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•LETTER TO THE EDITOR•

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Quantitative assessment of fibrosis-4 score and adverse clinical outcomes in patients with COVID-19

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Dear editor,

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global pandemic leading to a broad spectrum of clinical manifestations, from asymptomatic or mild-to-moderate symptoms, to severe illness, and even death. Accumulating evidence suggests that old age and underlying comorbidities, such as cardiovascular disease and diabetes mellitus (DM), are risk factors for progression and mortality of COVID-19. Recently, several studies have revealed a link between non-alcoholic fatty liver disease (NAFLD) and COVID-19 severity. NAFLD, which is renamed as metabolic-associated fatty liver disease (MAFLD), is a common liver disorder with a prevalence of about 25% in the global population. It is reported that MAFLD patients with increased fibrosis-4 (FIB-4) score are at higher risk of severe COVID-19 (Targher et al., 2020). As a simple non-invasive tool, FIB-4 score was initially developed to predict advanced liver fibrosis in chronic hepatitis C, and later validated in patients with MAFLD. But the potential of FIB-4 as a prognostic marker for disease severity and clinical outcomes of COVID-19 remains unknown. We therefore conducted a comprehensive meta-analysis to evaluate the association of FIB-4 score with disease severity and clinical outcomes, including admission to intensive care unit (ICU), need for invasive mechanical ventilation (IMV) and mortality, among COVID-19 patients.

A total of 22 studies involving 14,446 PCR-confirmed COVID-19 patients were finally included (Supplementary Methods and Figure S1 in Supporting Information). Among these studies, 11 investigations defined high FIB-4 index using the cut-off as over 3.25 which was categorized according to prior cut points validated to be a proxy of Ishak stage of hepatic fibrosis. There were 5 pieces of literature defining high FIB-4 index as a value over 2.67 which is considered at high risk of advanced fibrosis. As for the remaining 6 studies, high FIB-4 index was defined based on ROC curves for prediction of unfavorable outcomes (5 studies) or FIB-4 distribution (one study using highest quartile of FIB-4 of included patients). The main characteristics of included studies are shown in Table S1.

Eight studies involving 4,088 patients reported the mean elevation of FIB-4 in COVID-19 patients with unfavorable outcomes (Table S2 in Supporting Information). Overall, elevated baseline FIB-4 score was found in patients with unfavorable outcomes (MD=2.16, 95% CI: 1.16−3.16, $P<10^{-4}$; Figure 1A). Besides, COVID-19 patients with higher FIB-4 score were more likely to be hospitalized (OR=2.98, 95% CI: 1.46−6.07, P=0.003; Figure 1B) and progression to severe disease (OR=3.98, 95% CI: 2.08−7.63, $P<10^{-4}$; Figure 1B), compared to those with low FIB-4 score,

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with substantial between-study heterogeneity (I^2=90%). Although most of the included studies categorized high FIB-4 index using the conventional cut-offs, definition of high FIB-4 score varied across different studies. A further subgroup analysis based on definition of high FIB-4 score was then performed and significant results sustained (Figure S2 in Supporting Information). Meanwhile, the duration of hospital stay was significantly longer in patients with high FIB-4 score (MD=5.76 days, 95% CI: 2.95−8.56, $P<10^{-4}$; I^2=57%; Figure 1C). In addition, higher FIB-4 was associated with increased risk of ICU admission (OR=3.94, 95% CI: 2.68-5.77, $P<10^{-5}$; I^2=73%; Figure 1D) and need for IMV (OR=4.51, 95% CI: 2.70−7.54, $P<10^{-5}$; I^2=68%; Figure 1E) compared with low FIB-4 group.

In-hospital mortality was reported in 14 studies, involving 577 deaths. Higher FIB-4 score was associated with higher mortality (OR=5.16, 95% CI: 2.83−9.41, $P<10^{-5}$; I^2=86%; Figure 1F). After combining results from multivariate Cox proportional hazards model, FIB-4 score was also significantly associated with mortality with an overall HR of 2.72 (95% CI: 1.45−5.10, P=0.002, I^2=84%; Figure S3 in Supporting Information) adjusted for age, sex, and underlying diseases. After adjusting for age, sex, body mass index and comorbidities, the summary OR for unfavorable outcomes (death and severe illness) was 1.30 (95% CI: 1.12−1.51, P=0.001, I^2=84%; Figure S4 in Supporting Information) per 1-unit increment in FIB-4.

There was a moderate heterogeneity in the overall analysis. In meta-regression analysis, age (P=0.95), sex (P=0.92), sample size (P=0.65), and study design (P=0.25) did not significantly explain such heterogeneity (Table S3 in Supporting Information). Sensitivity analysis indicated that no single study influenced the pooled OR qualitatively, suggesting that this association was strong. The funnel-plot and statistic test showed absence of publication bias in the overall analysis (P=0.06, Figure S5 in Supporting Information).

In the present study, we performed a meta-analysis to evaluate the relationship between FIB-4 and COVID-19 severity. The robust results indicated that high FIB-4 score was associated with worse progression of COVID-19 and unfavorable outcomes. Although FIB-4 cut-offs varied across different studies, significant association was also observed after pooling data obtained from multivariate regression models with FIB-4 treated as a continuous variable. FIB-4 scoring system comprises four variables, including patient's age, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet count, which derive from routine laboratory tests. The prevalence of liver function test (LFT) abnormalities has been reported as high as 76.3% in COVID-19 patients, and higher AST has been found to be correlated to severe clinical course or mortality (Cai et al., 2020; Wijarnpreecha et al., 2021). However, emerging evidence has demonstrated that FIB-4 score is a better predictor for disease severity or outcomes compared with any of its components alone (Sterling et al., 2021).

The majority of included studies evaluated laboratory data collected on admission when patients were already infected with COVID-19. Thus, it is difficult to distinguish whether increased level of FIB-4 is related to preexisting chronic liver diseases or direct cytopathic effect of SARS-CoV-2. One study investigated pre-admission indices of patients before COVID-19 initiation, and suggested underlying chronic liver disease defined by higher FIB-4 score was correlated with higher risk of mortality in severe patients admitted to the ICU (Romero-Cristóbal et al., 2021). However, there was no other assessment used to confirm the relationship between severity of liver damage or pre-existent liver disease and FIB-4, which may not be truly indicative of histological fibrosis (Graupera et al., 2021). Another study conducted in COVID-19 patients without prior liver disease demonstrated that high FIB-4 score was independently associated with mortality, while steatosis was not associated with a worse outcome (Crisan et al., 2021). Of note, a recent mendelian randomization analysis also indicated that MAFLD is not a causal risk factor for severe COVID-19 (Li et al., 2022). In other words, high FIB-4 score may reflect the hepatic injury involved in COVID-19, rather than the presence of pre-existent advanced liver disease in patients infected with SARS-CoV-2. Furthermore, the study by Li et al. found that FIB-4 elevation was significantly associated with mortality in COVID-19, and this score eventually normalized only in the survivors, suggesting potential direct virological effects other than the impact brought by preexisting liver disease (Li et al., 2021). They also found that the FIB-4 level was correlated with SARS-CoV-2 plasma viral load and cytokine related to monocyte activation and interferon (IFN), indicating that virological effects, inflammation or a combination of these factors may play a role in FIB-4 elevation. In addition, a new study found abundant SARS-CoV-2 viral particles in hepatocytes of two COVID-19 cases with elevated aminotransferases, demonstrating that SARS-CoV-2 is able to infect liver and directly leads to liver impairment (Wang et al., 2020). Although this study analyzed a cohort of 156 COVID-19 patients and found elevation of ALT and AST was associated with disease severity, FIB-4 was not evaluated in this report. Thus, more researches are needed to unveil the underlying mechanism of the association between FIB-4 and disease severity in patients with COVID-19.

There are several limitations in our study. Firstly, although we performed the multivariate logistic regression analysis, we may not be able to properly adjust for age as it is included in the formula of the FIB-4. Secondly, there was moderate heterogeneity in our analyses. Varying FIB-4 cut-offs, undetermined hepatitis B/C co-infection status, and/or underlying comorbidities may be responsible for the presence of heterogeneity. Moreover, the majority of the literatures in-

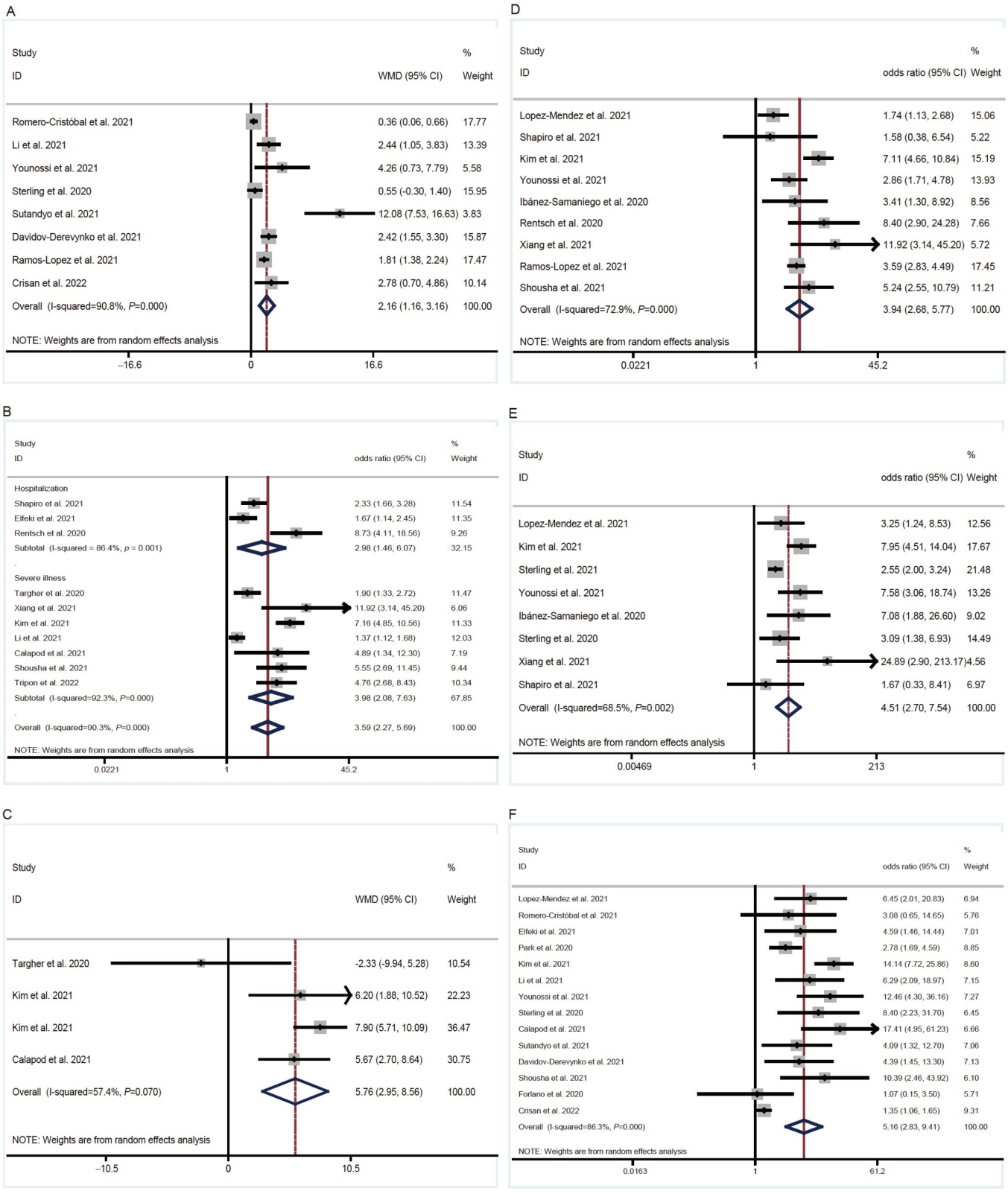

Figure 1 Forest plots for the pooled baseline FIB-4 score (A), risk of unfavorable outcomes (B), longer hospital duration (C), ICU admission (D), need for IMV (E), and mortality (F) in COVID-19 patients with higher FIB-4 index versus those with low FIB-4 score.

cluded in the present study is retrospective, while the recall and selection bias might exist.

As the number of patients infected with SARS-CoV-2 is still increasing rapidly, shortage of medical resources is a

critical issue facing most countries in the world. In order to manage the public health crisis, earlier diagnosis and simple indicators for severe COVID-19 are urgently needed. In conclusion, the present study suggested that FIB-4 may serve as a robust and effective tool for ruling out patients at higher risk of severe COVID-19, which can be easily calculated and used by frontline healthcare workers. Further studies are warranted to validate our findings in larger prospective cohorts, and to determine the optimal FIB-4 cut-off.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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SUPPORTING INFORMATION

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