (IU/L)) + 3.467 × ln (age (year)) - 0.014 × total cholesterol (mg/dl); GPR was calculated as: GGT (U/L)/platelet count (10^9/L). AAR was calculated as: AST (U/L)/ALT (U/L); API is the sum of age

(<30 = 0; 30–39 = 1; 40–49 = 2; 50–59 = 3; 60–69 = 4; >70 = 5) and platelet count (PLT × 10^9/L: 225 = 0; 200–224 = 1; 175–199 = 2; 150–174 = 3; 125–149 = 4; <125 = 5); S-index: 1000× GGT/Platelets × Albumin.

Transient Elastography

TE was used for all patients by FibroScan®-502 (Echosens, Paris, France) with a 3.5 MHz M probe to capture CAP and TE simultaneously.[20,21] Prior to this study, the operators had performed TE evaluations for at least 500 patients. The results of liver stiffness measurements (LSM) were expressed as kPa, and CAP was expressed in dB/m. The CAP values range from 100 to 400 dB/m, while the LSM values are expressed as kilopascals (kPa) and range from 1.5 to 75 kPa. If the success rate was more than 60% and the ratio of interquartile range to median under 30%, the median value of ten successful measurements was considered valid.

Liver Biopsy

All of the enrolled patients finished ultrasound-guided liver biopsy. Histological findings were reviewed by two experienced hepatic pathologists and consensus was reached in case of disagreement. The liver fibrosis was evaluated by using Scheuer scoring system,[22,23] which was staged on a 0–4 scale as follows: S0 no fibrosis; S1 fibrous portal expansion; S2 periportal or rare portal-portal septa; S3 fibrous septa with architectural distortion; S4 cirrhosis. Necroinflammatory activity grades were as follows: G0, no portal or periportal and lobular activity; G1, portal or periportal inflammation activity and minimal occasionally spotty lobular activity; G2, mild piecemeal portal or periportal necrosis and mild or focal lobular necrosis; G3, moderate piecemeal portal or periportal necrosis and moderate or noticeable liver change inside the lobule; and G4, severe piecemeal necrosis and severe or diffuse liver damage inside the lobule.[24]

Statistical Analysis

All data were analyzed by R software v3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). The diagnostic performances were analyzed by computing the areas under the receiver operating characteristics curves (AUROCs). The optimal diagnostic cut-off value for each degree of histological steatosis was found by maximizing the Youden Index. For each cut-off, a corresponding sensitivity and specificity values were also calculated. The diagnostic performances between two measures were compared using the DeLong test. The combination of different methods was performed by "ROCR" and "pROC" packages. AUROCs, specific and sensitivity values were calculated by the "pROC" package. "pROC" packages also used to compare the significance of AUROCs. For correlation studies, we carried out Pearson's statistical analyses. A *P*-value of less than 0.05 on a two-tailed test was considered significant.

Results

Patients' Characteristics and Histological Findings

During the study period, 436 patients with HBV who underwent liver biopsy and FibroScan were enrolled in this study. There were 14 cases (3.2%) concomitant NASH which reached disagreement of pathological diagnosis by two experienced hepatic pathologists. The majority (312/436) of the study subjects were male, and the median age was 39.61 years (18–65 years old). The distribution of liver biopsy-proven fibrosis were S0 8(1.8%), S1 224 (51.4%), S2 132 (30.3%), S3 43 (9.9%), S4 29 (6.7%). 18 cases (4.1%) of these patients with G0, 123 cases patients (28.2%) were G1, 247 cases patients (56.7%) were G3, just 48 cases patients were G3 and none patients with G4. The characteristics of all patients are given in Table 1.

Diagnostic Performance of AAR, API, APRI, FIB-4, Forns, GPR, S-Index and TE for Fibrosis Stages

The AUROC values of AAR, API, APRI, FIB-4, Forns, GPR, S-index and TE of the patients for predicting ≧S2 and ≧S3 fibrosis stages are shown in Table 2. The corresponding AUROC values of AAR, API, APRI, FIB4, Forns, GPR, S-index and TE were 0.588, 0.679, 0.667, 0.693, 0.701, 0.687, 0.697 and 0.796 for fibrosis grades ≧S2 and 0.584, 0.759, 0.712, 0.763, 0.793, 0.759, 0.791 and 0.836 for ≧S3. Compared with AUROC values of TE, Forns and

Table 1 Patients and Trial Characteristics of Included Studies

		n=436
Age (mean (SD))		39.61 (10.98)
Sex (%)	Female Male	124 (28.4) 312 (71.6)
ALT (mean (SD))		87.99 (107.36)
AST (mean (SD))		58.91 (81.82)
GGT (mean (SD))		68.88 (77.12)
ALP (mean (SD))		79.12 (31.24)
TBIL (mean (SD))		17.64 (11.76)
ALB (mean (SD))		44.74 (6.90)
GLU (mean (SD))		5.80 (1.60)
CHO (mean (SD))		4.52 (0.89)
TG (mean (SD))		1.42 (0.93)
HGB (mean (SD))		148.57 (16.84)
MCV (mean (SD))		89.90 (6.93)
PLT (mean (SD))		196.38 (70.35)
S (%)	0 1 2 3 4	8 (1.8) 224 (51.4) 132 (30.3) 43 (9.9) 29 (6.7)
G (%)	0 1 2 3	18 (4.1) 123 (28.2) 247 (56.7) 48 (11.0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptadase; ALP, alkaline phosphatase; TBIL, total bilirubin; ALB, albumin; GLU, glucose; CHO, cholesterol; HGB, hemoglobin; TG, triglyceride; MCV, mean corpuscular volume; PLT, platelet.

S-index showed similar diagnostic performance for ≧S3 fibrosis stage ($P = 0.127$ and $P = 0.09$). But the diagnostic performances of AAR, API, APRI, FIB-4, and GPR were significantly lower than TE for the fibrosis stage ≧S3. The diagnostic performance of TE in assessing hepatic fibrosis was excellent for fibrosis stage ≧S2 (all $P < 0.001$).

Table 2 Diagnostic Performances of Serum Markers and FibroScan for Significant Liver Fibrosis According to Optimal Cutoffs

		AUROC	Threshold	Specificity (%)	Sensitivity (%)	Accuracy (%)	AUROC vs TE
≧S2	AAR	0.588	0.649	52.155	65.196	58.257	<0.001
	API	0.679	3.5	67.241	59.314	63.532	<0.001
	APRI	0.667	0.568	69.397	58.824	64.45	<0.001
	FIB4	0.693	1.229	75.431	55.392	66.055	<0.001
	Forns	0.701	7.828	82.759	50.49	67.661	0.001
	GPR	0.687	0.55	74.569	57.353	66.514	<0.001
	S-index	0.697	0.113	65.517	65.196	65.367	<0.001
	TE	0.796	8.75	80.603	68.627	75	-
≧S3	AAR	0.584	0.649	47.253	72.222	51.376	<0.001
	API	0.759	4.5	73.352	70.833	72.936	0.015
	APRI	0.712	0.568	62.088	73.611	63.991	<0.001
	FIB4	0.763	1.252	69.231	73.611	69.954	0.011
	Forns	0.793	7.144	61.813	87.5	66.055	0.127
	GPR	0.759	0.866	82.692	62.5	79.358	0.008
	S-index	0.791	0.229	83.516	66.667	80.734	0.09
	TE	0.836	7.75	57.143	93.056	63.073	-

Abbreviations: TE, transient elastography; FIB-4, fibrosis 4 score; APRI, aspartate aminotransferase-to-platelet ratio index; AAR, aspartate aminotransferase-to-aspartate aminotransferase ratio; API, age-platelet index; GPR, gamma-glutamyl transpeptidase-to-platelet ratio.

Diagnostic Performance of Combination Serum Markers for Fibrosis Stages

The AUROC values of the combination of two serum markers are shown in Figure 1. TE is superior to the combination of serum markers when diagnosing the fibrosis stage ≧S2 (all $P < 0.001$). Combination of serum markers may not significantly increase AUROC values (Table 3). Similar results were found in the fibrosis stage ≧S3. For the fibrosis stage ≧S3, combination of serum markers may not significantly increase the diagnostic performance. There was no significance for Forns or S-index combined with other serum markers (Table 4).

Correlations Analysis of Clinical Characteristics and Stages of Fibrosis Patients

To observe the correlation of clinical characteristics, non-invasive measurements and fibrosis stages, we performed the correlation analysis that included the factors of AAR, Age, ALB, ALP, ALT, API, APRI, AST, CHO, FIB-4, Forns, GGT, GLU, GPR, HGB, MCV, PLT, Sex, S-index, TBIL, TG and TE. At the end, we found most of the factors significantly co-related with fibrosis stages ($P < 0.05$). The correlation coefficients were markedly highest in Forns (r=0.397), S-index (r=0.382) and TE (r=0.535) as compared to other factors (Table 5 and Figure 2).

Discordance Rates of Degree of Liver Fibrosis Between Sindex, Forns and TE, and Liver Biopsy

Among 436 patients with CHB, 204 patients were diagnosed ≧S2 and 72 patients were diagnosed ≧S3 by liver biopsy. All of 436 patients were divided into ≧S2 and ≧S3, respectively. We analyzed the discordance of Sindex-diagnosed, Forns-diagnosed and TE-diagnosed patients with ≧S2 and ≧S3. The discordance was defined as discordance of these two stages simultaneously. Detection rates of discordance were 8.9% (39/436) with S-index, 13.8% (60/436) with Forns and 13.5% (59/436) with TE. Twelve

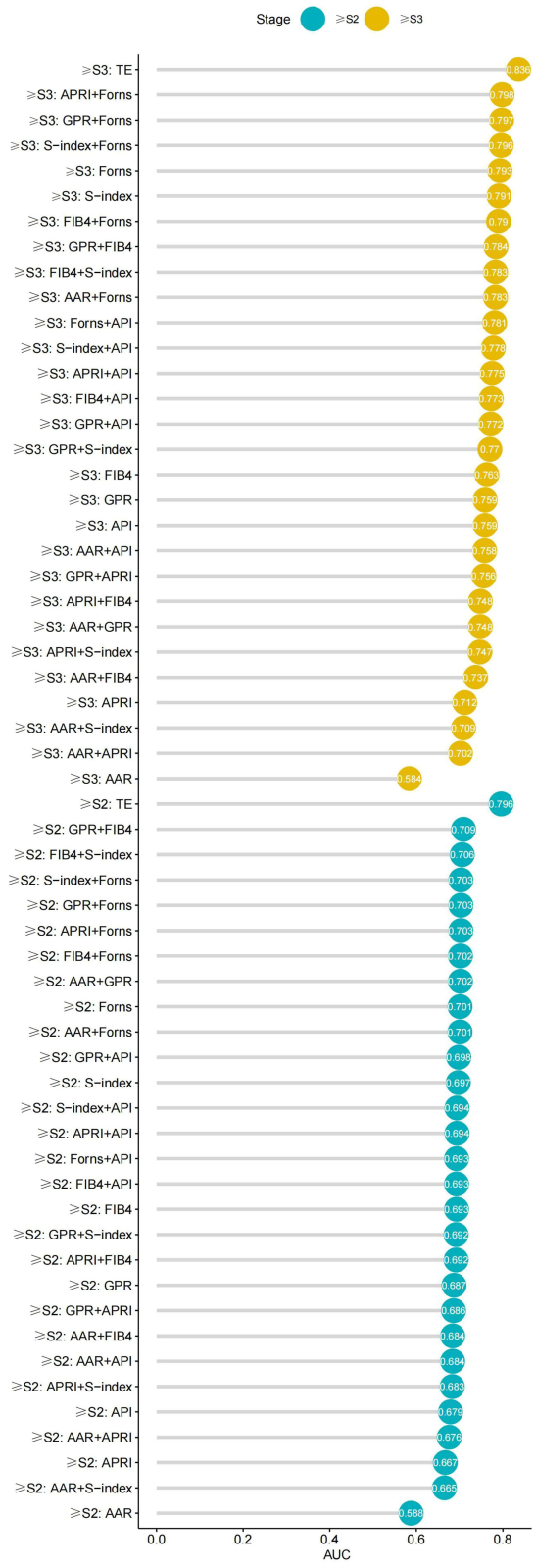

Figure 1 AUROC curves of AAR, API, APRI, FIB-4, Forns, GPR, S-index, TE and combination of two serum markers for fibrosis stage ≧S2 and ≧S3.

Table 3 Comparsion of Different Non-Invasive Tools for Fibrosis Stage ≧S2

Combination	AUROC	vs TE (AUROC=0.796)	vs Forns (AUROC=0.701)	vs S-Index (AUROC=0.697)
		P-value	*P*-value	*P*-value
AAR+API	0.684	<0.001	-	-
AAR+APRI	0.676	<0.001	-	-
AAR+FIB4	0.684	<0.001	-	-
AAR+GPR	0.702	<0.001	-	-
APRI+API	0.694	<0.001	-	-
APRI+FIB4	0.692	<0.001	-	-
FIB4+API	0.693	<0.001	-	-
Forns+AAR	0.701	0.001	0.682	-
Forns+API	0.693	0.001	0.378	-
Forns+APRI	0.703	0.001	0.736	-
Forns+FIB4	0.702	0.001	0.426	-
Forns+GPR	0.703	0.001	0.42	-
GPR+API	0.698	<0.001	-	-
GPR+APRI	0.686	<0.001	-	-
GPR+FIB4	0.709	0.001	-	-
S-index+AAR	0.665	<0.001	-	0.848
S-index+API	0.694	<0.001	-	0.995
S-index+APRI	0.683	<0.001	-	0.229
S-index+FIB4	0.706	0.001	-	0.667
S-index+Forns	0.703	0.001	0.245	0.823
S-index+GPR	0.692	<0.001	-	0.983

Abbreviations: TE, transient elastography; FIB-4, fibrosis 4 score; APRI, aspartate aminotransferase-to-platelet ratio index; AAR, aspartate aminotransferase-to-aspartate aminotransferase ratio; API, age-platelet index; GPR, gamma-glutamyl transpeptidase-to-platelet ratio.

patients were underestimated by S-index, 20 patients by Forns and 14 patients by TE for the stage ≧S2. For the stage ≧S3, 27 patients were underestimated by S-index, 51 patients by Forns and 5 patients by TE. Additionally, 27 patients had overestimated steatosis by S-index, 40 patients by Forns and 45 patients by TE for the stage ≧S2. For the stage ≧S3, 12 patients were overestimated steatosis by S-index, 9 patients by Forns and 54 patients by TE. Based on discordance of ≧S2 and ≧S3 stages simultaneously. We then performed multivariate stepwise regression analysis to detect the factors associated with discordance of results between each noninvasive diagnostic tool and liver biopsy. Finally, we found that the discordance with S-index was correlated with ALT (B = 0.001, $P = 0.03$), AST (B = −0.001, $P = 0.02$), GGT (B = 0.001, $P < 0.001$) and GLU (B = −0.031, $P < 0.001$). The discordance with Forns was correlated with age (B = 0.201, $P < 0.05$), sex (B = 0.004, $P < 0.05$), HGB (B = −0.004, $P < 0.05$) and PLT (B = 0.038, $P < 0.05$). However, there is no independent predictor was detected of discordance correlated with TE.

Table 4 Comparsion of Different Non-Invasive Tools for Fibrosis Stage ≧S3

Combination	AUROC	vs TE (AUROC=0.836)	vs Forns (AUROC=0.793)	vs S-index (AUROC=0.791)
		P-value	P-value	P-value
AAR+API	0.758	0.015	-	-
AAR+APRI	0.702	<0.001	-	-
AAR+FIB4	0.737	0.02	-	-
AAR+GPR	0.748	0.002	-	-
APRI+API	0.775	0.044	-	-
APRI+FIB4	0.748	0.012	-	-
FIB4+API	0.773	0.036	-	-
Forns+AAR	0.783	0.137	0.497	-
Forns+API	0.781	0.112	0.136	-
Forns+APRI	0.798	0.135	0.427	-
Forns+FIB4	0.79	0.124	0.61	-
Forns+GPR	0.797	0.112	0.252	-
GPR+API	0.772	0.035	-	-
GPR+APRI	0.756	0.004	-	-
GPR+FIB4	0.784	0.009	-	-
S-index+AAR	0.709	0.066	-	0.81
S-index+API	0.778	0.054	-	0.655
S-index+APRI	0.747	0.078	-	0.821
S-index+FIB4	0.783	0.098	-	0.889
S-index+Forns	0.796	0.134	0.197	0.882
S-index+GPR	0.77	0.006	-	0.136

Abbreviations: TE, transient elastography; FIB-4, fibrosis 4 score; APRI, aspartate aminotransferase-to-platelet ratio index; AAR, aspartate aminotransferase-to-aspartate aminotransferase ratio; API, age-platelet index; GPR, gamma-glutamyl transpeptidase-to-platelet ratio.

Discussion

Liver fibrosis testing has revolutionized the treatment of chronic liver disease, allowing for more accurate diagnosis and a more accurate assessment of the severity of the illness.[25] Liver fibrosis evaluation is critical to identifying individuals who are at risk of developing severe clinical problems and to determining therapy options for those with persistent HBV infection.[26] Patients showing hepatic fibrosis and especially ≧S3 are at significant risk for developing complications such as portal hypertension and hepatocellular carcinoma (HCC),[27–29] so they are considered to have priority for antiviral therapy and anti-fibrosis therapy. Antiviral medication may repair liver fibrosis if individuals get it early enough. Correct diagnosis and treatment of CHB patients with fibrosis can help to reduce morbidity and mortality and enhance the quality of life for these patients.[30,31] With the invisibility of liver scarring, many asymptomatic HBV carriers, even those who had no symptoms, will be discovered by screening for liver fibrosis in basic hospitals. However, the basic hospital lacks

Table 5 Correlations Between Non-Invasive Measurements and Stages of Fibrosis Patients

S Stage Correlation with	r	P-value
AAR	0.151	0.002
Age	0.208	<0.001
ALB	−0.262	<0.001
ALP	0.067	0.16
ALT	0.096	0.045
API	0.366	<0.001
APRI	0.309	<0.001
AST	0.221	<0.001
CHO	−0.038	0.427
FIB4	0.369	<0.001
Forns	0.397	<0.001
GGT	0.282	<0.001
GLU	0.078	0.104
GPR	0.352	<0.001
HGB	−0.183	<0.001
MCV	0.156	0.001
PLT	−0.319	<0.001
Sex	−0.136	0.004
S-index	0.382	<0.001
TBIL	0.195	<0.001
TG	0.039	0.422
TE	0.535	<0.001

Abbreviations: TE, transient elastography; FIB-4, fibrosis 4 score; APRI, aspartate aminotransferase-to-platelet ratio index; AAR, aspartate aminotransferase-to-aspartate aminotransferase ratio; API, age-platelet index; GPR, gamma-glutamyl transpeptidase-to-platelet ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; TBIL, total bilirubin; ALB, albumin; GLU, glucose; CHO, cholesterol; HGB, hemoglobin; TG, triglyceride; MCV, mean corpuscular volume; PLT, platelet.

imaging and serum biomarker testing devices. Seven non-invasive models based on the most prevalent clinical factors were developed in our study.

The stiffness of the liver may be measured using elastography methods such as FibroScan.[32] FibroScan is an effective diagnostic tool. However, the liver's metabolic activity has a substantial impact on the stiffness of the liver. This means that while assessing liver stiffness, it is necessary to consider the patient's biochemical condition. The extracellular matrix turnover alterations that occur during fibrogenesis are thought to be connected to serum indicators.[33,34] Noninvasive indicators or models such as APRI, FIB-4, Forns, and others have been suggested to predict the severity of liver fibrosis. It has been shown that the sensitivity and specificity of four noninvasive serum indicators, Forns, FIB-4,

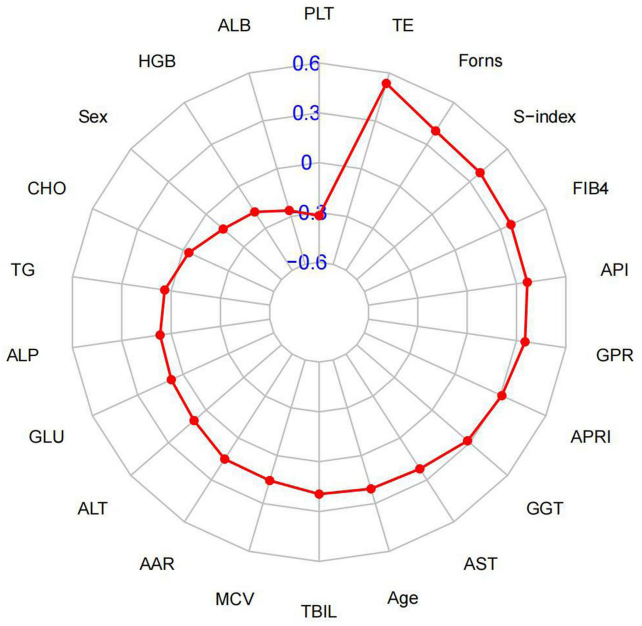

Figure 2 Correlations between non-invasive measurements and stages of fibrosis patients.

GPR (and APRI), may be used to identify and assess the severity of liver fibrosis in individuals who have been infected with the chronic hepatitis virus.[8,13] Detection rates in S2 might be as high as 0.7 in this study as well. This shows that the non-invasive models may have a positive influence on the development and progression of liver disease at important stages but cannot be used as a substitute for TE. However, several non-invasive models of phase≧S3, such as Forns and S-index, may achieve comparable diagnostic performance as TE, which may become a suitable index for clinical promotion. Most studies found that Forns and S-index had a greater diagnostic accuracy than other models, even if the AUROC values of models in various studies were substantially diverse.[35,36] Currently, however, the study sample size is too small, and the majority of studies are focused on NAFLD or HCV instead. In this study, we looked at a large group of HBV-positive individuals, a total of 436. Instead of using a low-efficiency diagnostic approach, we relied on TE as the gold standard for our work. We want to show how effective Forns and S index are in diagnosing liver fibrosis, compared to how effective TE imaging was in≧S3.These noninvasive serum indicators have been shown to be more effective when used in combination. When used in conjunction with the FIB-4 or APRI, GPR, according to Hu et al, might greatly increase the sensitivity and specificity of diagnosing hepatic fibrosis in CHB.[37] An investigation of how the mix of models affects diagnostic performance will be conducted in this project. No substantial increase in diagnostic performance can be achieved by combining non-invasive diagnostic models in a pairwise fashion. This might be because the included markers in these non-invasive models are so similar to one another. These patients' liver fibrosis was also evaluated in this research. According to this research, the coefficient of S-index (r = 0.382), Forns (r = 0.397), and the coefficient of TE (r = 0.535) all strongly linked with the stage of liver fibrosis, although the correlations were less than those for TE. ALP, CHO, TG, ALP, and GLU had inadequate diagnostic performance for clinical use. PLT and GGT are the common components of Forns and S-index. Serum GGT may be a good predictive marker of liver fibrosis. GGT is a key enzyme in glutathione metabolism. It is a cell-surface heterodimeric glycoprotein and highly expressed in the biliary epithelium, kidney tubules and brain capillaries.[38] In some researches, regression analysis demonstrated that GGT was the independent predictor of liver fibrosis.[39,40] Compared with AST and ALT, GGT has a stronger association with fibrosis stage and inflammation stage in HBV infected patients,[41,42] which is consistent with our research result. However, differentiation of liver fibrosis by GGT has a unique role in HBV. In patients with hepatitis B, the mean GGT level in the low activity group was significantly lower than in the high activity group ($P < 0.05$). In the hepatitis C patients, no significant difference was found between two groups with regard to GGT levels.[43] The mechanism of the

increasing in GGT activity in liver fibrosis remains unclear. Some researches suggested that the GGT alteration in hepatitis and liver cirrhosis is associated with the increased GGT synthesis in the liver. It is an adaptive response to the pathological changes and result in an overflow of the enzyme into the bloodstream.[44] Hepatic fibrosis non-invasive models containing GGT (Forns and S-index) showed higher diagnostic value than models containing AST or ALT (APRI, AAR and FIB-4) in HBV patients.[39,45,46] The effect and mechanism of GGT on HBV-related liver fibrosis need further basic researches.

A number of flaws are found in our research. To begin with, our research is based on a retrospective design with a small sample size. This study did not include critical clinical data like CRP and cell count. A possible reason for this is that our investigation did not detect the overestimation of the impact of high ALT levels indicated in earlier studies.[47,48]

Forns and S-index were proven to be a good blood marker for determining hepatic fibrosis grades ≧S2 and ≧S3 in this investigation. For grades ≧S3, Forns and the S-index may perform as well as TE in terms of diagnostic accuracy. When serum models were combined, the diagnostic value was only slightly elevated above that of using a single model. Patients who previously had no idea they had hepatitis B might now be identified by primary serological screening and treated as soon as possible.

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Author Contributions

All authors met the following conditions:

1. Made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation.
2. Took part in drafting, revising or critically reviewing the article.
3. Agreed on the journal to which the article has been submitted and agreed to be accountable for all aspects of the work.
4. Agreed on the final approval of the version to be published.
5. Agreed to take responsibility and be accountable for the contents of the article.

Disclosure

All authors declare no competing interests in this work.

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