

# Diagnostic and Prognostic Value of Aspartate Transaminase-to-platelet Ratio Index, Gamma-glutamyl Transpeptidase-to-platelet Ratio, and Fibrosis-4 for Compensated Hepatitis B-related Liver Cirrhosis

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## ABSTRACT

The aim of this study was to investigate a serodiagnostic model as a substitute for liver stiffness measurement (LSM) for diagnosing compensated liver cirrhosis (LC). This retrospective study included 150 patients with compensated hepatitis B-related LC and 153 with chronic Hepatitis B virus (HBV) infection. It was conducted from May 2017 to June 2022 at Qinghai University Affiliated Hospital, China. The values of LSM, aspartate transaminase-to-platelet ratio index (APRI), gamma-glutamyl transpeptidase-to-platelet ratio (GPR), and fibrosis-4 (FIB-4) were evaluated in all admitted patients. The diagnostic value of APRI, GPR, FIB-4, and LSM was assessed using the receiver operating characteristic (ROC) curve. FIB-4 score (AUC=0.842; specificity=77.8%; sensitivity=80.7%; cut-off=2.824) was the best substitute for LSM from the three serum scoring models. The Cox regression model indicated that a FIB-4 score  $\geq 2.824$  was an independent predictor of prognosis for compensated hepatitis B-related LC (HR=1.15, 95%CI: 1.07-1.23,  $p<0.001$ ). This study's findings suggested that FIB-4 could be the best substitute for LSM and may help to assess LC prognosis.

**Key Words:** APRI, GPR, FIB-4, LSM, Diagnosis, Liver cirrhosis.

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Liver cirrhosis (LC) is a terminal liver disease with various aetiologies and is a common cause of death globally.<sup>1</sup> It can be categorised into compensated stage (asymptomatic stage) or a decompensated stage (symptomatic stage) according to severity; the decompensated stage is associated with higher mortality. Recent studies have confirmed that compensated LC can be evaluated using non-invasive tools.<sup>2</sup> These include transient elastography (TE) and serum scoring models, which can assess the degree of liver fibrosis (LF) or LC by calculating the liver stiffness measurement (LSM) value, which is one of the most valuable diagnostic and evaluation methods for LC besides liver biopsy. However, LSM is not widespread in primary healthcare clinics. Therefore, identifying serodiagnostic models such as aspartate transaminase-to-platelet ratio index (APRI), gamma-glutamyl transpeptidase-to-platelet ratio (GPR), and fibrosis-4 (FIB-4) to predict LF and compensated LC is crucial.

In this study, it was aimed to compare the accuracy or performance of these scores in predicting LC and identify the best substitute for LSM.

The Ethics Committee of the Qinghai University Affiliated Hospital approved this retrospective case-control study (registration number: SL-2019058). All patients provided written informed consent. All patients who had received LSM and been diagnosed with compensated hepatitis B-related LC or chronic HBV infection between May 2017 and June 2022 at the hospital were included in the study. Diagnostic criteria for chronic HBV infection and compensated hepatitis B-related LC were based on The Guidelines of Prevention and Treatment for Chronic Hepatitis B (China, version 2019).<sup>3</sup> The inclusion criteria were meeting the diagnostic criteria for chronic HBV infection or compensated hepatitis B-related cirrhosis and patients who received LSM. The exclusion criteria were coexistent haematological diseases, co-infection with other hepatitis viruses, the presence of other liver diseases, such as primary liver cancer, autoimmune liver disease, drug-induced liver disease, alcohol-related or metabolic-related liver disease, decompensated LC, and acute liver failure; and having recently been on antiplatelet treatment.

Patients were divided into group A (patients diagnosed with chronic HBV infection) and group B (patients diagnosed with compensated hepatitis B-related LC); they were further divided into the control and observation groups within groups A and B, respectively.

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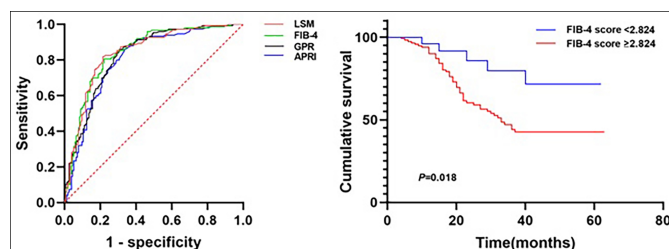
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**Table I: Demographic, baseline laboratory data, and three models of groups A and B [mean ± SD/median (IQR)/n(%)].**

Variable	Group A (n=153)	Group B (n=150)	z/t/c <sup>2</sup>	p
Age (years)	50.58±11.62	55.42±11.10	-3.705	<0.001
Male	92 (60.13)	101 (67.33)	1.699	0.192
LSM (kpa)	6.10 (4.50)	18.95 (24.75)	-10.259	<0.001
AST (U/L)	27.00 (17.50)	44.00 (54.25)	-6.959	<0.001
ALT (U/L)	29.00 (27.00)	36.00 (64.75)	-2.653	0.008
GGT (U/L)	25.00 (46.5)	68.50 (127.25)	-7.407	<0.001
ALP (U/L)	87.00 (40.50)	124.00 (64.50)	-6.909	<0.001
CHE (U/L)	7728.00 (3812.00)	4678.50 (3837.50)	-7.098	<0.001
TBIL (umol/L)	16.10 (13.30)	25.05 (22.52)	-5.836	<0.001
WBC (×10 <sup>9</sup> /L)	4.81 (2.06)	3.93 (2.63)	-4.109	<0.001
HB (g/L)	151.00 (33.00)	136.50 (47.25)	-4.396	<0.001
PLT (×10 <sup>9</sup> /L)	160.00 (104.50)	83.50 (66.25)	-8.758	<0.001
APRI	0.48 (0.69)	1.80 (2.54)	-9.200	<0.001
FIB-4	1.56 (1.21)	5.33 (5.47)	-10.304	<0.001
GPR	0.36(0.80)	2.06(3.71)	-9.790	<0.001

**Figure 1: Diagnostic and prognostic values of the FIB-4 score.**

The data were collected regarding gender, age, haemoglobin (Hb), white blood cell (WBC), platelets (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST),  $\gamma$ -glutamyltransferase (GGT), alkaline phosphatase (ALP), cholinesterase (CHE), total bilirubin (TBIL), and LSM values. The calculation of the three scoring models is as follows:

$$\text{APRI} = [\text{AST}/\text{ULN (upper limit of normal)} \times 100] / \text{PLT} (\times 10^9/\text{L})$$

$$\text{GPR} = \text{GGT}/\text{ULN} \times 100 / \text{PLT} (\times 10^9/\text{L})$$

$$\text{FIB-4} = [(\text{age} \times \text{AST})] / [(\text{PLT} (\times 10^9/\text{L}) \times \sqrt{\text{ALT}})]$$

The diagnostic value of the three scoring models and LSM was assessed using the receiver operating characteristic (ROC) curve. The best serum scoring model was that model, which had a diagnostic value closest to the LSM. Furthermore, subgroup analysis was performed in group B, which was divided into groups B1 (patients whose score  $\geq$  the optimal cut-off value) and B2 (patients whose score < the optimal cut-off value) based on the optimal cut-off of the best scoring model. The two subgroups were followed up, and the final events were the onset of decompensated cirrhosis, complications (such as ascites, esophagogastric variceal bleeding, spontaneous peritonitis, hepatic encephalopathy, and liver cancer) or death. The follow-up period was from May 2017 to June 2022. Finally, a multivariate Cox model was used to identify independent risk factors affecting the prognosis of compensated hepatitis B-related LC.

Statistical processing was performed using SPSS 25.0, and graphs were generated using GraphPad Prism 8 software.

Continuous data are expressed as mean  $\pm$  standard deviation or median (interquartile range [IQR]) and were compared using the t-test or Mann-Whitney U test. Statistical significance was set at  $p < 0.05$ .

A total of 303 patients were included in this study and were assigned to either the chronic HBV infection group (group A,  $n=153$ ) or the compensated hepatitis B-related cirrhosis group (group B,  $n=150$ ). During follow-up, 51 patients had decompensation of liver disease, 32 died of cirrhosis-related complications, 11 from ascites, 5 from esophagogastric variceal bleeding, and 3 from primary liver cancer. By the time follow-up was completed, 72 patients had no decompensation, and 27 patients were lost to follow-up.

The gender composition ratio did not significantly differ between the two groups. Group B had significantly higher values for age, LSM, AST, ALT, GGT, and ALP, but lower CHE, WBC, Hb, and PLT than that in group A. Group B had significantly higher APRI, FIB-4, and GPR scores ( $p < 0.001$ , Table I) than that in group A. The APRI ( $r_s=0.39$ ), FIB-4 ( $r_s=0.36$ ), and GPR ( $r_s=0.31$ ) were positively correlated with the LSM value in group B according to Spearman correlation analysis ( $p < 0.001$ ).

The areas under the curve (AUCs) of APRI, FIB-4, GPR, and LSM were 0.806, 0.842, 0.825, and 0.841, respectively ( $p < 0.001$ ). The FIB-4 score had the largest AUC (0.842), which was the closest to the LSM value, indicating that the FIB-4 score may be a better substitute for LSM. The specificity and sensitivity of the FIB-4 score were 0.778 and 0.807, respectively, and the best cut-off was 2.824 (Figure 1).

The optimal cut-off of the FIB-4 score was 2.824, and group B was divided into group B1 (patients with a FIB-4 score  $\geq 2.824$ ,  $n=121$ ) and group B2 (patients with a FIB-4 score < 2.824,  $n=29$ ). Subsequently, these two subgroups were followed from May 2017 to June 2022. Compared with group B2 (median survival time: 52 months [95%CI: 44.1–59.6]), group B1 (median survival time: 33 months [95%CI:

26.3-39.7)] had a significantly lower cumulative survival rate (log-rank  $\chi^2=5.629$ ,  $p=0.018$ , Figure 1). "Survival" here means no progression of compensated hepatitis B-related LC or no death. LSM, APRI, GPR, and FIB-4 scores were included in the multivariate Cox regression model. Multivariate Cox regression analysis indicated that a higher FIB-4 score ( $\geq 2.824$ ) was an independent prognostic predictor for compensated hepatitis B-related LC (HR=1.15, 95%CI: 1.07-1.23,  $p < 0.001$ ).

Liver biopsy is an expansive and invasive medical procedure with possible complications, such as pain (20%), bleeding (0.5%), infection, and abdominal organ injury, which may restrict its clinical use.<sup>4</sup> There are no advanced medical devices in some rural and non-modernised areas worldwide but only access to routine blood tests, liver function tests, and other fundamental tests. These findings promote the progress of convenient and non-invasive serum diagnosis of LC.

In summary, the mechanism of serum diagnostic models evaluating LF or LC is currently unclear; however, this uncertainty does not affect their application. Undoubtedly, FibroScan (especially LSM) is better than non-invasive serum scoring models for the early diagnosis of advanced LF and compensated LC.<sup>5,6</sup> The present findings also confirmed that LSM had a more significant diagnostic value than APRI, GPR, or FIB-4 in predicting compensated hepatitis B-related cirrhosis. FIB-4, which had the largest AUC, was the best serum scoring model to diagnose LC; therefore, it could be the best substitute for FibroScan in rural and non-modernised healthcare clinics. In addition, patients with a higher FIB-4 score ( $\geq 2.82$ ) had poorer prognoses and required prompt treatment. Non-invasive serum diagnostic methods are of considerable value; however, they cannot replace conventional tests such as special laboratory tests, imaging tests, ultrasound examinations, and liver biopsies in comprehensive hospitals. This study has some limitations, including the single-centre nature of research, a small patient cohort, and a lack of contrast with other aetiologies of cirrhosis. Further studies are required to provide a more representative outlook on the findings.

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## ETHICAL APPROVAL:

This study obtained approval from the Ethics Committee of the Qinghai University Affiliated Hospital (registration number: SL-2019058).

## PATIENTS' CONSENT:

All patients provided their written informed consent and agreed to the use of clinical data for publication and academic research.

## COMPETING INTEREST:

The authors declared no competing interest.

## AUTHORS' CONTRIBUTION:

JT: Substantial contributions to the conception and design, analysis of data, and drafted the manuscript.

WL, XM, QA: Acquisition and arrangement of data, follow-up investigation of patients.

SK, XW: Review and editing, and gave some important intellectual advice.

All the authors have approved the final version of the manuscript to be published.

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