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# Assessing the consistency of FIB-4, APRI, and GPR in evaluating significant liver fibrosis and cirrhosis in COVID-19 patients with concurrent liver diseases

Pan Yan[2†], Xiaoping Yu[3†], Zhu Chen[4†], Lijuan Lan[1], Jun Kang[1], Bennan Zhao[1] and Dafeng Liu[1,5*]

## Abstract

**Objective** This study investigated the consistency of the FIB-4, APRI, and GPR indices in assessing significant liver fibrosis and cirrhosis in patients with Coronavirus Disease 2019(COVID-19) who also suffer from various liver diseases, providing references for the clinical selection and application for non-invasive assessment methods.

**Methods** The study evaluated 744 COVID-19 patients with coexisting liver diseases: 508 cases with non-alcoholic fatty liver disease (NAFLD), 158 cases with chronic hepatitis B (CHB), and 78 cases with a combination of both ailments. FIB-4, APRI, and GPR were employed to assess significant liver fibrosis and cirrhosis. Concordance among the methods was determined using Kappa analysis, and receiver operating characteristic (ROC) curves helped identify the optimal cutoff values for each index.

**Results** For COVID-19 patients with NAFLD, Kappa values for significant liver fibrosis were 0.81, 0.90, 0.80, and 0.79, and for cirrhosis, they were 0.88, 0.97,0.88, and 0.88, respectively (all $p < 0.05$). Among those with CHB, Kappa values were 0.81, 0.81, 0.83, and 0.75 for fibrosis, and0.87, 0.91, 0.88, and 0.92 for cirrhosis (all $p < 0.05$). In patients with coexisting liver diseases, the values were 0.87, 0.86, 0.86, and 0.78 for fibrosis, and 0.67, 0.69, 0.54, and 0.81for cirrhosis (all $p < 0.05$). Linear trend analysis revealed significant relationships between FIB-4 values, APRI values, GPR values, and the severity of COVID-19 ($\chi^2$ trend: 15.205,35.114, and 13.973, respectively, all $p < 0.001$), between FIB-4 values and APRI values and the coronavirus negative conversion time (all $p < 0.05$) in COVID-19 with NAFLD, and between FIB-4 values and GPR values and the coronavirus negative conversion time in patients with COVID-19 with CHB(all $p < 0.05$).

**Conclusion** Using the current cutoff values, the non-invasive assessments demonstrated almost perfect consistency in evaluating significant liver fibrosis and cirrhosis in COVID-19 patients with liver diseases, though FIB-4 and GPR showed moderate consistency in cirrhosis evaluation in patients with coexisting liver conditions. Moreover, it also

†Pan Yan, Xiaoping Yu and Zhu Chen contributed equally to this work.

*Correspondence:
Dafeng Liu
ldf312@126.com

Full list of author information is available at the end of the article

indicated that increased liver fibrosis correlates with more severe COVID-19 and prolonged coronavirus negative conversion time.

**Keywords** Coronavirus disease 2019(COVID-19), Non-alcoholic fatty liver disease(NAFLD), Chronic hepatitis B(CHB), Non-invasive assessment, Liver fibrosis, Cirrhosis, Kappa value

## Introduction

The global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has presented a substantial threat to public health. As of September 2, 2022, the total number of confirmed cases of infection reached 607, 013,841, with a reported death toll of 6,508,326 [1].

Coronaviruses had been shown to damage the liver through both direct and indirect mechanisms [1]. One of the mechanisms of direct liver injury is the cytokine storm mechanism, which included immune-mediated liver damage caused by severe inflammatory responses following SARS-CoV-2 infection. This mechanism is supported by the higher serum levels of inflammatory markers [IL-6, IL-2, C-reactive protein (CRP), and serum ferritin] [2]. Additionally, autopsy liver biopsies obtained from patients who died from COVID-19 revealed T-cell hyperactivation and microvesicular steatosis, indicating that the liver injury is most likely immune-mediated [3]. Another mechanism occurred through the transfer of the virus from the gastrointestinal tract to the liver. Coronaviruses induced systemic chronic inflammation, and intestinal barrier dysfunction played a major role in triggering and amplifying the inflammatory processes, thereby leading to the translocation of coronaviruses into the portal circulation and inducing hepatic inflammation [4]. Indirect liver injury may primarily occur through the following pathways: One of the mechanisms is the vascular-associated mechanism of COVID-19-mediated liver injury [5, 6]. An early series of autopsy liver biopsies from COVID-19 patients reported that at least 50% of the patients exhibited portal or sinusoidal vascular thrombosis [6], and COVID-19 patients also demonstrated coagulopathy and endotheliopathy [7]. Another mechanism was drug-induced liver injury. Clinical treatment recommendations for COVID-19 include the use of antiviral drugs such as tocilizumab, remdesivir, hydroxychloroquine, azithromycin, and traditional Chinese medicine. All of these medications have the potential to induce hepatotoxicity in certain patients [8–10].

A study involving 618 hospitalized COVID-19 patients revealed that chronic liver disease(OR 5.88, 95%CI 2.39–14.46; $p<0.001$) was an independent risk factor for poor prognosis [11]. Histological examinations have demonstrated that liver injury was more prevalent in patients with concurrent fatty liver and chronic viral hepatitis [12]. Moreover, the incidence of liver injury was higher in patients with severe coronavirus disease 2019 (COVID-19) [13]. Ji et al. [14]reported that 50% of 202 COVID-19-positive patients exhibited abnormal liver function at admission, with 75% developing liver dysfunction during hospitalization.

The global burden of pre-existing liver disease is significant, resulting in approximately 2 million deaths annually due to chronic liver disease, including chronic viral hepatitis such as chronic hepatitis B (CHB) and non-alcoholic fatty liver disease (NAFLD) [15]. Coronavirus infection can cause liver damage and/or exacerbate the progression of chronic liver diseases. Chronic liver injury may lead to liver fibrosis and subsequently advance to cirrhosis and hepatocellular carcinoma [16–19]. Therefore, the detection and staging of liver fibrosis is crucial.

Liver biopsy remains the gold standard for diagnosing liver fibrosis; however, the procedure had rarely been performed in patients with COVID-19. This was largely due to the urgency of their clinical conditions, which often surpass concerns about elevated liver enzyme levels. Additionally, the risks associated with invasive testing generally discourage biopsies in infected patients [12]. Moreover, liver biopsies assess only a limited part of the liver structure, which may result in false-negative findings, and this invasive procedure may carry the risk of serious complications [20–22].

Consequently, non-invasive methods for evaluating liver fibrosis, such as serologic tests, are necessary. Examples include the four-factor fibrosis index (FIB-4), the aspartate aminotransferase to platelet ratio index (APRI), and the gamma-glutamyl transpeptidase to platelet ratio (GPR), and other [23].

There were many studies on the use of FIB-4, APRI, and GPR for assessing liver fibrosis and cirrhosis in populations with chronic liver diseases, but most studies mainly focused on the assessment capabilities of non-invasive models. For instance, Lemoine et al. [24] confirmed that in a large cohort of 721 patients with HBV mono-infection, GPR demonstrated superior diagnostic performance over APRI and FIB-4 in predicting significant fibrosis and cirrhosis. A study indicated that 84% of patients with suspected NAFLD-related advanced fibrosis would be identified by the FIB-4 index and avoid a liver biopsy [25]. Regardless of HBeAg positivity or negativity, GPR exhibited optimal performance in predicting varying degrees of liver fibrosis [26].

However, in COVID-19 patients, most studies aimed to investigate the association between non-invasive assessment models and mortality in this population. For

example, FIB-4 scores was easily applicable and may be used to predict mortality in COVID-19 patients, but patients with chronic liver disease were excluded [26]. A study indicated patents with APRI higher than 1.5 and FIB-4 scores higher than 3.25 were, respectively 2.69 times and 3.13 times more likely to die during hospitalization for SARS-CoV-2 infection, but exclusion criteria accounted for patients who suffered from cirrhosis [27]. And another study investigated FIB-4, and APRI may be good predictors for death and discharge within 28 days in hospitalized patients with COVID-19 [28].

There are limited research on the non-invasive assessment of liver fibrosis and cirrhosis in COVID-19 patients with concurrent liver diseases, particularly literature on the consistency of FIB-4, APRI, and GPR in assessing significant liver fibrosis and cirrhosis. Additionally, few studies have identified the most effective assessment methods for different liver conditions to enhance diagnostic accuracy. Although FIB-4, APRI, and GPR are widely used, each non-invasive assessment method has distinct strengths and weaknesses, for example, the FIB-4 is the most rigorously studied biomarker for fibrosis in NAFLD and NASH [29, 30]. Moreover, FIB-4 requires minimal information for calculation, making it a cost-effective and implementable tool in primary care settings [31]. APRI is a reliable tool to differentiate between patients with no fibrosis and patients with advanced fibrosis/cirrhosis, but it can not reliably discriminate between intermediate stages of fibrosis [32]. GPR demonstrated higher diagnostic performance than FIB-4 and APRI for assessing significant liver fibrosis and cirrhosis in patients with chronic hepatitis B [33]. However, the biggest drawback of three non-assessment methods is inability to differentiate between specific stages of fibrosis. The accuracy of these assessments is also influenced by the chosen cutoff values, which can significantly affect the results.

Therefore, to fill the research gap, this study employs three common non-invasive assessment methods—FIB-4, APRI, and GPR—to evaluate the degree of liver fibrosis in COVID-19 patients with various liver diseases. By selecting appropriate cutoff values from existing literature, this study investigates the consistency of these methods in yielding assessment results.

## Materials and methods

### Study population

This cross-sectional study involved 744 patients diagnosed with COVID-19 and various liver diseases. These patients were admitted to the First and Second hospital isolation ward and presented at Public Health Clinical Center of Chengdu from January 16, 2020, to September 30, 2021. The study received approval from the Ethics Committee of Public Health and Clinical Center of Chengdu (No.: PJ-K2020-26-01). The need for written informed consent was waived by the Ethics Committee due to the retrospective nature of the study, the use of anonymized data, and the urgent need to evaluate an emerging infectious disease.

### Inclusion criteria

Participants were included if they met the following criteria: (1) 18 years ≤ age ≤ 65 years [34]; (2) hospitalization with COVID-19;(3)initial positive test result for SARS-CoV-2; (4) liver steatosis identified by abdominal ultrasound within the past 6 months, a clinical diagnosis of non-alcoholic fatty liver disease (NAFLD), or a history of NAFLD; and/or (5)chronic hepatitis B (CHB) [33];

### Exclusion criteria

Patients were excluded if they: (1) age < 18 years; (2) age > 65 years [34]; (3) without COVID-19; (4) without liver disease; or (5) had liver conditions other than NAFLD, CHB, or a combination of NAFLD and CHB [35]; (6) Liver decompensation, or (7) immunosuppressive status (such as HIV infection, cancer, organ transplantation, bone marrow transplantation, or use of immunosuppressive agents within the last 3 months); (8) heavy alcohol consumption: history of alcohol consumption < 30 g/day for men and < 20 g/day for women [35–37].

ALT declines with advancing age and this generate lower specificity when testing individuals older than 65 years and unless an alternative cutoff is used [34]. Moreover, immunosuppressive status and/or heavy alcohol consumption may have an impact on the results.

Therefore, age, alcohol consumption, and immunosuppression status were restricted to control the impact of confounding factors on the results of this study.

### Grouping standards

The study comprised 744 patients with COVID-19 and various liver diseases. Of them, 508 patients (68.4%) with NAFLD were categorized into the COVID-19 with NAFLD group, 158 patients (21.2%) with CHB were assigned to the COVID-19 with CHB group, and 78 patients (10.4%) with coexistence of the two liver diseases were classified into the COVID-19 with NAFLD-CHB group.

### Diagnostic, clinical classification, and cure criteria

The diagnostic, clinical classification, and cure criteria for COVID-19 were based on the seventh edition of the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance [38]. NAFLD was characterized by macrovesicular or predominantly macrovesicular steatosis involving more than 5% of hepatocytes, which may be accompanied by mild nonspecific inflammation, the criteria of

disease diagnosis for NAFLD referred to Guidelines of prevention and treatment for nonalcoholic fatty liver disease: a 2018 update [39]; CHB was diagnosed as the persistent positivity of serum HBsAg and/or HBV DNA for >6 months, which was based on Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection [40]; and for liver fibrosis and cirrhosis were based on Guidelines for diagnosis and treatment of hepatic fibrosis with integrated traditional Chinese and Western medicine (2019 edition) [41]: Liver fibrosis is primarily characterized by the excessive proliferation and deposition of extracellular matrix (ECM) in liver tissue, which leads to abnormal changes in the tissue structural and impairing the normal physiological functions of the liver. The persistence of fibrosis, accompanied by the necrosis and apoptosis of normal hepatocytes and the accumulation of ECM, leads to the gradual replacement of liver parenchyma by scar tissue formed by ECM, resulting in cirrhosis, portal hypertension, or hepatocellular carcinoma, and ultimately leading to liver failure [42].

The METAVIR liver histopathological scoring system was used as a reference: non-significant fibrosis(< F2): no fibrosis or stellate enlargement of the portal area without the formation of fibrous septa; significant fibrosis (≥ F2): enlargement of the portal area with the formation of sparse fibrous septa or numerous fibrous septa; and cirrhosis (≥ F4) [23, 41, 43].

### Liver fibrosis score

The FIB-4, APRI, and GPR scores were calculated using the following published formulas [44].

$$FIB-4 = (AST\ value\ (U/L)) \times\ age\ (years) \Big/ \sqrt{(\ \text{platelet count}(10^9/\text{L})) \times\ (\text{ALT value (U/L)})}$$

$$APRI = (AST\ value\ (U/L) \Big/ upper\ limit\ of\ normal\ AST\ value\ (U/L)) \Big/ (\ platelet\ count(109/L)\ \times\ 100$$

$$GPR = (GGT\ value\ (U/L)) \Big/ upper\ limit\ of\ normal\ GGT\ value\ (U/L)) \Big/ (\ platelet\ count(109/L)\ \times\ 100$$

### Diagnostic thresholds of non-invasive assessment models for significant fibrosis and cirrhosis

Because there are limited research on the non-invasive assessment of liver fibrosis and cirrhosis in COVID-19 patients with concurrent liver diseases, so the cutoff values in this study were derived from general liver disease populations. Diagnostic thresholds for non-invasive assessments of significant liver fibrosis and cirrhosis were established using metrics such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), Youden's index, and the area under the ROC curve(AUROC).The cutoff values for COVID-19 patients with NAFLD and those with NAFLD-CHB were detailed in Table 1.

For COVID-19 patients with CHB, the optimal GPR cutoff values for predicting significant fibrosis and cirrhosis were 0.32(AUROC = 0.80, 95% CI: 0.72–0.88) and 0.56(AUROC = 0.83, 95% CI: 0.72–0.94), respectively [47], and GPR demonstrated a higher predictive value compared to FIB-4 (AUROC = 0.66, 95% CI: 0.56–0.76, $p = 0.003$) and APRI (AUROC = 0.66, 95% CI: 0.57–0.76, $p < 0.001$). The diagnostic accuracy for significant fibrosis was maximized using cutoff values yielding the highest Youden's index; these values were 0.58 for APRI and 2.07 for FIB-4, with accuracy rates of 65.2% and 71.1%, respectively. For cirrhosis diagnosis, the highest accuracy was attained at a specificity of 80%, with APRI and FIB-4

**Table 1** Diagnostic thresholds for non-invasive assessment models for significant fibrosis and cirrhosis in patients with COVID-19 and NAFLD or NAFLD-CHB

| | | Cutoff values | Sensitivity (%) | Specificity (%) | AUC | PPV(%) | NPV(%) | Ref |
|---|---|---|---|---|---|---|---|---|
| COVID-19 with NAFLD | | | | | | | | |
| FIB-4 | ≥F2 | 1.3 | 84.4 | 68.5 | 0.85 | | | [45] |
| | ≥F4 | 3.25 | 38 | 96 | 0.84 | | | |
| APRI | ≥F2 | 1.5 | 84 | 96.1 | 0.83 | | | |
| GPR | ≥F2 | 0.49 | 83 | 80 | 0.86 | | | [37] |
| | ≥F4 | 0.74 | 100 | 100 | 0.92 | | | |
| COVID-19 with NAFLD-CHB | | | | | | | | |
| FIB-4 | ≥F2 | 0.77 | 86 | 36 | | 37 | 84 | [46] |
| | ≥F4 | 0.91 | 100 | 49 | | 14 | 100 | |
| APRI | ≥F2 | 0.41 | 80 | 59 | | 47 | 87 | |
| | ≥F4 | 0.55 | 100 | 69 | | 21 | 100 | |
| GPR | ≥F2 | 0.49 | 83 | 80 | | 65 | 91 | |
| | ≥F4 | 0.74 | 100 | 100 | | 100 | 100 | |

cutoff values of 1.33 and 2.49, achieving accuracy rates of 72.3% and 75.9%, respectively [48].

### Data collection

Data were systematically collected and recorded, including gender, age, underlying conditions(such as hypertension, hyperlipidemia, diabetes, and cardiac disease), clinical and demographic data, lymphocyte counts, and their subsets from 744 subjects.The accuracy, completeness, and authenticity of the data were strictly maintained, and a comprehensive database was established.

**Table 2** Patients' characteristics

| Characteristic | COVID-19 with NAFLD(*n* = 508) | COVID-19 with CHB(*n* = 158) | COVID-19 with NAFLD-CHB(*n* = 78) | *P* value |
|---|---|---|---|---|
| Age | 40.90 ± 11.15 | 40.09 ± 12.14 | 43.03 ± 10.78 | 0.103 |
| coronavirus negative conversion time | 12.74 ± 10.41 | 14.66 ± 10.26 | 14.95 ± 11.74 | 0.08 |
| PLT | 244.61 ± 60.00 | 200.30 ± 64.52 | 224.79 ± 53.28 | < 0.001 |
| ALT | 52.78 ± 38.97 | 30.80 ± 21.08 | 54.99 ± 67.65 | < 0.001 |
| AST | 31.52 ± 15.85 | 28.52 ± 12.79 | 34.97 ± 39.41 | 0.005 |
| ALP | 75.13 ± 21.23 | 70.11 ± 27.92 | 71.47 ± 23.45 | 0.002 |
| GGT | 47.93 ± 37.10 | 25.90 ± 18.89 | 46.46 ± 40.93 | < 0.001 |
| Albumin | 42.87 ± 3.71 | 41.42 ± 4.21 | 42.21 ± 6.22 | < 0.001 |
| TBIL | 9.39 ± 4.76 | 9.95 ± 5.38 | 9.83 ± 5.04 | 0.387 |
| FIB-4 | 0.85 ± 0.57 | 1.30 ± 1.04 | 1.03 ± 0.63 | < 0.001 |
| APRI | 0.38 ± 0.26 | 0.47 ± 0.45 | 0.44 ± 0.40 | 0.000 |
| GPR | 0.42 ± 0.36 | 0.30 ± 0.30 | 0.44 ± 0.47 | < 0.001 |
| Male(%) | 435(85.6) | 101(63.9) | 64(82.1) | < 0.001 |
| Female(%) | 73(14.4) | 57(36.1) | 14(17.9) | |
| Cardiopathy(%) | 19(3.7) | 2(1.3) | 2(2.6) | 0.281 |
| Hypertension(%) | 94(18.5) | 8(5.1) | 18(23.1) | < 0.001 |
| Diabetes(%) | 55(10.8) | 10(6.3) | 9(11.5) | 0.223 |
| Hyperlipidemia (%) | 126(24.8) | 20(12.7) | 15(19.2) | 0.004 |
| asymptomatic infected(%) | 159(31.3) | 52(32.9) | 23(29.5) | 0.003 |
| Mild types(%) | 75(14.8) | 44(27.8) | 11(14.1) | |
| Moderate types (%) | 254(50.0) | 62(39.3) | 44(56.4) | |
| Severe types(%) | 11(2.2) | | | |
| Critical types(%) | 7(1.4) | | | |
| Liver function abnormalities(%) | 331(65.2) | 89(56.3) | 58(74.4) | 0.022 |

Note: Data are expressed as means with standard deviations or percentages

Abbreviations: NAFLD, non-alcoholic fatty liver disease; CHB, chronic hepatitis B; NAFLD-CHB, co-infection of NAFLD and CHB; PLT, platelets count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, Gamma-glutamyl transpeptidase; TBIL, total bilirubin; FIB-4,Fibrosis-4 index; APRI, aspartate aminotransferase-to-platelet ratio index; GPR, gamma-glutamyl transpeptidase-to-platelet ratio

### Statistical analysis

Statistical analyses and plotting were conducted using SPSS software version 27.0. Quantitative data exhibiting a normal distribution are presented as mean standard deviation ( $\overline{x}\pm$ s). Group comparisons utilized independent sample t-tests and analysis of variance (ANOVA). Qualitative data were expressed as percentages, with intergroup comparisons performed using the chi-square test. Non-parametric rank sum tests were employed to investigate the relationship between clinical symptoms of COVID-19 and the FIB-4, APRI, and GPR scores. Trends in the occurrence of severe COVID-19 were assessed using chi-square tests for FIB-4, APRI, and GPR assessments, while ANOVA tested the relationship of these scores to the duration of virus negative conversion. Multivariable logistic regression was used to control for confounding factors. Fleiss kappa analysis was used to evaluate concurrent concordance among all three non-invasive assessment methods, while pairwise kappa analysis was applied for comparisons between any two methods. The interpretation of kappa values was as follows: <0.2 indicated "slight" consistency; 0.2–0.39 considered "fair"; 0.4–0.59 suggested moderate consistency; 0.6–0.79 as "substantial"; and 0.8-1.0 denoted "excellent" or "almost perfect" level of concordance. A significance level of $\alpha = 0.05$ was set for all analyses.

## Results

### Baseline characteristics of study patients

Significant differences were observed in quantitative indices such as platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, FIB-4, APRI, and GPR among three groups (all $P < 0.05$). Additionally, there were statistically significant differences in gender distribution, COVID-19 clinical staging, and the percentage of liver function abnormalities among three groups (all $P < 0.05$). Detailed baseline data were shown in Table 2.

### Multivariable logistic regression analysis of factors associated with the degree of liver fibrosis in COVID-19 patients with concurrent liver diseases

Multivariable logistic regression analysis indicated that factors including gender, heart disease, diabetes, Hypertension and hyperlipidemia demonstrated no statistically significant impact on the degree of liver fibrosis in COVID-19 patients with coexisting liver diseases (all $p > 0.05$), as demonstrated in Table 3. This was likely

**Table 3** Multivariable logistic regression analysis of factors associated with the degree of liver fibrosis in COVID-19 patients with concurrent liver diseases

| | | B | Standard error | *P* value | Exp(B) | 95% CI |
|---|---|---|---|---|---|---|
| COVID-19 with NAFLD | | | | | | |
| ≥F2 | gender | 0.870 | 1.024 | 0.367 | 2.386 | 0.361–15.788 |
| | Cardiopathy | 1.316 | 1.452 | 0.365 | 3.729 | 0.217–64.149 |
| | Hypertension | 0.777 | 1.024 | 0.448 | 2.176 | 0.293–16.181 |
| | Diabetes | 0.379 | 1.270 | 0.776 | 1.46 | 0.121–17.589 |
| | Hyperlipidemia | 0.862 | 0.301 | 0.427 | 2.368 | 1.312–4.275 |
| ≥F4 | gender | 0.117 | 1.007 | 0.908 | 1.124 | 0.156–8.088 |
| | Cardiopathy | 0.829 | 1.509 | 0.583 | 2.291 | 0.119–44.141 |
| | Hypertension | 0.162 | 1.071 | 0.880 | 1.176 | 0.144–9.586 |
| | Diabetes | 0.814 | 0.534 | 0.127 | 2.256 | 0.793–6.423 |
| | Hyperlipidemia | 0.358 | 0.365 | 0.327 | 1.43 | 0.669–2.925 |
| COVID-19 with CHB | | | | | | |
| ≥F2 | gender | 0.293 | 0.533 | 0.583 | 1.340 | 0.471–3.808 |
| | Cardiopathy | -13.993 | 219.050 | 0.995 | 6.261 | 0.472–21.440 |
| | Hypertension | 1.128 | 0.909 | 0.215 | 3.089 | 0.520–18.333 |
| | Diabetes | 0.807 | 0.868 | 0.353 | 2.242 | 0.409–12.297 |
| | Hyperlipidemia | 0.154 | 0.725 | 0.831 | 1.167 | 0.282–4.831 |
| ≥F4 | gender | 1.080 | 0.747 | 0.148 | 2.944 | 0.681–12.721 |
| | Cardiopathy | -0.978 | 1.119 | 0.382 | 0.376 | 0.042–3.371 |
| | Hypertension | -0.032 | 1.449 | 0.982 | 0.969 | 0.057–16.566 |
| | Diabetes | -0.520 | 1.440 | 0.718 | 0.595 | 0.035–9.994 |
| | Hyperlipidemia | -2.175 | 1.204 | 0.071 | 0.114 | 0.011–1.204 |
| COVID-19 with NAFLD-CHB | | | | | | |
| ≥F2 | gender | 0.936 | 0.692 | 0.176 | 2.549 | 0.657–9.889 |
| | Cardiopathy | -1.130 | 1.511 | 0.455 | 0.323 | 0.017–6.249 |
| | Hypertension | 1.490 | 0.749 | 0.057 | 4.436 | 1.022–19.242 |
| | Diabetes | 0.159 | 0.848 | 0.852 | 1.172 | 0.223–6.170 |
| | Hyperlipidemia | -0.396 | 0.697 | 0.570 | 0.673 | 0.172–2.640 |
| ≥F4 | gender | -0.096 | 1.050 | 0.927 | 0.909 | 0.116–7.123 |
| | Cardiopathy | 0.367 | 0.866 | 0.672 | 1.443 | 0.265–7.872 |
| | Hypertension | -1.185 | 1.028 | 0.249 | 0.306 | 0.041–2.291 |
| | Diabetes | 0.849 | 1.289 | 0.510 | 2.338 | 0.187–29.258 |
| | Hyperlipidemia | 0.236 | 1.109 | 0.831 | 1.267 | 0.144–11.123 |

Note: < F2: Non-significant liver fibrosis; ≥F2: Significant liver fibrosis; ≥F4: Cirrhosis

because these factors were already accounted for in the selection of cutoff values. Therefore, the cutoff values established in this study were also suitable for liver disease patients with comorbidities.

### Liver enzymeanalysis at admission in COVID-19 patients combined with different liver diseases

At admission, significant differences in ALT, GGT, and albumin levels were identified among three groups (all $P<0.001$), those COVID-19 patients with NAFLD and with NAFLD-CHB had higher ALT, GGT, and albumin levels cpmpared with those COVID-19 patients with CHB, as illustrated in Table 2; Fig. 1.

### Non-invasive assessment models for significant fibrosis and cirrhosis using FIB-4, APRI, and GPR

Evaluations of non-significant liver fibrosis, significant fibrosis, and cirrhosis using FIB-4 and APRI assessments revealed statistically significant differences among three groups (all $p<0.001$), and the percentage of cirrhosis using FIB-4 and APRI assessments in those COVID-19 patients with CHB and with NAFLD-CHB were higher than that in those those COVID-19 patients with NAFLD, as shown in Table 4.

### FIB-4, APRI, and GPR values impacting on disease severity of COVID-19 patients

In COVID-19 patients with concurrent NAFLD, significant differences in FIB-4, APRI, and GPR values were observed across clinical stages (all $p<0.05$). Notably, FIB-4 values in the moderate and severe type groups

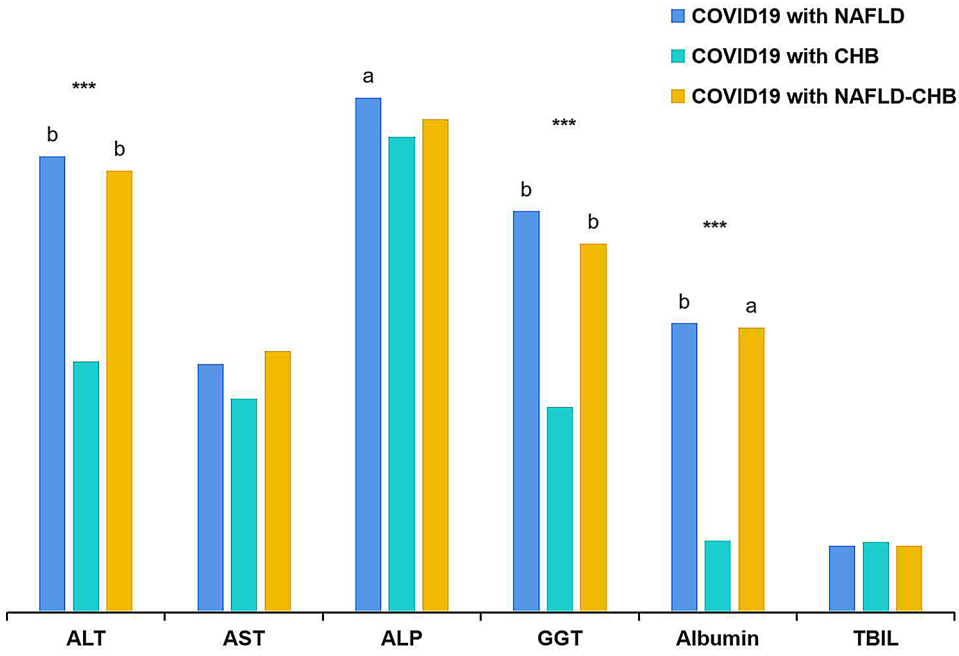


**Fig. 1** Analysis of liver enzymes at admission in patients with COVID-19 combined with different liver diseases. $^{***}P$ <0.001; $^{a}P$ <0.05; $^{b}P$ <0.001, compared with COVID-19 patients and CHB

**Table 4** Evaluation of liver fibrosis severity in COVID-19 patients with different liver diseases using FIB-4, APRI, and GPR

| | | COVID-19 with NAFLD(*n* = 508) | COVID-19 with CHB(*n* = 158) | COVID-19 with NAFLD-CHB(*n* = 78) | *P* value |
|---|---|---|---|---|---|
| FIB-4 | < F2 | 455(89.6) | 135(85.4) | 34(43.6) | < 0.001 |
| | ≥F2 | 47(9.3) | 6(3.8) | 3(3.8) | |
| | ≥F4 | 6(1.2) | 17(10.8) | 41(52.6) | |
| APRI | < F2 | 505(99.4) | 124(78.5) | 51(78.5) | < 0.001 |
| | ≥F2 | | 30(19.0) | 10(19.0) | |
| | ≥F4 | 3(0.6) | 4(2.5) | 7(2.5) | |
| GPR | < F2 | 367(72.2) | 118(74.7) | 56(71.8) | 0.916 |
| | ≥F2 | 79(15.6) | 24(15.2) | 11(14.1) | |
| | ≥F4 | 62(12.2) | 16(10.1) | 11(14.1) | |

Note: Data are presented as percentages

< F2: Non-significant liver fibrosis; ≥F2: Significant liver fibrosis; ≥F4: Cirrhosis

were significantly different from those in asymptomatic and mild type groups (all $p < 0.05$). APRI values showed significant differences between the moderate and severe type groups compared to asymptomatic individuals. Additionally, GPR values differed significantly between the moderate type group and asymptomatic individuals, as well as between the severe type group and the mild type group (all $p < 0.05$) (Fig. 2 (a-c)), as illustrated in Fig. 2.

### Linear trend analysis of critical COVID-19 and non-invasive assessments: FIB-4, APRI, and GPR

For this analysis, severe and critical types of COVID-19 were combined into a single "severe" group, while all other cases were categorized as "non-severe". Because no severe cases were observed in patients with COVID-19 combined with chronic hepatitis B or those with both liver diseases, the analysis focused on patients with COVID-19 and concurrent NAFLD. The $\chi^2$ trend test results showed that higher FIB-4, APRI, and GPR assessments were associated with an increased incidence of severe COVID-19. A significant linear relationship was found between the degree of liver fibrosis and the incidence of severe COVID-19, with $\chi^2$ trend values of 15.205, 35.114, and 13.973, respectively(all $p < 0.001$), as shown in Table 5.

### Linear trend analysis of FIB-4, APRI, and GPR with coronavirus negative conversion time

The results of the ANOVA trend test indicated that in patients with COVID-19 and NAFLD, higher FIB-4 and APRI values were correlated with extending coronavirus negative conversion time. A significant linear relationship between both FIB-4 and APRI values and the coronavirus negative conversion time was observed (all $p < 0.05$) (Fig. 3 (a, b)). Similarly, in patients with COVID-19 combined with CHB, a significant linear trend was also found between FIB-4 and GPR values and the coronavirus negative conversion time (all $p < 0.05$) (Fig. 3 (c, d)), as illustrated in Table 6; Fig. 3.

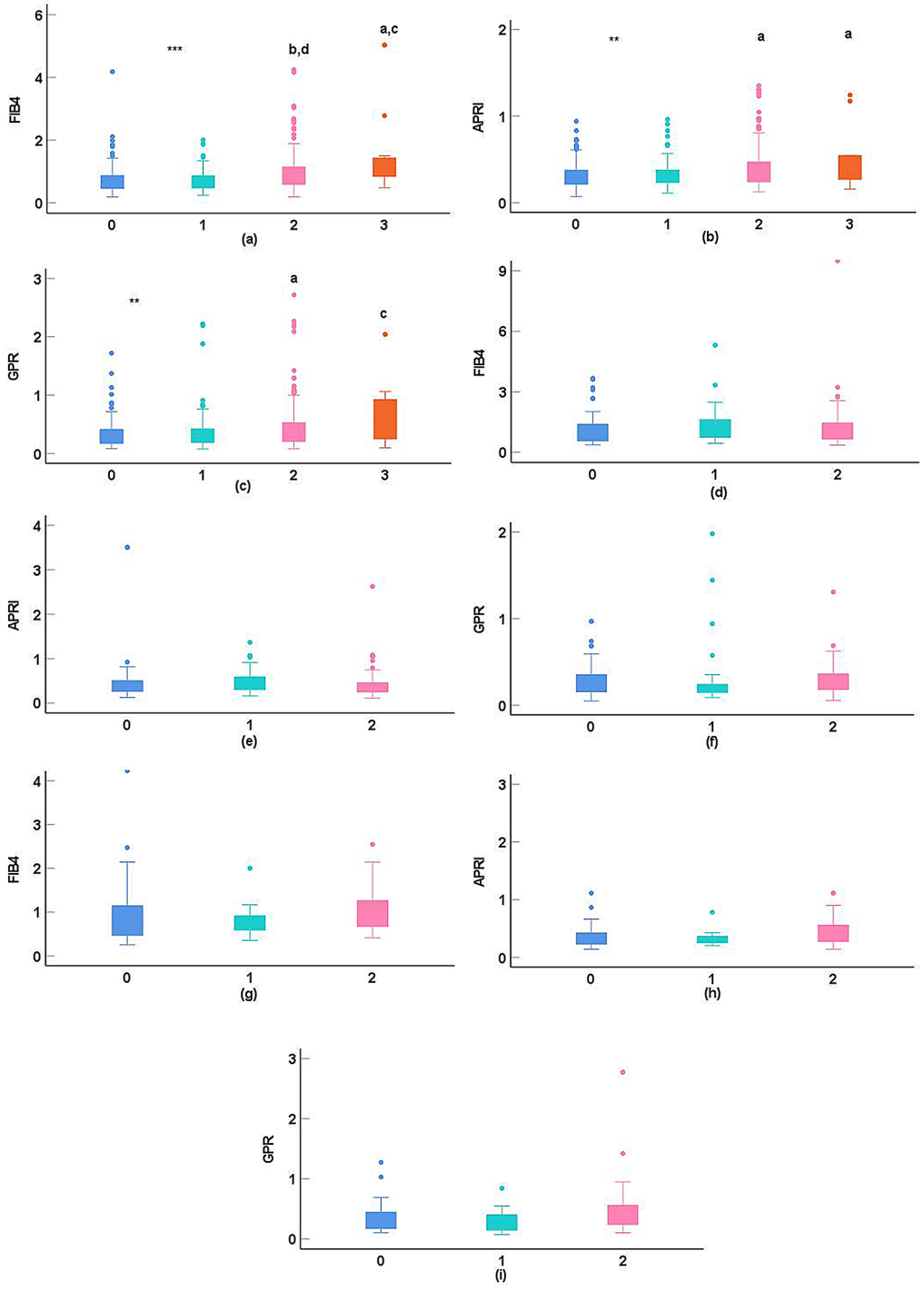


**Fig. 2** FIB-4, APRI, and GPR values impacting on disease severity of COVID-19 patients. (**a**–**c**): Effect on FIB-4, APRI, and GPR in COVID-19 with NAFLD. (**d**–**f**): Effect on FIB-4, APRI, and GPR in COVID-19 with CHB. (**g**–**i**): Effect on FIB-4, APRI, and GPR in COVID-19 with NAFLD-CHB. 0: Asymptomatic; 1: Mild; 2: Moderate; 3: Severe. $^{**}P$ <0.01; $^{***}P$ <0.001. $^{a}p$<0.05, $^{b}p$<0.01, compared with Asymptomatic $^{c}p$<0.05, $^{d}p$<0.01, compared with Mild

**Within-group concordance analysis of significant liver fibrosis and cirrhosis assessed using FIB-4, APRI, and GPR**

Kappa values for the assessment of significant liver fibrosis using all three methods—FIB-4, APRI, and GPR, simultaneously, as well as for pairwise comparisons of any two methods, are presented below. For patients with COVID-19 and NAFLD, the Kappa values for significant liver fibrosis were 0.81, 0.90, 0.80, and 0.79, respectively (all $p < 0.05$), and for cirrhosis were 0.88,0.97,0.88, and 0.88, respectively(all $p < 0.05$) (Table 7). For patients with

**Table 5** Linear trend analysis of severe COVID-19 incidence using FIB-4, APRI, and GPR

| | | < F2 | ≥F2 | ≥F4 | $\chi^2$value | *P* trend |
|---|---|---|---|---|---|---|
| FIB-4 | non-severe | 441(90.0) | 45(9.2) | 4(0.8) | 15.205 | < 0.001 |
| | severe | 12(66.7) | 4(22.2) | 2(11.1) | | |
| APRI | non-severe | 489(99.8) | | 1(0.2) | 35.114 | < 0.001 |
| | severe | 16(88.9) | | 2(11.1) | | |
| GPR | non-severe | 361(73.7) | 74(15.1) | 55(11.2) | 13.973 | < 0.001 |
| | severe | 7(38.9) | 4(22.2) | 7(38.9) | | |

Note: Data are expressed as percentages

< F2: Non-significant fibrosis; ≥F2: Significant fibrosis;≥F4: Cirrhosis

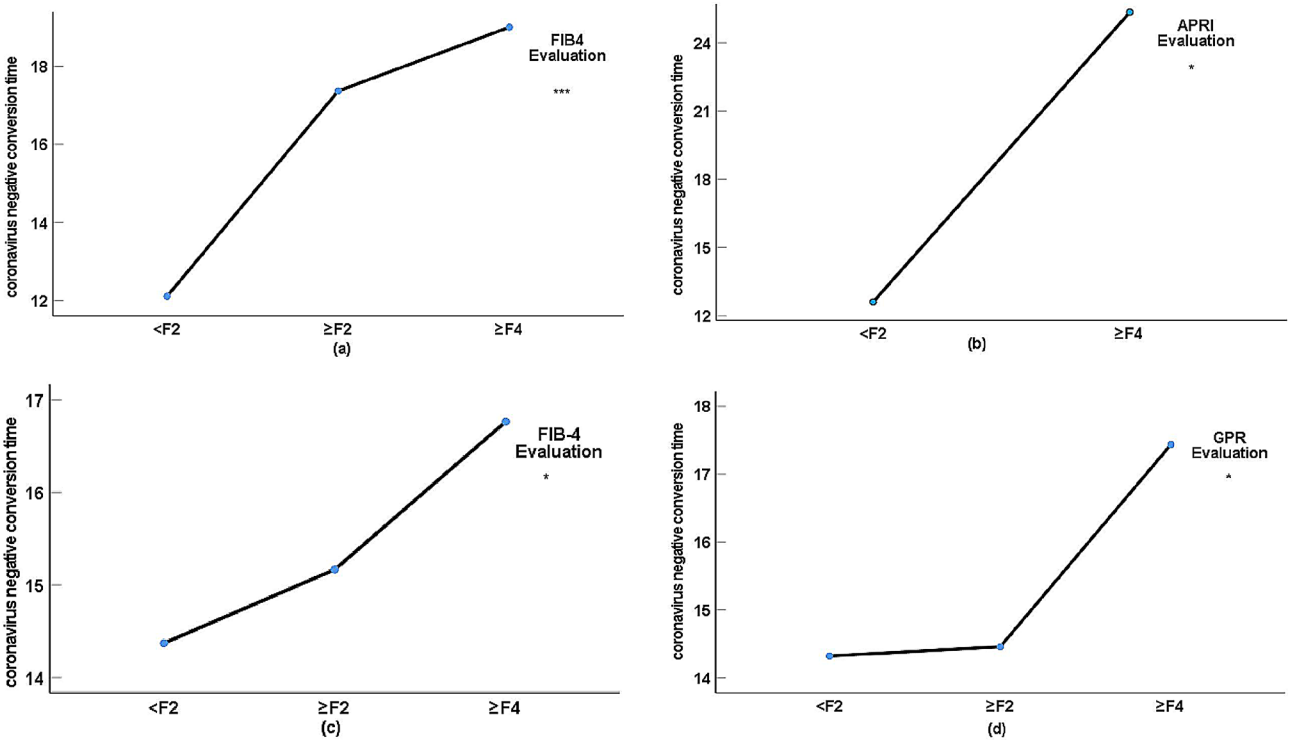


**Fig. 3** Impact of FIB-4, APRI, and GPR on coronavirus negative conversion time (**a**, **b**): Effects of FIB-4 and APRI on coronavirus negative conversion time in COVID-19 with NAFLD. (**c**, **d**): Effects of FIB-4 and GPR on coronavirus negative conversion time in COVID-19 with CHB. < F2: non-significant liver fibrosis; ≥F2: significant liver fibrosis; ≥F4: cirrhosis. $^{*}P$ <0.05,$^{***}P$<0.001

COVID-19 and CHB, the Kappa values for significant liver fibrosis were 0.81, 0.81,0.83, and 0.75, respectively(all $p < 0.05$), and for cirrhosis were 0.87,0.91,0.88, and 0.92, respectively (all $p < 0.05$) (Table 8). Among patients with COVID-19 combined with coexistence of two liver diseases, the Kappa values for significant liver fibrosis were 0.87,0.86,0.86, and 0.78,respectively (all $p < 0.05$),and for cirrhosis were 0.67,0.69,0.54, and 0.81, respectively(all $p < 0.05$) (Table 9).

## Discussion

In our study, we selected three groups of patients with COVID-19 and various liver diseases to assess significant liver fibrosis and cirrhosis using FIB-4, APRI, and GPR simultaneously, as well as any combination of two methods. Kappa analysis was subsequently conducted to evaluate the consistency of these non-invasive assessment methods.

The results indicated that the consistency in evaluating non-significant liver fibrosis, significant liver fibrosis, and cirrhosis among patients with COVID-19 combined with NAFLD and COVID-19 with CHB was very strong, regardless of whether FIB-4, APRI, and GPR were used simultaneously or in combination with two methods. Especially when using FIB-4 and APRI, the assessment of liver fibrosis and cirrhosis was almost perfect level of concordance(kappa ≥ 0.8) in COVID-19 with NAFLD. In COVID-19 with CHB, the consistency in assessing significant liver fibrosis with FIB-4 and GPR, as well as in assessing cirrhosis with APRI and GPR, was excellent (kappa ≥ 0.8), respectively. In patients with COVID-19 and coexisting NAFLD and CHB, the consistency of

**Table 6** The impact of FIB-4, APRI, and GPR on coronavirus negative conversion time

| | | COVID-19 with NAFLD($n=508$) | COVID-19 with CHB($n=158$) | COVID-19 with NAFLD-CHB($n=78$) |
|---|---|---|---|---|
| FIB-4 | < F2 | 12.11 ± 10.08 | 14.37 ± 10.66 | 14.24 ± 7.20 |
| | ≥F2 | 17.37 ± 12.24 | 15.17 ± 7.65 | 11.00 ± 3.46 |
| | ≥F4 | 19.00 ± 9.88 | 16.76 ± 7.55 | 15.83 ± 14.82 |
| | *P* trend | < 0.001 | 0.036 | 0.556 |
| APRI | < F2 | 12.61 ± 10.41 | 14.21 ± 10.85 | 13.08 ± 6.69 |
| | ≥F2 | | 16.53 ± 7.91 | 24.4 ± 24.52 |
| | ≥F4 | 25.33 ± 2.52 | 14.50 ± 6.25 | 15.00 ± 10.87 |
| | *P* trend | 0.035 | 0.38 | 0.246 |
| GPR | < F2 | 11.70 ± 9.72 | 14.32 ± 10.72 | 14.71 ± 12.31 |
| | ≥F2 | 16.08 ± 13.23 | 14.46 ± 9.57 | 19.00 ± 13.52 |
| | ≥F4 | 14.32 ± 9.46 | 17.44 ± 7.44 | 12.09 ± 4.16 |
| | *P* trend | 0.65 | 0.025 | 0.808 |

**Table 7** Intragroup consistency of non-invasive assessment models for significant fibrosis and cirrhosis in patients with COVID-19 and NAFLD

| | | < F2 | ≥F2 | ≥F4 |
|---|---|---|---|---|
| FIB-4, APRI, GPR | Kappa value | 0.83 | 0.81 | 0.88 |
| | *P* value | < 0.01 | < 0.01 | < 0.001 |
| FIB-4 with APRI | Kappa value | 0.89 | 0.90 | 0.97 |
| | *P* value | < 0.001 | < 0.001 | < 0.001 |
| FIB-4 with GPR | Kappa value | 0.70 | 0.80 | 0.88 |
| | *P* value | < 0.05 | < 0.01 | < 0.001 |
| APRI with GPR | Kappa value | 0.70 | 0.79 | 0.88 |
| | *P* value | < 0.05 | < 0.05 | < 0.001 |

Note: 0.6–0.79 as "substantial"; and 0.8-1.0 denoted "excellent" or "almost perfect" level of concordance

**Table 8** Intragroup consistency of non-invasive assessment models for significant fibrosis and cirrhosis in patients with COVID-19 and CHB

| | | < F2 | ≥F2 | ≥F4 |
|---|---|---|---|---|
| FIB-4, APRI, GPR | Kappa value | 0.77 | 0.81 | 0.87 |
| | *P* value | < 0.05 | < 0.01 | < 0.01 |
| FIB-4 with APRI | Kappa value | 0.88 | 0.81 | 0.91 |
| | *P* value | < 0.001 | < 0.01 | < 0.001 |
| FIB-4 with GPR | Kappa value | 0.78 | 0.83 | 0.88 |
| | *P* value | < 0.05 | < 0.01 | < 0.001 |
| APRI with GPR | Kappa value | 0.78 | 0.75 | 0.92 |
| | *P* value | < 0.05 | < 0.05 | < 0.001 |

Note: 0.6–0.79 as "substantial"; and 0.8-1.0 denoted "excellent" or "almost perfect" level of concordance

the three non-invasive methods, as well as the combinations of APRI and GPR in assessing significant liver fibrosis, and cirrhosis was the almost perfect consistency (kappa ≥ 0.8), respectively. Furthermore, FIB-4 and APRI in assessing non-significant liver fibrosis was substantial (kappa: 0.6–0.79). However, the consistency between FIB-4 and GPR in evaluating non-significant liver fibrosis and cirrhosis was moderate (kappa: 0.4–0.59).

**Table 9** Intragroup consistency of non-invasive assessment models for significant fibrosis and cirrhosis in patients with COVID-19 andNAFLD-CHB

| | | < F2 | ≥F2 | ≥F4 |
|---|---|---|---|---|
| FIB-4, APRI, GPR | Kappa value | 0.62 | 0.87 | 0.67 |
| | *P* value | < 0.05 | < 0.01 | < 0.05 |
| FIB-4 with APRI | Kappa value | 0.72 | 0.86 | 0.69 |
| | *P* value | < 0.05 | < 0.01 | < 0.05 |
| FIB-4 with GPR | Kappa value | 0.55 | 0.86 | 0.54 |
| | *P* value | < 0.05 | < 0.01 | < 0.05 |
| APRI with GPR | Kappa value | 0.70 | 0.78 | 0.81 |
| | *P* value | < 0.05 | < 0.05 | < 0.01 |

Note: 0.4–0.59 suggested moderate consistency; 0.6–0.79 as "substantial"; and 0.8-1.0 denoted "excellent" or "almost perfect" level of concordance

From our study results, the evaluation outcomes for COVID-19 patients with NAFLD-CHB were more complex, which may be related to the fact that the clinical manifestations of coexisting dual liver diseases are more complicated than those of a single liver disease. For example, some studies had shown that CHB patients with concurrent NAFLD exhibit a higher hepatitis B surface antigen (HBsAg) clearance rate and may suppress HBV viral replication [49–51]. Hepatic steatosis had an impact on the HBV DNA clearance rate, HBeAg seroconversion, and ALT recovery rate in CHB patients undergoing antiviral therapy [52]. However, other related studies had confirmed that concurrent NAFLD may exacerbate the degree of liver fibrosis in patients [51, 53, 54]. Additionally, it was challenging to differentiate between NAFLD-mediated hepatocellular inflammatory injury and HBV-mediated immune-related inflammatory necrosis in CHB patients with concurrent NAFLD in clinical practice. In addition, the relationship between chronic HBV infection and metabolic factors still requires further research. Furthermore, the consistency between FIB-4 and GPR in evaluating non-significant liver fibrosis and cirrhosis was moderate in our study, and the reason may be as follows: for the diagnosis of cirrhosis, the AUROC of GPR was significantly higher than FIB-4 (0.92 vs. 0.73, $p < 0.001$). And for the diagnosis of significant fibrosis, GPR had a relatively higher PPV compared with FIB-4 (65% and 37%, respectively) [46]. However, we still need to optimize the cutoff values to improve the consistency of FIB-4 and GPR assessments.

In summary, for clinical application, FIB-4 and APRI are recommended to assess liver fibrosis and cirrhosis in COVID-19 patients with concurrent NAFLD. In COVID-19 patients with CHB, FIB-4 and GPR are recommended for significant liver fibrosis, while APRI and GPR are recommended for cirrhosis. For patients with COVID-19 and coexisting NAFLD and CHB, APRI and GPR are particularly recommended for cirrhosis evaluation.

Currently, there is limited literature on the consistency of FIB-4, APRI, and GPR in assessing significant liver

fibrosis and cirrhosis in patients with COVID-19 complicated by different liver diseases. Most studies mainly focused on the assessment capabilities of non-invasive models for liver fibrosis and cirrhosis.

Both the aspartate aminotransferase to platelet ratio index (APRI) and FIB-4 include variables associated with hepatic fibrosis, establishing their correlation with various stages of fibrosis [55]. Research indicated that by incorporating age, AST, ALT, and platelet levels, the FIB-4 index could effectively exclude significant liver fibrosis in chronic hepatitis B. However, FIB-4 may underestimate significant fibrosis in younger patients with lower platelet counts and may overestimate fibrosis in patients experiencing disease exacerbation. Nevertheless, it remained more accurate than APRI in ruling out severe fibrosis in chronic hepatitis B [56].

When evaluating the consistency between APRI and liver biopsy, studies have shown that APRI demonstrated better concordance with liver biopsy results for the diagnosis of cirrhosis in patients with autoimmune hepatitis [57]. However, APRI exhibited moderate diagnostic performance in predicting significant fibrosis, advanced fibrosis, and cirrhosis in patients with chronic hepatitis B [58]. In a study by Ekin et al. [59], nine non-invasive models were established, revealing that both APRI and GPR had AUROC values exceeding 0.70 for significant fibrosis, advanced fibrosis, and cirrhosis. GPR showed higher AUROC values for determining advanced fibrosis, while FIB-4 was more effective for diagnosing cirrhosis.

In the study conducted by LIU et al. [23], it was found that the FIB-4 index particularly effective for predicting significant liver fibrosis in patients with Hepatitis B e Antigen (HBeAg) positive. The AUROC values for predicting extensive fibrosis and cirrhosis using GPR and FIB-4 were significantly higher than those obtained with APRI. In contrast, among HBeAg negative patients, GPR and APRI demonstrated significantly greater AUROC values than FIB-4 for predicting both significant and extensive fibrosis, with GPR showing a higher AUROC for cirrhosis compared to APRI.

In patients with NAFLD, studies had demonstrated that employing APRI for liver fibrosis assessment can obviate the need for invasive liver biopsy histopathology [32]. A systematic review by Lee et al. [60] indicated that while FIB-4 and APRI have limited utility in predicting fibrosis staging, they could effectively predict liver disease morbidity and mortality at levels comparable to liver biopsy. Additionally, APRI was identified as a better predictor of advanced fibrosis than FIB-4 in affected patients and was suitable for ruling out advanced fibrosis in individuals without disease [25]. However, some literature had indicated that there was no significant difference in the area under the curve (AUC) for GPR, APRI, and FIB-4 when assessing significant liver fibrosis in patients with NAFLD [37].

In patients with coexisting NAFLD and CHB, Li et al. [46]. reported no statistically significant difference in the ability of GPR and APRI to predict cirrhosis. GPR demonstrated a strong negative predictive value (NPV) for ruling out significant fibrosis, severe fibrosis, and cirrhosis.However, the positive predictive value (PPV) for diagnosing these conditions was relatively low. Similarly, in this study, the PPV for diagnosing significant and severe fibrosis, as well as cirrhosis with APRI and FIB-4, was also low and even lower than that of GPR.

To sum up, the predictive accuracy of liver fibrosis assessment varies among the three methods—FIB-4, APRI, and GPR—depending on the specific liver disease and the stage of hepatic fibrosis in most studies. Consequently, selecting an appropriate non-invasive method for assessing liver fibrosis staging across different liver diseases poses a challenge, particularly as there is limited research on non-invasive liver fibrosis assessment in patients with COVID-19 and concurrent liver diseases.

The results of this study established a foundation for the clinical application of non-invasive assessment methods, such as FIB-4, APRI, and GPR, in evaluating significant hepatic fibrosis and cirrhosis in patients with COVID-19 and concurrent liver diseases. In addition to analyzing the consistency of these non-invasive methods for assessing hepatic fibrosis, our study examined their relationship with the clinical severity of COVID-19, the incidence of severe disease, and the time to coronavirus negative conversion.

when assessing the relationship between critical COVID-19 and non-invasive assessments: FIB-4, APRI, and GPR, we found a significant linear relationship between the degree of liver fibrosis and the incidence of severe COVID-19 in patients with NAFLD, indicating that the degree of liver fibrosis also influenced the incidence of severe COVID-19. Furthermore, our study also identified a significant linear relationship between FIB-4 and APRI values and the coronavirus negative conversion time in patients with COVID-19 with NAFLD. Similarly, in patients with COVID-19 combined with CHB, a significant linear trend was also found between FIB-4 and GPR values and the coronavirus negative conversion time. This suggested that increased liver fibrosis correlates with a longer time to coronavirus negative conversion. The potential reasons may include the following: one was due to changes in the immune system [61], SARS-CoV-2 infection can trigger an exaggerated immune response, leading to a life-threatening cytokine storm characterized by the release of pro-inflammatory cytokines and inflammatory markers [62]. NAFLD had been associated with decreased baseline lung function, and an increase in the degree of liver fibrosis correlated

with a more pronounced decline in forced vital capacity [63], and this risk was exacerbated in patients with advanced liver disease [64]. Furthermore, the presence of NAFLD in patients with community-acquired pneumonia had been linked to a higher rate of 30-day all-cause mortality, particularly in individuals with advanced liver fibrosis [61]. Another reasons was that some medications used to treat SARS-CoV-2 may pose hepatotoxic risks. For instance, prolonged high-dose use of corticosteroids can increase the risk of hepatitis B virus reactivation [65, 66]. Chronic hepatitis B directly contributes to the severity of SARS-CoV-2 infection and COVID-19 hospitalization, independent of potential confounding factors such as smoking, Body Mass Index(BMI), and type 2 diabetes [67, 68].

Additionally, our findings had been confirmed by other researches. Evidence suggested that NAFLD not only adversely affected lung function in healthy populations but also had an independent association with the severity of COVID-19 in infected patients, regardless of obesity or other metabolic syndromes, highlighting its significance as a risk factor for exacerbations and severity of COVID-19 [61]. Targher et al. [67] reported a significant correlation between increased liver fibrosis scores and the risk of developing severe COVID-19 disease.

Liu et al. [69]demonstrated that NAFLD was a risk factor for prolonged time to viral negativity, positively correlating with the duration of viral turnover. A study by Ji et al. [4] similarly found that patients with NAFLD faced a higher risk of severe COVID-19 and extended viral shedding. Our research further confirmed these findings, revealing a significant linear relationship between FIB-4 and APRI values and the time to coronavirus negative conversion in patients with COVID-19 and NAFLD. This suggested that increased liver fibrosis correlates with a longer time to coronavirus negative conversion.

In summary, although this is a cross-sectional study. It is still an earlier study on the consistency of FIB-4, APRI, and GPR in assessing significant liver fibrosis and cirrhosis in patients with COVID-19 complicated by different liver diseases. Furthermore, the results further confirm the clinical utility of non-invasive assessment methods, providing support for the further promotion of FIB-4, APRI, GPR, and other non-invasive models in the clinical practice of assessing liver fibrosis and cirrhosis, especially in the clinical application of infectious diseases combined with different liver diseases.

However, this study lacks liver biopsy data for COVID-19 patients with concurrent liver diseases. Consequently, no consistency test was performed between non-invasive assessment methods and the gold standard of liver biopsy, which may potentially affect the assessment capability. In the future, incorporating more liver biopsy data from COVID-19 patients and identifying optimal cutoff values for each non-invasive assessment model based on these data will enhance the clinical application of non-invasive assessment models.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03770-w.

Supplementary Material 1

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**Author contributions**
PY: Conceptualization, Study design, Execution, Data acquisition, Analysis and interpretation, Funding acquisition, Resources provision, Supervision, Validation, Writing - original draft, Writing - review & editing.
XY: Conceptualization, Study design, Execution, Data acquisition, Analysis and interpretation, Funding acquisition, Resources provision, Supervision, Validation, Writing - original draft, Writing - review & editing.
ZC: Conceptualization, Study design, Execution, Data acquisition, Analysis and interpretation, Funding acquisition, Resources provision, Supervision, Validation, Writing - original draft, Writing - review & editing.
LL: Conceptualization, Study design, Execution, Data acquisition, Analysis and interpretation, Funding acquisition, Resources provision, Supervision, Validation, Writing - original draft, Writing - review & editing.
JK: Conceptualization, Study design, Execution, Data acquisition, Analysis and interpretation, Funding acquisition, Resources provision, Supervision, Validation, Writing - original draft, Writing - review & editing.
BZ: Conceptualization, Study design, Execution, Data acquisition, Analysis and interpretation, Funding acquisition, Resources provision, Supervision, Validation, Writing - original draft, Writing - review & editing.
DL: Conceptualization, Study design, Execution, Data acquisition, Analysis and interpretation, Funding acquisition, Resources provision, Supervision, Validation, Writing - original draft, Writing - review & editing.

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**Data availability**
All data used in this study are available from the corresponding author upon request: Dafeng Liu, E-mail: liudf312@126.com. This statement is consistent with the the manuscript file.

## Declarations

**Ethics approval and consent to participate**
This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of- helsinki/). Ethical approval for this research was obtained from the Ethics Committee of the Public Health and Clinical Center of Chengdu (No.: PJ-K2020-26-01). The ethics committee/institutional review board waived the requirement for written informed consent from the participants or their legal guardians/next of kin due to the retrospective nature of the study, the use of anonymized data, and the provision of comprehensive verbal and written information to all patients regarding the study's purpose and potential implications. The study was conducted in accordance with local legislation and institutional requirements.

**Consent for publication**
All of the participants understand that the information will be published without their child or ward's/their relative's (circle as appropriate) name attached but that full anonymity cannot be guaranteed. All of the participants understand that the text and any pictures or videos published in the article will be freely available on the internet and may be seen by the general public. The pictures, videos and text may also appear on other websites or in print

and may be translated into other languages or used for commercial purposes. All of the participants were offered the opportunity to read the manuscript.

**Competing interests**
The authors declare no competing interests.

**Author details**
[1]The First Ward of Internal Medicine, Public Health Clinical Centre of Chengdu, Chengdu, Sichuan Province 610060, China
[2]School of Public Health, Chengdu Medical College, Chengdu, Sichuan Province 610500, China
[3]School of Preclinical Medicine, Chengdu University, Chengdu, Sichuan Province 610106, China
[4]Department of Drug Clinical Trial Center, Public Health Clinical Centre of Chengdu, Chengdu, Sichuan Province 610060, China
[5]No.377 Jingming Road, Jinjiang District, Chengdu City, Sichuan Province Chengdu 610060, China

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