Review Article
Liver Fibrosis Scores and Hospitalization, Mechanical Ventilation, Severity, and Death in Patients with COVID-19: A Systematic Review and Dose-Response Meta-Analysis

Menglu Liu,1 Kaibo Mei,2 Ziqi Tan,3 Shan Huang,4 Fuwei Liu,5 Chao Deng,6 Jianyong Ma,7 Peng Yu1,3,8 and Xiao Liu18

1Department of Cardiology, The Seventh People’s Hospital of Zhengzhou, Zhengzhou, Henan, China
2Department of Anesthesiology, The People’s Hospital of Shangrao, Shangrao, Jiangxi, China
3Department of Endocrine, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
4Department of Psychiatry, The Third People’s Hospital of Gan Zhou, Ganzhou, Jiangxi, China
5Department of Cardiology, The Affiliated Ganzhou Hospital of Nanchang University, Ganzhou, Jiangxi, China
6Department of Cardiology, The Affiliated Hospital of Jiangxi University of Chinese Medicine, Nanchang, Jiangxi, China
7Department of Pharmacology and Systems Physiology, University of Cincinnati College of Medicine, Cincinnati, OH, USA
8Institute for the Study of Endocrinology and Metabolism in Jiangxi, Nanchang, China

Correspondence should be addressed to Peng Yu; yupeng_jxndefy@163.com and Xiao Liu; kellyclarkwei@vip.qq.com

Received 6 December 2021; Accepted 18 February 2022; Published 29 March 2022

Academic Editor: Giovanni Marasco

Copyright © 2022 Menglu Liu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background and Aim. The relationship between liver fibrosis scores and clinical outcomes in patients with COVID-19 is not compressively assessed. Methods. We identified relevant cohort studies that assessed the relationship between liver fibrosis scores (e.g., FIB-4, NAFLD fibrosis score (NFS), and aspartate aminotransferase to platelet ratio index (APRI)) and associated prognosis outcomes by searching the PubMed, EMBASE, and medRxiv databases. The potential dose-response effect was performed using a stage robust error meta-regression. Results. Sixteen studies with 8,736 hospitalized patients with COVID-19 were included. One-point score in FIB-4 increase was significantly associated with increased mechanical ventilation (RR: 2.23, 95% CI: 1.37–3.65, \(P < 0.001\)), severe COVID-19 (RR: 1.82, 95% CI: 1.53–2.16, \(P < 0.001\)), and death (RR: 1.47, 95% CI: 1.31–1.65, \(P < 0.001\)), rather than hospitalization (RR: 1.35, 95% CI: 0.72–2.56, \(P = 0.35\)). Furthermore, there is a significant positive linear relationship between FIB-4 and severe COVID-19 (\(P_{\text{nonlinearity}} = 0.12\)) and mortality (\(P_{\text{nonlinearity}} = 0.18\)). Regarding other liver scores, one unit elevation in APRI increased the risk of death by 178% (RR: 2.78, 95% CI: 1.10–6.99, \(P = 0.03\)). Higher NFS (≥1.5) and Forns index were associated with increased risk of severe COVID-19 and COVID-19-associated death. Conclusion. Our dose-response meta-analysis suggests high liver fibrosis scores are associated with worse prognosis in patients with COVID-19. For patients with COVID-19 at admission, especially for those with coexisting chronic liver diseases, assessment of liver fibrosis scores might be useful for identifying high risk of developing severe COVID-19 cases and worse outcomes.

1. Introduction

Chronic liver diseases occur very commonly worldwide and have become one of the major global health burdens [1]. Hepatic fibrosis is the early histological change before the development of cirrhosis which is the end sequela in many liver diseases (e.g., hepatitis B or hepatitis C virus infection, chronic alcoholism, and nonalcoholic fatty liver disease (NAFLD)) [2]. Noninvasive liver fibrosis scores have been developed to screen the extent of liver fibrosis (e.g., fibrosis-4 (FIB-4), NAFLD fibrosis score (NFS), and aspartate aminotransferase to platelet ratio index (APRI)) in chronic liver diseases and validated to use as prognostic indicators [3,4], for NAFLD [5,6], liver cancer [7], and patients infected with chronic hepatitis virus [8]. Moreover, they were also identified as diagnostic indicators in other population, such as
the general population or patients with established cardiovascular diseases [6,9].

Coronavirus disease 2019 (COVID-19), which is caused by SARS-CoV-2, resulted in over 5 million deaths worldwide. Accumulating evidence suggests that COVID-19 is more than a respiratory disease. Broad spectra of extrapulmonary manifestations, including heart, liver, and microvascular injuries, were also widely observed in patients with COVID-19. These extrapulmonary manifestations served as the strongest predictors for severity and mortality due to COVID-19 [10,11]. With the ongoing COVID-19 pandemic, preexisting chronic liver diseases are found to be one of the highest prevalent comorbidities [12]. Ji et al. reported that the NAFLD has been reported in up to 38% of patients with COVID-19, and it has been associated with a worse prognosis [13,14]. Moreover, the liver fibrosis score that assesses the advanced fibrosis (e.g., FIB-4 and NFS) was also correlated with increased risk for mechanical ventilation (MV), intensive care, and mortality [15,16]; however, with inconsistent results [17–19]. Furthermore, we noted that the liver fibrosis scores and clinical outcomes in patients with COVID-19 were not comprehensively assessed. Given these circumstances, this systematic review and meta-analysis aimed to evaluate the relationship between liver fibrosis scores and adverse outcomes in patients with COVID-19, as well as potential dose-response association.

2. Methods

This study is a PRISMA-compliant (2021) systematic review and meta-analysis [20]. In addition, the protocol was prospectively registered with the international prospective register of systematic reviews (PROSPERO), and the registration number is CRD42021265872 (see Supplementary Table S1).

2.1. Search Strategy. Four databases such as PubMed, Embase, medRxiv, and Cochrane Library were initially searched, up to June 5th 2021. The search terms on liver fibrosis scores (such as FIB-4, NFS, and APRI) and clinical outcomes (hospitalization, MV, intensive care unit (ICU) admission, severe COVID-19, and mortality) in patients with COVID-19 were used with no language restriction. Furthermore, case-control studies and articles reporting unadjusted results were excluded to reduce bias. Two authors (XL and PY) independently conducted the above process, and inconsistencies were rectified by discussing with the third author.

2.3. Data Collection and Quality Assessment. Data were extracted based on the prespecified inclusion criteria. The following information was abstracted: study characteristics (first author’s name, publication year, country in which the study was conducted, and study design), patient characteristics (sample size, age, and sex), exposures (number of fibrosis cases), and outcomes (number of events, adjusted ORs/RRs/HRs and the corresponding 95% CI, and adjustments).

The Newcastle–Ottawa quality scale (NOS) was applied to assess the quality of nonrandomized studies. Studies with a NOS of ≥6 stars were considered as moderate to high-quality articles [21].

2.4. Statistical Analysis. We used the random effect model to make our results more reliable, considering the potential heterogeneity. The study-specific RRs and 95% CIs for one-point increment in liver fibrosis scores were calculated using the Greenland and Longnecker method [22]. The nonlinear dose-response relationship was fitted following the method described by Xu and Doi [23]. It requires at least two levels of quantitative exposure categories and the corresponding RRs and variance estimates [23]. If the liver fibrosis score was not directly reported or reported in ranges, we estimated the midpoint of each category by averaging the lower and upper boundaries of that category [24,25]. If the highest or lowest class was open-ended, we assumed that the open-ended interval length was the same as the adjacent interval [26]. In this study, the OR and HR were equally treated as RR according to our previous articles [22]. ICU admission was also defined as severe COVID-19 as we previously described [27]. We evaluated the degree of heterogeneity among the studies included in the analysis using the $I^2$ test (25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively) [27,28]. Sensitivity analyses were performed by omitting each study in turn. Stata software (version 16.0) and RevMan software (version 5.3, Cochrane Collaboration, Nordic Cochrane Center Copenhagen, Denmark) were used for statistical analysis. All statistical tests were double-sided, and $P < 0.05$ considered statistically significant.

3. Results

3.1. Study Selection. As shown in Figure 1, 1737 studies were initially retrieved by searching the PubMed, Cochrane Library, medRxiv, and Embase databases. We excluded 421 duplicated records and 285 articles, which were not relevant to the study objective after reviewing the title and abstract. Sixteen articles [15,16,18,19,29–40] were finally included after excluding 15 reports for the following reasons: (1) reports that did not report the relevant clinical outcomes or
target population \((N=8)\), (2) elucidations that were case reports or consisted only of comments \((N=5)\), and (3) studies that reported results with an unadjusted estimate effect \((N=2)\). The detailed exclusion criteria for each study are described in Supplementary Table S3.

### 3.2. Study Characteristics and Study Quality

The basic characteristics of the studies included are described in Table 1. Overall, sixteen cohorts (fifteen retrospective \([15–19,29–34,36–40]\) and one prospective \([35]\)) involving 8,736 hospitalized patients with COVID-19 were included. All COVID-19 cases were diagnosed by real-time PCR. The mean age ranged from 47 to 72 years, and five reports were from the US. Five studies were from Europe, and six publications were from Asia. Ten \([15,16,29,31–34,36,38]\) articles reported FIB-4, three \([30,35,40]\) reported aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio, one \([39]\) reported NFS, one reported FIB-4 and NFS \([37]\), and one \([19]\) assessed FIB-4 and Forns index score. All studies were found to be acceptable \((N\geq6)\) elucidations assessed by the NOS (see Supplementary Table S4).

### 3.3. Dose-Response Relationship between FIB-4 and Clinical Outcomes in COVID-19

Thirteen \([15–29, 31–34, 36–38]\) studies reported FIB-4 and associated clinical outcomes in patients with COVID-19. Two studies reported hospitalization, two elucidations reported MV, five studies reported severity, and six studies reported death (Table 1). As shown in Figure 2, one-point score increase in FIB-4 was significantly associated with the increased MV \((RR: 2.23, 95\% CI: 1.37–3.65, P = 0.001, I^2 = 0\%)\), severe COVID-19 \((RR: 1.82, 95\% CI: 1.53–2.16, P < 0.001, I^2 = 0\%)\), and death \((RR: 1.47, 95\% CI: 1.31–1.65, P < 0.001, I^2 = 0\%)\), rather than hospitalization \((RR: 1.35, 95\% CI: 0.72–2.56, P = 0.35, I^2 = 0\%)\). All the pooled results showed no evidence of heterogeneity. In addition, there was a linear association between FIB-4 and severe COVID-19 \((P_{\text{nonlinearity}} = 0.12)\) and death \((P_{\text{nonlinearity}} = 0.18)\) in patients with COVID-19 (Figure 3).

### 3.4. Association between Other Liver Fibrosis Scores and Clinical Outcomes in COVID-19

Three studies reported an association between the AST/ALT ratio and death. The results showed that one unit elevation in AST/ALT ratio
| Author, year, country | Study design | Sample size | Population | Data source | Age, female | Liver score reported (outcomes) | Estimate effect | Adjustments |
|-----------------------|--------------|-------------|------------|-------------|------------|--------------------------------|---------------|-------------|
| Xiang, 2020 [38], China | Retrospective cohort | 267 | COVID-19 | Guangzhou No. 8 People’s hospital | 47, 54 | FIB-4 (IMV) | 1 1.45 4.18 (0.39–45.23) 10.16 (0.80–128.51) | Sex, hypertension, DM, heart diseases, liver diseases, kidney diseases, psychological disorders, time from admission to symptom onset date, D-dimer, and CRP |
| Cristóbal, 2021 [19] Spain | Retrospective cohort | 214 | COVID-19 | Hospital General Universitario Gregorio Marañón | 59, 28 | FIB-4 (death) | Per 1 unit 1.31 (0.99–1.72) 1.41 (1.11–1.81) | Charlson comorbidity index, the acute physiology and chronic health evaluation II, and serum ferritin |
| Elfeki, 2021 [16], USA | Retrospective cohort | 373 | COVID-19 with metabolic syndrome | UnityPoint Clinic or Hospital in the state of Iowa | 62, 48 | FIB-4 (hospitalization) | <1.30 1 1.30–2.67 1.52 (0.37–6.34) 2.22 (1.20–4.12) | Type 2 DM and CKD |
| Samaniego, 2021 [31], Spain | Retrospective cohort | 160 | COVID-19 | 5 tertiary-level hospitals in the region of Madrid | 55, 66 | FIB-4 (severe COVID-19) | <1.30 1 1.30–2.67 1.67 (1.06–2.64) 0.96 (0.84–1.10) | Hypertension, respiratory disease, and bilirubin, LDH acute C-reactive protein |
| Li, 2021 [32], USA | Retrospective cohort | 202 | COVID-19 | Two large academic centers in Boston, Massachusetts | 58, 46 | FIB-4 (death) | Per 1 unit 1 1.81 (2.10–18.80) 1.63 (1.22–2.17) | Sex, BMI, ethnicity, hypertension, diabetes, remdesivir use, and history of liver diseases, baseline troponin T, CRP, lymphocyte count, LDH, and D-dimer |
| Author, year, country | Study design | Sample size | Population | Data source | Age, female | Liver score reported (outcomes) | Estimate effect | Adjustments |
|-----------------------|--------------|-------------|------------|-------------|------------|--------------------------------|----------------|-------------|
| Calapod, 2020[15], Romania | Prospective cohort | 138 | COVID-19 with type II DM | Bucharest Emergency University | 66, 42 | FIB-4 (severe COVID-19) | 1 | Sex, BMI, dyspnea, ferritin, CRP, AST, and ALT |
| Forlano, 2020[18], USA | Retrospective cohort | 193 | COVID-19 with NAFLD | Imperial College Healthcare NHS Trust | 66, 67 | FIB-4 (death) | 1 | Male, presence of type 2 DM, hypertension, dyslipidemia |
| Targher, 2021[37], China | Retrospective cohort | 310 | NAFLD | Four sites in Zhejiang province | 48, 62 | FIB-4 (severe COVID-19) | 1 | Sex, obesity, diabetes, and presence/absence of MAFLD |
| Park, 2020[33], South Korea | Retrospective cohort | 1005 | COVID-19 | Five tertiary hospitals of Daegu | 72, 54 | FIB-4 (death) | 1 | DM, COPD, lymphocyte count, e-GFR, SIRS on admission |
| Sterlin, 2020[36], USA | Retrospective cohort | 256 | COVID-19 | Virginia Commonwealth University Medical Center in Richmond | 58, 45 | FIB-4 (IMV) | 1 | DM, kidney, cardiovascular diseases, and respiratory diseases |
| Author, year, country | Study design | Sample size | Population | Data source | Age, female | Liver score reported (outcomes) | Estimate effect | Adjustments |
|-----------------------|-------------|-------------|------------|-------------|------------|-------------------------------|---------------|-------------|
| Rentsch, 2020[34], UK | Retrospective cohort | 3,789 | COVID-19 | VA National Corporate Data Warehouse on Members of the VA Birt | 65, 10 | FIB-4 (hospitalization) \< 1.45 \(=\) 1.45–3.25 \(=\) >3.25 | 2.96 (1.69–5.17) | Race, CKD, COPD, DM, hypertension, vascular disease, ACEI/ARB, NASIDs, SBP, oxygen saturation, albumin, e-GFR, hemoglobin, white blood cell count, lymphocyte count, VACS index score# |
| Yao, 2021[39], China | Retrospective cohort | 342 | RT-PCR | Hospitals of Jiangsu province | | NFS (severe COVID-19) \(<\ 1.5 \geq\ 1.5\) | Ref. 11.05 (1.19,102.43) | Age, gender, BMI, hypertension, diabetes |
| Biliotti, 2020[29], Italy | Retrospective cohort | 299 | COVID-19 | INMI Lazzaro Spallanzani | 54 | FIB-4 (ICU admission or death) \(<\ 2.67 \geq\ 2.67\) | Ref. 1.35 (1.04–1.75) | Presence of severe pneumonia, obesity, and C-reactive protein |
| Fu, 2020[40], China | Case-cohort | 200 | COVID-19 | Second Affiliated Hospital of Anhui Medical University | 50.7, NA | AST/ALT (death) per 1 | 3.22 (1.59, 6.56) | Total bilirubin, alanine aminotransferase, creatinine, urea nitrogen, uric acid, creatine kinase, myoglobin, lactate dehydrogenase, aspartate aminotransferase |
| Sarin, 2020[35], international | Retrospective cohort | 228 | COVID-19 with preexisting chronic liver disease | APASL-ACLF Research Consortium Registry Study | 51,47 | AST/ALT (death) per 1 | 1.4 (2.5–5.4) | Total bilirubin |
| Goel, 2020[30], USA | Retrospective cohort | 551 | COVID-19 | St Luke’s University Hospital | 63, NA | AST/ALT (death) per 1 | 2.75 (1.63–4.65) | Age, hypertension, diabetes, heart failure, chronic kidney disease, malignancy, chronic pulmonary disease, and chronic liver disease, total bilirubin, and the inflammatory marker |

COPD: chronic obstructive lung disease; CKD: chronic kidney diseases; NASIDs: nonsteroidal anti-inflammatory drugs; MAFLD, metabolic dysfunction-associated fatty liver disease; e-GFR, estimated glomerular filtration rate; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase. #The VACS Index score is a validated measure of physiologic injury combining age, aspartate and alanine transaminase, albumin, creatinine, hemoglobin, platelets, white blood cell count, hepatitis C status, and body mass index.
increased the risk of death by 178% (RR: 2.78, 95% CI: 1.10–6.99, \( P = 0.03 \), I\(^2\) = 76%). The heterogeneity was not significant when excluding the study by Sarin et al., and the results did not change (RR: 4.51, 95% CI: 1.59–12.77, \( P = 0.005 \), I\(^2\) = 38%). Targher et al. [37] reported that higher NFS (≥1.5) increased the risk of developing severe COVID-19 by ten-fold after adjustments. Romero-Cristobal et al. [19] showed that a one-point increment in the Forns index increased the risk of death by 41% through a multivariate analysis.

3.5. Publication Bias and Sensitive Analysis. Publication bias was not evaluated because of the limited number of studies according to the guideline (\(N < 10\)) [41]. The results were stable in the sensitive analysis by omitting one study at a time (Supplementary Figure S1).

4. Discussion

To our best of knowledge, this is the first comprehensive meta-analysis that assessed the live fibrosis scores and

| Study or Subgroup | log(Odds Ratio) | SE | Weight (%) | Odds Ratio | Odds Ratio |
|-------------------|----------------|----|------------|------------|------------|
|                   |                |    |            | IV, Random, 95% CI | IV, Random, 95% CI |
| Elfeki, 2021, USA | -0.01426       | 0.025197 | 51.4     | 0.99 [0.94, 1.04] | [0.94, 1.04] |
| Rentsch, 2020, UK | 0.636402       | 0.111098 | 48.6     | 1.89 [1.52, 2.35] | [1.52, 2.35] |
| Total (95% CI)    |                |    | 100.0     | 1.35 [0.72, 2.56] | [0.72, 2.56] |
| Heterogeneity: \( \tau^2 = 0.21; \chi^2 = 32.62, df = 1 (P < 0.00001); I^2 = 97\% \) |
| Test for overall effect: \( Z = 0.93 (P = 0.35) \) | |

**Figure 2:** Association between FIB-4 and clinical outcomes in patients with COVID-19. FIB-4 was analyzed for continuous analysis (per one-point increase). (a) Hospitalization. (b) MV. (c) Severe COVID-19. (d) Death. Abbreviation: MV, mechanical ventilation.
clinical outcomes in patients with COVID-19, as well as the potential dose-response relationship. Based on current evidence, we showed that all available liver fibrosis scores, including FIB-4, Forn, NFS, and AST/ALT ratio, were associated with a worse prognosis in patients with COVID-19. Moreover, there was a positive linear relationship between the FIB-4 and severe COVID-19 and death.

Several noninvasive methods were developed using serum biomarkers (e.g., FIB-4, NFS, and APRI) to assess liver fibrosis [42]. Previous studies have shown that liver fibrosis is associated with increased mortality due to cardiovascular risk and all-cause mortality in patients with liver diseases or the general population [9,43,44]. In the present study, we found a positive association between liver fibrosis scores and adverse outcomes. These results were consistent with the recent findings, which reported worse outcomes in COVID-19 patients with preexisting chronic liver diseases [45]. For example, FIB-4 was found to be an independent factor of mortality among hospitalized COVID-19 patients with imaging- or liver biopsy-proven NAFLD [46]. Sachdeva et al. found that the NLFAD was a strong predictor for mortality in patients infected with SARS-CoV-2 [13,45]. It should be noted that the prevalence of chronic liver diseases is low (3%) in previous pooled analysis [47], which might be vastly underestimated. The rate of liver fibrosis assessed by the liver fibrosis score is much larger than the prevalence of liver fibrosis [42]. Previous studies have shown that liver fibrosis is associated with increased mortality due to cardiovascular risk and all-cause mortality in patients with liver diseases or the general population [9,43,44]. In the present study, we found a positive linear relationship between the FIB-4 and severe COVID-19 and death.

Several noninvasive methods were developed using serum biomarkers (e.g., FIB-4, NFS, and APRI) to assess liver fibrosis [42]. Previous studies have shown that liver fibrosis is associated with increased mortality due to cardiovascular risk and all-cause mortality in patients with liver diseases or the general population [9,43,44]. In the present study, we found a positive association between liver fibrosis scores and adverse outcomes. These results were consistent with the recent findings, which reported worse outcomes in COVID-19 patients with preexisting chronic liver diseases [45]. For example, FIB-4 was found to be an independent factor of mortality among hospitalized COVID-19 patients with imaging- or liver biopsy-proven NAFLD [46]. Sachdeva et al. found that the NLFAD was a strong predictor for mortality in patients infected with SARS-CoV-2 [13,45]. It should be noted that the prevalence of chronic liver diseases is low (3%) in previous pooled analysis [47], which might be vastly underestimated. The rate of liver fibrosis assessed by the liver fibrosis score is much larger than the prevalence of chronic liver diseases. For example, the cohort in the study by Sterling et al. had a high frequency of increased FIB-4 (52% had a FIB-4 level of >2.67 and 42% had a FIB-4 level of >3.25); however, there was low prevalence of known underlying liver disease (6%). In general, FIB-4 or NFS scores have shown higher negative predictive value but lower positive predictive value. That is to say, they have better accuracy in excluding rather than in identifying advanced fibrosis. The presence of advanced fibrosis might be underestimated in COVID-19 patients. Therefore, these liver fibrosis scores provide valuable information for patients with liver comorbidities with COVID-19 and can be an effective prognostic marker for predicting their prognosis.

Moreover, the current evidence shows that FIB-4 and NFS did not perform accurately in some population, such as younger patients (<35 years) and lean and morbidly obese adults [48,49]. The average mean age and BMI of included studies ranged from 47 to 72 years and 24.1 to 30.8 kg/m², respectively. Moreover, subgroup analyses stratified by mean age and mean BMI cannot be performed due to data restriction. The prognosis role of liver fibrosis in the COVID-19 population should be further studied.

It should be pointed out that these noninvasive assessments should be interpreted with caution due to more complexities during COVID-19 progression. Apart from the underestimated prevalence of NAFLD, we speculated that the elevation of these indicators was likely due to multiple factors but was linked to the COVID-19 disease pathogenesis and severity [10,11]. Muscular injuries and hepatic cellular and portal system alterations due to SARS-CoV-2 infection and systemic inflammation play a role in these outcomes. The components of these scores, such as AST, ALT, and platelet levels, largely fluctuated with the natural history of COVID-19 [32]. Several studies showed that the AST and ALT were significantly increased due to the high incidence of liver injury in COVID-19 patients [50]. The FIB-4 level was correlated to SARS-CoV-2 plasma RNA level as well as monocyte-associated cytokine levels [32]. Therefore, we should figure out whether the prevalence of liver fibrosis in COVID-19 can be solely attributed to chronic liver diseases and whether the associated incidence of liver injury can be caused by COVID-19.

There might be several potential mechanisms in the pathogenesis of chronic liver disease. Inflammation has a vital role in the pathogenesis of liver fibrosis [51]. Chronic inflammation is firmly established, and advanced liver disease is characterized by low-grade systemic inflammation caused by activated immune cells [51]. These activated cells serve as a vital source of cytokines and chemokines (e.g., interleukin-6, interleukin-18, and interleukin-17). Furthermore, Li et al. showed
a positive association between FIB-4 scores and interleukin-6 levels in patients with COVID-19 [32]. Some researchers proposed that this elevated interleukin-6, which is partly secreted by activated macrophages induced during liver fibrosis, might induce inflammatory response proteins in the hepatocytes (such as CRP (C-reactive protein), ferritin, complement, and clotting factors) [31]. Meanwhile, as it is known, an excessive inflammatory response is a relative phenomenon of severe COVID-19 cases. Therefore, it is reasonable to speculate that liver fibrosis may increase the risk of exacerbated inflammatory responses.

Overall, our results showed that the liver fibrosis scores were associated with the worst prognosis and might be a simple marker for predicting the severity and mortality in patients with COVID-19. All the components of these liver fibrosis scores (e.g., age, AST, and ALT) were accessible, and determining the levels of these markers was inexpensive. However, importantly, we did not assess the correlation between the presence of fibrosis and the most accurate assessment test, liver biopsy. Admittedly, liver biopsy is the current gold standard test for assessing liver fibrosis. However, it is unfeasible, probably unethical, and difficult to perform routinely. Furthermore, liver fibrosis scores were the results of multiple and complex factors involved in the natural progression of SARS-CoV-2 infection and should not be merely considered as an assessment for liver fibrosis.

4.1. Strength and Limitation. This is the first meta-analysis to comprehensively assess the liver fibrosis scores and associated clinical outcomes in patients with COVID-19 and elucidate the positive linear association between the FIB-4 and adverse outcomes. Our study inevitably has several limitations. Firstly, this is an analysis of observational research, which cannot prove causation. Secondly, the number of studies included was relatively limited, and prospective, longitudinal, larger studies were needed to validate the predictive ability of liver fibrosis scores. Thirdly, as the components of liver fibrosis scores varied during trajectories of COVID-19, the inconsistent timepoint of assessment included in evaluations, the studies inevitably increased the instability of predicting adverse outcomes in patients with the COVID-19. Fourthly, the specificity of FIB-4 for determining advanced fibrosis in patients ≥65 years decreases significantly and may overestimate the liver fibrosis level [49]. However, we cannot perform a subgroup stratified analysis by age. Further studies should focus on determining if there is an age difference.

5. Conclusion

Overall, our results suggested that liver fibrosis scores, such as FIB-4, NFS, AST/ALT ratio, and Forns index were significantly associated with the increased risk of MV, severe COVID-19, and mortality. For patients with COVID-19 at admission, especially for those with coexisting chronic liver diseases, assessment of liver fibrosis scores might be useful for identifying high risk of developing severe COVID-19 cases and worse outcomes.

Data Availability

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

Disclosure

Liu and Kaibo Mei are co-first authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors’ Contributions

X-L. and P-Y were responsible for the entire project and revised the draft. S-H, K-B-M, and C-D performed the data extraction, statistical analysis, drafted the first version of the manuscript, and interpreted the data. All authors participated in the interpretation of the results and prepared the final version of the manuscript. Menglu Liu and Kaibo Mei contributed equally.

Acknowledgments

The authors acknowledge all people who fought against COVID-19. This work was supported by a grant from the Natural Science Foundation in Jiangxi Province (Nos. 201924ACBL21037 and 202004BCJL23049) and the National Natural Science Foundation of China (Nos. 81760050, 82100869, and 21866019).

Supplementary Materials

Figure S1: sensitive analysis between liver fibrosis scores and clinical outcomes in patients with COVID-19 by omitting one study at a time. A: severe COVID-19; B: death. Supple- mental Table S1: PRISMA 2020. Table S2: search strategy. Table S3: studies excluded with reasons. Supple- mental Table S4: Newcastle–Ottawa Scale (NOS) scores for included studies. (Supplementary Materials)

References

[1] S. K. Asrani, H. Devarbhavi, J. Eaton, and P. S. Kamath, “Burden of liver diseases in the world,” Journal of Hepatology, vol. 70, no. 1, pp. 151–171, 2019.
[2] L. Caballeria, G. Pera, I. Arteaga et al., “High prevalence of liver fibrosis among European adults with unknown liver disease: a population-based study,” Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association, vol. 16, pp. 1138–1145 e5, 2018.
[3] S. McPherson, S. F. Stewart, E. Henderson, A. D. Burt, and C. P. Day, “Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease,” Gut, vol. 59, no. 9, pp. 1265–1269, 2010.
[4] J. Lee, Y. Vali, J. Bourisier et al., “Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: a systematic review,” Liver International, vol. 41, no. 2, pp. 261–270, 2021.
[5] F. Salomone, A. Micek, and J.Godos, "Simple scores of fibrosis and mortality in patients with NAFLD: a systematic review with meta-analysis," *Journal of Clinical Medicine*, vol. 7, 2018.

[6] A. Unalp-Arida and C. E. Ruhl, "Liver fibrosis scores predict liver disease mortality in the United States population," *Hepatology*, vol. 66, pp. 84–95, 2017.

[7] T. Akiyama, Y. Miyamoto, K. Imai et al., "Fibrosis-4 index, a noninvasive fibrosis marker, predicts survival outcomes after hepatectomy for colorectal cancer liver metastases," *Annals of Surgical Oncology*, vol. 27, no. 9, pp. 3534–3541, 2020.

[8] C.-J. Liu, T.-C. Tseng, W.-T. Yang et al., "Profile and value of FIB-4 in patients with dual chronic hepatitis C and B," *Journal of Gastroenterology and Hepatology*, vol. 34, no. 2, pp. 410–417, 2019.

[9] Y. Schonmann, H. Yeshua, I. Bentov, and S. Zelber-Sagi, "Liver fibrosis marker is an independent predictor of cardiovascular morbidity and mortality in the general population," *Digestive and Liver Disease*, vol. 53, no. 1, pp. 79–85, 2021.

[10] S. Behzad, L. Aghaghasvini, A. R. Radmard, and A. Gholamrezaneshad, "Extrapulmonary manifestations of COVID-19: radiologic and clinical overview," *Clinical Imaging*, vol. 66, pp. 35–41, 2020.

[11] L. Falasca, R. Nardacci, D. Colombo et al., "Postmortem findings in Italian patients with COVID-19: a descriptive full autopsy study of cases with and without comorbidities," *The Journal of Infectious Diseases*, vol. 222, no. 11, pp. 1807–1815, 2020.

[12] K. T. Baigain, S. Badal, B. B. Baigain, and M. J. Santana, "Prevalence of comorbidities among individuals with COVID-19: a rapid review of current literature," *American Journal of Infection Control*, vol. 49, no. 2, pp. 238–246, 2021.

[13] D. Ji, E. Qin, J. Xu et al., "Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study," *Journal of Hepatology*, vol. 73, no. 2, pp. 451–453, 2020.

[14] M. Parohan, S. Yaghoubi, and A. Seraji, "Liver injury is associated with severe coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of retrospective studies," *Hepatology Research: The Official Journal of the Japan Society of Hepatology*, vol. 50, pp. 924–935, 2020.

[15] O. P. Calapod, A. M. Marin, M. Onisai, L. C. Tribus, C. S. Pop, and C. Fierbinteanu-Bratievici, "The impact of increased FIB-4 score in patients with type II diabetes mellitus on Covid-19 disease prognosis," *Medicina*, vol. 57, 2021.

[16] M. A. Elfeki, J. Robles, Z. Akhtar et al., "Impact of Fibrosis-4 index prior to COVID-19 on outcomes in patients at risk of non-alcoholic fatty liver disease," *Digestive Diseases and Sciences*, vol. 1–7, 2021.

[17] I. Lopez-Mendez, J. Aquino-Matus, S. M.-B. Gall et al., "Association of liver steatosis and Fibrosis with clinical outcomes in patients with SARS-CoV-2 infection (COVID-19)," *Annals of Hepatology*, vol. 20, Article ID 100271, 2021.

[18] R. Forlano, B. H. Mullish, S. K. Mukherjee et al., "In-hospital mortality is associated with inflammatory response in NAFLD patients admitted for COVID-19," *PLoS One*, vol. 15, no. 10, Article ID e0240400, 2020.

[19] M. Romero-Cristobal, A. Clemente-Sanchez, P. Pineiro et al., "Possible unrecognised liver injury is associated with mortality in critically ill COVID-19 patients," *Therapeutic Advances in Gastroenterology*, vol. 14, Article ID 17562848211023410, 2021.

[20] M. J. Page, J. E. McKenzie, P. M. Bosuuy et al., "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews," *BMJ (Clinical Research ed.)*, vol. 372, p. n71, 2021.

[21] X. Liu, C. Long, Q. Xiong et al., "Association of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with risk of COVID-19, inflammation level, severity, and death in patients with COVID-19: a rapid systematic review and meta-analysis," *Clinical Cardiology*, 2020.

[22] X. Liu, N. Guo, W. Zhou et al., "Resting heart rate and the risk of atrial fibrillation," *International Heart Journal*, vol. 60, no. 4, pp. 805–811, 2019.

[23] C. Xu and D. Sar, "The robust error meta-regression method for dose-response meta-analysis," *International Journal of Evidence-Based Healthcare*, vol. 16, p. 138, 2017.

[24] X. Liu, L. Guo, K. Xiao et al., "The obesity paradox for outcomes in atrial fibrillation: evidence from an exposure-effect analysis of prospective studies," *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*, vol. 21, Article ID e12970, 2020.

[25] X. Liu, W. Wang, Z. Tan et al., "The relationship between vitamin D and risk of atrial fibrillation: a dose-response analysis of observational studies," *Nutrition Journal*, vol. 18, no. 1, p. 73, 2019.

[26] H. Zhao, K. Mei, L. Yang, X. Liu, and L. Xie, "Green tea consumption and risk for esophageal cancer: a systematic review and dose-response meta-analysis," *Nutrition*, vol. 87–88, Article ID 111197, 2021.

[27] L. Fu, X. Liu, Y. Su, J. Ma, and K. Hong, "Prevalence and impact of cardiac injury on COVID-19: a systematic review and meta-analysis," *Clinical Cardiology*, vol. 44, no. 2, pp. 276–283, 2021.

[28] J. P. T. Higgins and S. Green, *Handbook for Systematic Reviews of Interventions*, John Wiley & Sons, Hoboken, NJ, USA, 2011.

[29] E. Biliotti, P. Piselli, U. Visco Comandini et al., "The Fibrosis-4 index is associated with Intensive Care Unit (ICU) admission in middle-aged patients with COVID-19," *Digestive and Liver Disease*, vol. 53, pp. S21–S22, 2021.

[30] H. Goel, F. Harmouch, K. Garg et al., "The liver in COVID-19: prevalence, patterns, predictors, and impact on outcomes of liver test abnormalities," *European Journal of Gastroenterology Hepatology*, vol. 33, 2020.

[31] H. Kuo, F. Harmouch, M. J. Page et al., "The liver in COVID-19: prevalence, patterns, predictors, and impact on outcomes of liver test abnormalities," *European Journal of Gastroenterology Hepatology*, vol. 33, 2020.

[32] L. Ibáñez-Samaniego, F. Bigelli, C. Usón et al., "Elevation of liver fibrosis index FIB-4 is associated with poor clinical outcomes in patients with COVID-19," *The Journal of Infectious Diseases*, vol. 222, no. 5, pp. 726–733, 2020.

[33] Y. Li, J. Regan, J. Fajnzylber et al., "Liver fibrosis index Fib-4 is associated with mortality in COVID-19," *Hepatology Communication*, vol. 5, 2020.

[34] J. E. McKenzie, P. M. Bosuuy et al., "Liver fibrosis index FIB-4 as a predictor for mortality in hospitalised patients with COVID-19: a retrospective multicentre cohort study," *BMJ Open*, vol. 10, no. 11, Article ID e041989, 2020.

[35] C. T. Ronchts, F. Kidwai-Khan, J. P. T. Tate et al., "COVID-19 testing, hospital admission, and intensive care among 2,026,227 United States veterans aged 54-75 years," *medRxiv (The Preprint Server for Health Sciences)*, vol. 2020, 2020.

[36] S. K. Sarin, A. Choudhury, A. Choudhury et al., "Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; the APCOLIS Study (APASL COVID-19 liver injury spectrum study)," *Hepatology International*, vol. 14, no. 5, pp. 690–700, 2020.

[37] R. K. Sterling, T. Oakes, T. S. Gal, M. P. Stevens, M. deWit, and A. J. Sanyal, "The Fibrosis-4 index is associated with need
for mechanical ventilation and 30-day mortality in patients admitted with coronavirus disease 2019,” *The Journal of Infectious Diseases*, vol. 222, no. 11, pp. 1794–1797, 2020.

[37] G. Targher, A. Mantovani, C. D. Byrne et al., ”Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores,” *Gut*, vol. 69, no. 8, pp. 1545–1547, 2020.

[38] F. Xiang, J. Sun, P.-H. Chen et al., “Early elevation of FIB-4 liver fibrosis score is associated with adverse outcomes among patients with COVID-19,” *Clinical Infectious Diseases*, vol. 73, 2020.

[39] R. Yao, L. Zhu, J. Wang et al., ”Risk of severe illness of COVID-19 patients with NAFLD and increased NAFLD fibrosis scores,” *Journal of Clinical Laboratory Analysis*, vol. 35, Article ID e23880, 2021.

[40] L. Fu, J. Fei, H.-X. Xiang et al., “Influence factors of death risk among COVID-19 patients in Wuhan, China: a hospital-based case-cohort study,” *medRxiv*, 2020.

[41] J. P. T. Higgins and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions*John Wiley & Sons, Hoboken, NJ, USA, 2011.

[42] E. Vilar-Gomez and N. Chalasani, ”Non-invasive assessment of non-alcoholic fatty liver disease: clinical prediction rules and blood-based biomarkers,” *Journal of Hepatology*, vol. 68, no. 2, pp. 305–315, 2018.

[43] K. M. Irvine, L. F. Wockner, M. Shanker et al., ”The enhanced liver fibrosis score is associated with clinical outcomes and disease progression in patients with chronic liver disease,” *Liver International*, vol. 36, no. 3, pp. 370–377, 2016.

[44] H. S. Chun, J. S. Lee, H. W. Lee et al., ”Association between the severity of liver fibrosis and cardiovascular outcomes in patients with type 2 diabetes,” *Journal of Gastroenterology and Hepatology*, vol. 36, 2021.

[45] S. Sachdeva, H. Khandait, J. Kopel, M. M. Aloysius, R. Desai, and H. Goyal, ”NAFLD and COVID-19: a pooled analysis,” *SN Comprehensive Clinical Medicine*, vol. 2, no. 12, pp. 2726–2729, 2020.

[46] Z. M. Younossi, M. Stepanova, B. Lam et al., ”Independent predictors of mortality among patients with NAFLD hospitalized with COVID-19 infection,” *Hepatology Communications*, 2021.

[47] A. J. Kovalic, S. K. Satapathy, and P. J. Thuluvath, ”Prevalence of chronic liver disease in patients with COVID-19 and their clinical outcomes: a systematic review and meta-analysis,” *Hepatology International*, vol. 14, pp. 1–9, 2020.

[48] F. Eren, E. Kaya, and Y. Yilmaz, ”Accuracy of Fibrosis-4 index and non-alcoholic fatty liver disease fibrosis scores in metabolic (dysfunction) associated fatty liver disease according to body mass index: failure in the prediction of advanced fibrosis in lean and morbidly obese individuals,” *European Journal of Gastroenterology and Hepatology*, vol. 34, no. 1, pp. 98–103, 2022.

[49] S. McPherson, T. Hardy, J.-F. Dufour et al., ”Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis,” *American Journal of Gastroenterology*, vol. 112, no. 5, pp. 740–751, 2017.

[50] Y. Wang, L. Shi, Y. Wang, and H. Yang, ”An updated meta-analysis of AST and ALT levels and the mortality of COVID-19 patients,” *The American Journal of Emergency Medicine*, vol. 40, pp. 208–209, 2021.

[51] T. Kisseleva and D. Brenner, ”Molecular and cellular mechanisms of liver fibrosis and its regression,” *Nature Reviews Gastroenterology & Hepatology*, vol. 18, no. 3, pp. 151–166, 2021.