

The Age, Gamma-Glutamyl Transpeptidase and Platelet Index: A Novel Noninvasive Model for Predicting Hepatocellular Carcinoma in Patients with Hepatitis B Virus-Related Liver Cirrhosis

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Background and Aims: High incidence of hepatocellular carcinoma (HCC) exists in patients with liver cirrhosis (LC), but the predictive accuracy of noninvasive scoring systems (NSSs) is yet to be elucidated. The present study aimed to evaluate the predictive ability of fibrosis-4 (FIB-4), aminotransferase-to-platelet ratio index (APRI), and gamma-glutamyl transpeptidase to platelet ratio (GPR) in patients with LC, and to establish a new model with more accuracy.

Methods: Data from 94 patients with compensated LC and 134 patients with decompensated cirrhosis (DC) were collected. The prediction accuracy of NSSs, including APRI, GPR, and FIB-4, was compared.

Results: During a median follow-up of 37.5 months, 9 patients in the compensated LC group and 38 in the DC group developed HCC. For 228 patients, the area under the receiver operating characteristic curve (AUROC) of APRI, GPR, and FIB-4 was 0.596, 0.625, and 0.654, respectively. Multivariable logistic analysis showed that age, gamma-glutamyl transpeptidase (GGT), and platelet (PLT) were independent risk factors for HCC development, and a new model encompassing age, GGT, and PLT was superior to NSSs (all $P < 0.05$). With an optimal cutoff value of 0.216, Model (Age_GGT_PLT) achieved 68.09% sensitivity and 69.61% specificity.

Conclusion: NSSs, including APRI, GPR, and FIB-4, has a non-optimal accuracy in predicting HCC development in patients with HBV-related LC. Thus, the new model consisting of age, GGT, and PLT may be more accurate than NSSs.

Keywords: hepatocellular carcinoma, risk score, liver cirrhosis, decompensated cirrhosis, gamma-glutamyl transpeptidase

Background

Hepatocellular carcinoma (HCC) accounts for 90% of liver cancers and hence, is a major health burden in Asia.^{1,2} Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection is the leading course of HCC development.² Although the risk of HCC can be reduced by antivirals^{3,4} the incidence of HCC remains high in patients with liver cirrhosis (LC).^{3,5,6}

Liver fibrosis is a major risk factor for HCC development.^{7,8} Noninvasive scoring systems (NSSs), including fibrosis-4 (FIB-4), aminotransferase-to-platelet ratio index (APRI), and gamma-glutamyl transpeptidase to platelet ratio (GPR),

have a moderate accuracy of liver fibrosis evaluation and adequately predict the long-term outcomes.^{9,10} FIB-4 is a valuable risk marker for HCC development after HCV eradication.^{8,11,12} Data from a small sample-size study suggested that a combination of APRI and alpha-fetoprotein (AFP) can predict HCC development in patients with HCV-related decompensated cirrhosis (DC).¹³

For patients with chronic hepatitis B (CHB), both FIB-4 and APRI were useful in predicting HCC development.^{14,15} FIB-4 at 1-year of treatment was superior to FIB-4 before treatment in predicting HCC.¹⁶ However, another study showed that elevated FIB-4 was not reliable for HCC risk stratification in non-Asia CHB patients.¹⁷ Data from West Africa showed that the sensitivity of APRI score >2 for diagnosis of cirrhosis was only 45.4%.¹⁸ A high level of APRI was maintained in patients who developed HCC.¹⁹ Nishikawa et al reported that FIB-4 rather than APRI could be a valuable predictor for HCC development in CHB patients undergoing entecavir treatment.²⁰ In addition, APRI combined with FIB-4 could stratify HCC in CHB patients with low-level viremia.²¹ Zhu et al reported that GPR was better than FIB-4 in predicting HCC development for elderly CHB patients.²² Notably, the NSSs in HBV-related DC was limited.

Regarding the patients with DC who are at high-risk for liver biopsy, whether NSSs can predict HCC development is yet to be elucidated. Herein, we investigated the predictive accuracy of FIB-4, APRI, and GPR in patients with HBV-related DC and long-term antiviral therapy, and a new model was established.

Methods

Patients and the Primary Endpoint

A total of 307 patients with HBV-related LC were enrolled in the third People's hospital of Changzhou from May 2010 to July 2020. The patients were divided into compensated LC and DC groups based on the criteria of Chinese guidelines for the prevention and treatment of CHB (2019 version).²³ LC was diagnosed according to the histological, ultrasonographic, or endoscopic evidence, while patients with ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, variceal bleeding or hepatorenal syndrome, were diagnosed as DC. HCC was diagnosed according to the guidelines for the diagnosis and treatment of primary liver cancer in China (2019 edition).²⁴ All patients received nucleos(t)ide analogues (NAs) treatment and were followed up for at least 6 months. Patients who developed HCC during these 6 months of follow-up were excluded. Patients had malignant tumor or other hepatitis virus co-infection at admission, had detectable HBV DNA at the end of follow-up, or lost to follow-up were also excluded.

The protocol was approved by the Ethics Committee of the third People's hospital of Changzhou according to the Declaration of Helsinki, 2013 (Approval No. 02A-A20210005), and written informed consent was obtained from all participants.

Score Systems

NSSs, including FIB-4,¹² APRI,¹⁹ and GPR,²² were evaluated, as described previously.

Statistical Analysis

Data were presented as median (interquartile range, IQR) for continuous variables and frequencies for categorical values. Mann–Whitney *U*-test and chi-square test were employed as required. Correlation analysis was performed using Pearson's correlation analysis. Logistic regression analysis was performed to analyze the risk factors for HCC development. The predictive accuracy of NSSs was compared according to the area under the receiver operating characteristic curve (AUROC) using MedCalc version 15.2.2 software for Windows (Medcalc software, Mariakerke, Belgium). The data were analyzed using SPSS version 25.0 (Armonk, NY, USA), and $P < 0.05$ was considered statistically significant.

Results

Characteristics of Patients

Until the last follow-up on May 4, 2022, data from 228 patients who achieved sustained virological response were analyzed. 94/228 patients were diagnosed with compensated LC, and 134/228 patients presented DC. During a median

Table 1 Characteristics of Patients with and without HCC Development During Follow-Up

Variables	Non-HCC (n=181)	HCC (n=47)	Z or χ^2	P-value
Age (years)	50.0 (45.0–60.0)	58.0 (51.0–64.0)	-3.822	<0.01
Male, n (%)	119 (65.7)	33 (70.2)	0.335	0.56
Diabetes, n (%)	52 (28.7)	17 (36.2)	0.979	0.32
DC, n (%)	96 (53.0)	38 (80.9)	11.911	<0.01
ALT, U/L	33.0 (21.0–65.0)	30.0 (23.0–57.0)	0.073	0.94
GGT, U/L	50.0 (25.5–79.0)	66.0 (28.0–108.0)	1.709	0.09
TBil, $\mu\text{mol/L}$	22.5 (15.4–34.7)	19.6 (14.5–31.3)	0.680	0.50
PLT, E+09/L	96.0 (56.5–141.0)	74.0 (55.0–102.0)	2.493	0.01
AFP, ng/mL	4.6 (2.3–10.5)	6.2 (3.2–24.0)	1.899	0.06
GPR	0.5 (0.3–1.1)	0.8 (0.4–1.7)	2.635	<0.01
APRI	41.2 (21.4–104.7)	62.7 (37.5–102.9)	2.024	0.04
FIB-4	3.5 (1.8–7.7)	6.3 (4.1–9.2)	3.257	<0.01
MELD	10.0 (8.0–13.0)	9.0 (8.0–13.0)	0.192	0.85
Diabetes, n (%)	52 (28.7)	17 (36.2)	0.979	0.32
Duration of follow-up, months	38.0 (31.0–69.0)	29.0 (20.0–54.0)	3.279	<0.01

Notes: Comparison was conducted using Mann–Whitney *U*-test (median and IQR) for continuous variables and chi-square test for categorical values.

Abbreviations: HCC, hepatocellular carcinoma; DC, decompensated cirrhosis; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; TBil, total bilirubin; PLT, platelet; AFP, alpha-fetoprotein; GPR, gamma-glutamyl transpeptidase to platelet ratio; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4 index; MELD, model for end-stage liver disease.

follow-up of 37.5 months, 9 patients in the compensated LC group and 38 patients in the DC group developed HCC ($\chi^2=11.911$, $P<0.01$).

As shown in Table 1, patients with HCC were older than those without HCC ($Z=3.822$, $P<0.01$). Moreover, patients with HCC had fewer platelets (PLTs, $P=0.01$) and higher GPR, APRI, and FIB-4 than those without HCC ($Z=2.635$, 2.024, and 3.257, respectively, all $P<0.05$). Strikingly, the follow-up was longer in patients without than those with HCC ($P<0.01$).

Development of a New Risk Model Incorporating Age, GGT, and PLT

As shown in Table 1, univariate analysis showed that age ($P<0.01$), GGT ($P=0.09$), PLT ($P=0.01$), and AFP ($P=0.06$) are associated with HCC development. Multivariable analysis showed that age (odds ratio (OR): 1.067, 95% confidence interval (CI): 1.029–1.106, $P<0.01$), GGT (OR: 1.005, 95% CI: 1.001–1.010, $P=0.03$), and PLT (OR: 0.993, 95% CI: 0.986–1.000, $P=0.04$) were the independent risk factors for HCC development (Table 2). Then, a new model was

Table 2 Risk Factors for HCC Development in Patients with Liver Cirrhosis

Baseline Variables	B	Odds Ratio	95% CI	P-value
Age, years	0.065	1.067	1.029–1.106	<0.01
GGT, U/L	0.005	1.005	1.001–1.010	0.03
Platelets, E+09/L	-0.007	0.993	0.986–1.000	0.04
Constant	-4.664			<0.01

Abbreviations: CI, 95% confidence interval; GGT, gamma-glutamyl transpeptidase.

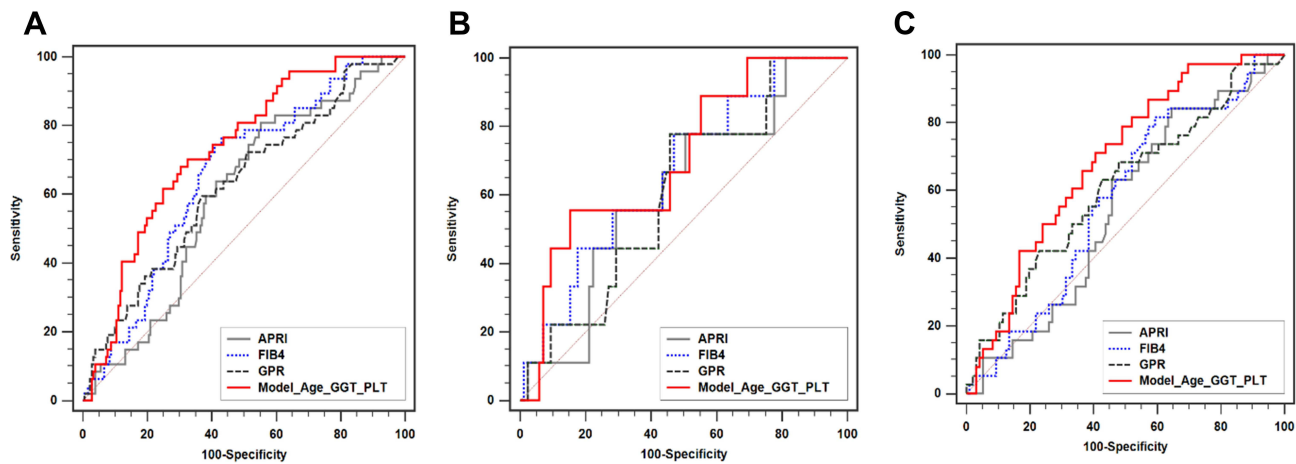


Figure 1 Comparison of AUROC between Model (Age_GGT_PLT) and NSSs. **(A)** total population, **(B)** patients with compensated LC, **(C)** patients with DC. **Abbreviations:** AUROC, area under the receiver operating characteristic curve; NSS, noninvasive scoring systems; DC, decompensated cirrhosis; LC, liver cirrhosis; GGT, gamma-glutamyl transferase; PLT, platelet; GPR, gamma-glutamyl transpeptidase to plate ratio; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, fibrosis-4 index.

developed: Model (Age_GGT_PLT)(y=1). The AUROC of Model (Age_GGT_PLT) was 0.729, which was significantly higher than APRI, GPR, and FIB-4 (AUROC: 0.596, 0.625, and 0.654, respectively, all $P < 0.05$) (Figure 1A). For patients with DC, Model (Age_GGT_PLT) had a higher AUROC (0.689) than APRI and FIB-4 (AUROC: 0.545, and 0.573, respectively; $P = 0.01$ and 0.03 , respectively) (Figure 1C), but not higher than GPR (AUROC: 0.608, $P = 0.16$) (Figure 1C).

Moreover, for the 228 patients, FIB-4 had a higher AUROC than APRI ($P < 0.01$) (Figure 1A). On the other hand, no significant difference was detected in AUROC between the three NSSs for both compensated LC and DC groups (Figure 1B and C).

Correlation Between APRI, GPR, FIB-4, and Model (Age_GGT_PLT)

Model (Age_GGT_PLT) was positively correlated with APRI, GPR, and FIB-4 (all $P < 0.05$). For patients with DC, Model (Age_GGT_PLT) was also positively correlated with MELD score and AFP (both $P < 0.05$). In addition, APRI, GPR, and FIB-4 showed a positive correlation with MELD and AFP (all $P < 0.05$) (Figure 2).

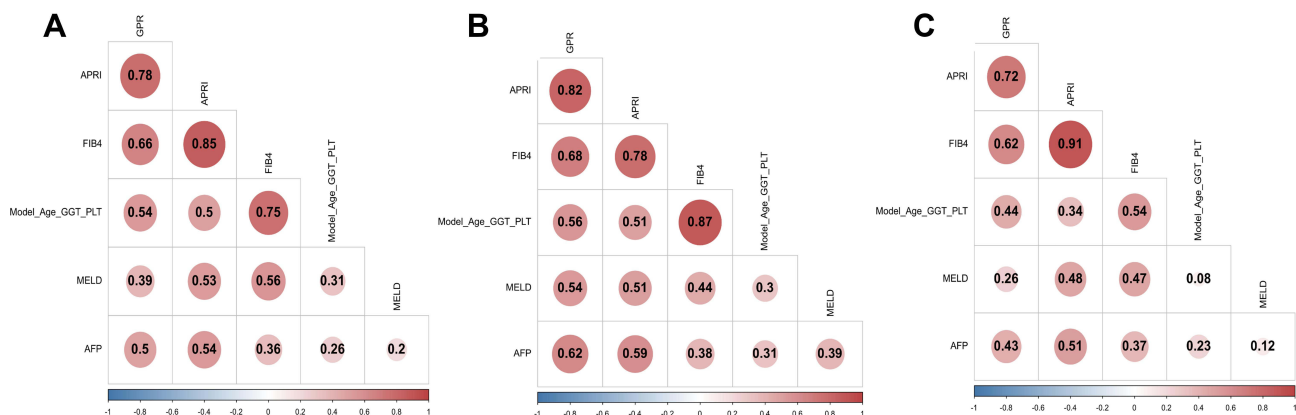


Figure 2 Correlation analysis between Model (Age_GGT_PLT), NSSs, MELD, and AFP. **(A)** total population, **(B)** patients with compensated LC, **(C)** patients with DC. **Abbreviations:** NSSs, noninvasive scoring systems; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein; GGT, gamma-glutamyl transpeptidase; PLT, platelet.

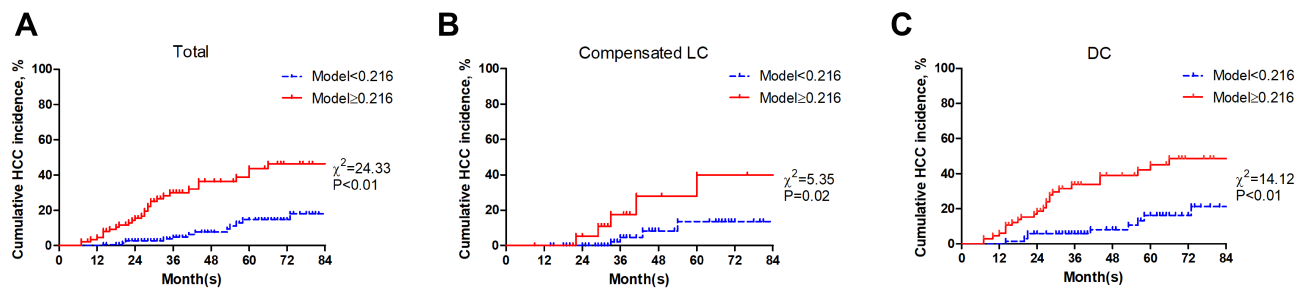


Figure 3 Kaplan–Meier analysis of Model (Age_GGT_PLT) in patients with liver cirrhosis. **(A)** total population, **(B)** patients with compensated LC, **(C)** patients with DC. **Abbreviations:** LC, liver cirrhosis; DC, decompensated cirrhosis; GGT, gamma-glutamyl transpeptidase; PLT, platelet.

Risk Stratification for Cumulative Incidence of HCC

With an optimal cutoff value of 0.216, Model (Age_GGT_PLT) achieved 68.09% sensitivity and 69.61% specificity (Youden index=0.377). Then, the patients were divided into two groups: low-risk (Model (Age_GGT_PLT) <0.216) and high-risk (Model (Age_GGT_PLT) ≥0.216). The patients were well stratified in both compensated LC and DC groups (both $P < 0.05$) (Figure 3).

Discussion

Herein, we evaluated the predictive accuracy of NSSs in patients with LC, which showed that APRI, GPR, and FIB-4 have a non-optimal ability to predict HCC development. Multivariate analysis showed that age, GGT, and PLT were independent risk factors for HCC development. A model encompassing age, GGT, and PLT was superior to NSSs in predicting HCC development, especially for patients with DC.

Although a sustainable virological response was achieved, the incidence of HCC remained high in patients with liver cirrhosis, especially in those with DC.⁶ Recent studies reported that the risk of HCC differs extensively across etiologies, age, and sex in patients with cirrhosis.^{25,26} Thus, HCC surveillance in elderly patients with HBV or HCV-related LC is imperative. NSSs, including APRI, GPR, FIB-4, is a risk factor for HCC development in patients with CHB and fatty liver disease.^{16,27,28} In the present study, APRI, GPR, and FIB-4 presented similar abilities in predicting HCC development in patients with DC, but neither was optimal according to AUROC (all <0.7). Thus, it is speculated that cirrhosis influences the predictive accuracy of NSSs.

The present study showed that age, GGT, and PLT are the independent risk factors for HCC development in patients with LC. Data from another study showed that serum GGT during antiviral treatment is associated with HCC development in non-cirrhotic elderly patients; however, the correlation was not significant in cirrhotic patients.²⁹ In the present study, the new model incorporating age, GGT, and PLT, was superior to NSSs in the total population and in patients with DC, but not in those with compensated LC, which could be attributed to the limited sample size in the compensated LC group. In addition, Kaplan–Meier analysis showed that the new model was valuable in both compensated LC and DC groups. Since a high risk of HCC exists in patients with DC, the new model is recommended in clinical practice.

Strikingly, the present study has several limitations. First, it is a single-center study with a limited sample size, thereby necessitating prospective multi-center study to substantiate these results. Second, HBV DNA at baseline, the genotypes, and mutations of HBV were not analyzed. Third, the family history of HCC was not collected in the present study.

Conclusions

NSSs, including APRI, GPR, and FIB-4, presents a non-optimal accuracy in predicting HCC development, and a new model consisting of age, GGT, and PLT provides an accurate prediction in patients with HBV-related DC and sustained virological response.

Abbreviations

HCC, hepatocellular carcinoma; LC, liver cirrhosis; DC, decompensated cirrhosis; CHB, chronic hepatitis B; HBV, hepatitis B virus; HCV, hepatitis C virus; NSS, noninvasive scoring system; FIB-4, fibrosis-4; APRI, aminotransferase-to-platelet ratio index; GPR, gamma-glutamyl transpeptidase to platelet ratio; MELD, model for end-stage liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; AFP, alpha-fetoprotein; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio; PLT, platelet; AUROC, area under the receiver operating characteristic curve; Model (Age_GGT_PLT), a model consisting of age, gamma-glutamyl transpeptidase, and platelet.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Third People's Hospital of Changzhou. All methods were carried out according to the Declaration of Helsinki, 2013, and written informed consent was obtained from all participants.

Consent for Publication

Consent for publication was obtained from all participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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