

Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores

A recent study reported that patients with severe COVID-19 were more likely to have non-alcoholic fatty liver disease (NAFLD) compared with those with non-severe COVID-19 illness.¹ However, the prognosis of NAFLD (recently renamed metabolic dysfunction-associated fatty liver disease (MAFLD)²) is determined by the severity of liver fibrosis.^{3,4} We therefore postulated that patients with MAFLD with increased non-invasive liver fibrosis scores are at higher risk of severe illness from COVID-19.

We studied 310 patients with laboratory-confirmed COVID-19 who were consecutively hospitalised at four sites in Zhejiang Province, China, between January and February 2020. Some of these patients (n=150) have been included in a prior study examining the association between obesity and COVID-19 severity.⁵ Patients with viral hepatitis, excessive alcohol consumption, chronic pulmonary diseases or active cancers were excluded. Clinical and laboratory data were collected at hospital admission. All patients were screened for hepatic steatosis by computed tomography and subsequently diagnosed as MAFLD.⁶ The originally validated cut-points for fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS) were used to categorise liver fibrosis probability as low, intermediate or high.⁷ COVID-19 severity was classified as severe and non-severe.⁸ The study protocol was approved by the local ethics committees of the four hospitals.

In our cohort of 310 confirmed cases of COVID-19, 94 (30.3%) patients had MAFLD. As shown in [table 1](#), patients with MAFLD with intermediate or high FIB-4 scores were more likely to be older, obese, have diabetes and have higher NFS, higher liver enzymes, higher C reactive protein, as well as lower levels of lymphocyte count, platelet count, triglycerides and high-density lipoprotein cholesterol compared with their counterparts with low FIB-4 score or those without MAFLD. Notably, the severity

Table 1 Main clinical and biochemical characteristics of patients with laboratory-confirmed COVID-19, stratified by the presence or absence of imaging-defined MAFLD with increasing levels of FIB-4 score

| | No MAFLD | MAFLD with low FIB-4 (≤1.3) | MAFLD with intermediate FIB-4 (1.3–2.67) | MAFLD with high FIB-4 (>2.67) | P value |
|--|----------------------|-----------------------------|--|-------------------------------|---------|
| N | 216 | 44 | 36 | 14 | |
| Age (years) | 45.9±15.4 | 41.2±14.2 | 54.2±10.8 | 59.9±9.1 | <0.001 |
| Male sex (%) | 43.5 | 54.6 | 63.9 | 57.1 | 0.086 |
| BMI (kg/m ²) | 23.0±3.2 | 26.5±4.7 | 26.6±3.2 | 26.1±2.8 | <0.001 |
| Obesity (%) | 25.9 | 61.4 | 75.0 | 64.3 | <0.001 |
| Current smokers (%) | 8.8 | 2.3 | 11.1 | 7.1 | 0.768 |
| Systolic blood pressure (mm Hg) | 130±17 | 136±15 | 136±16 | 136±14 | 0.047 |
| Diastolic blood pressure (mm Hg) | 80±11 | 84±11 | 82±11 | 79±8 | 0.117 |
| Prior diabetes (%) | 7.4 | 20.4 | 13.9 | 28.6 | 0.010 |
| White blood count (×10 ⁹ /L) | 4.90 (3.9–6.2) | 5.35 (4.5–6.7) | 4.69 (3.8–6.6) | 4.90 (3.2–5.8) | 0.254 |
| Neutrophil count (×10 ⁹ /L) | 3.05 (2.2–4.1) | 3.49 (2.6–4.2) | 3.0 (2.4–4.7) | 3.20 (1.9–4.5) | 0.759 |
| Lymphocyte count (×10 ⁹ /L) | 1.20 (0.9–1.6) | 1.40 (1.2–2.0) | 1.10 (0.7–1.3) | 0.92 (0.7–1.14) | <0.001 |
| Haemoglobin (g/L) | 132.4±16 | 136.6±15 | 135.5±12 | 135.8±17 | 0.305 |
| Platelet count (×100 000/mm ³) | 211±72 | 246±75 | 183±64 | 125±24 | <0.001 |
| Prothrombin time (s), n=211 | 12.1±1.3 | 11.9±2.3 | 12.2±1.2 | 12.3±1.1 | 0.754 |
| APTT (s), n=211 | 31.5±3.8 | 32.7±5.4 | 32.8±3.7 | 35.3±7.4 | 0.026 |
| D-dimer (mg/L), n=183 | 0.18 (0.11–0.29) | 0.21 (0.1–0.5) | 0.21 (0.1–0.4) | 0.27 (0.1–0.4) | 0.432 |
| C reactive protein (mg/L) | 7.9 (1.9–24.9) | 8.6 (2.9–23.6) | 25.4 (8.7–53.3) | 25.5 (8.7–53.4) | <0.001 |
| Procalcitonin (ng/mL), n=190 | 0.05 (0.03–0.25) | 0.08 (0.04–0.25) | 0.06 (0.04–0.10) | 0.20 (0.08–0.25) | 0.077 |
| Albumin (g/L), n=286 | 41.4 (38.0–44.5) | 42.3 (37.3–44.6) | 41.0 (36.9–43.1) | 38.6 (37.7–42.8) | 0.348 |
| Total bilirubin (μmol/L) | 10.5 (7.0–15.5) | 10.1 (7.5–15.6) | 12.0 (9.5–16.6) | 15.3 (11.8–17.3) | 0.025 |
| AST (IU/L) | 22 (17–27) | 23 (19–32) | 32 (26–50) | 44 (29–83) | <0.001 |
| ALT (IU/L) | 18 (13–27) | 30 (22–52) | 28 (22–48) | 27 (16–82) | <0.001 |
| GGT (IU/L) | 21 (14–33) | 31 (22–54) | 51 (24–81) | 49 (32–102) | <0.001 |
| Elevated AST>40 IU/L (%) | 7.9 | 9.1 | 27.8 | 57.1 | <0.001 |
| Elevated ALT >40 IU/L (%) | 13.0 | 29.6 | 30.6 | 42.9 | <0.001 |
| Total cholesterol (mmol/L) | 3.98±0.8 | 4.11±0.9 | 3.73±0.7 | 3.82±1.0 | 0.217 |
| Triglycerides (mmol/L) | 1.15 (0.9–1.7) | 1.61 (1.0–2.1) | 1.48 (1.1–1.8) | 1.11 (0.9–1.6) | <0.005 |
| HDL cholesterol (mmol/L) | 1.18±0.4 | 0.96±0.2 | 1.06±0.2 | 1.09±0.4 | <0.005 |
| LDL cholesterol (mmol/L) | 2.23±0.7 | 2.54±0.8 | 2.10±0.7 | 2.20±0.8 | 0.116 |
| Hospital stay (days) | 18 (13–24) | 18 (13–22) | 22 (16–29) | 17 (6–23) | 0.122 |
| NAFLD fibrosis score, n=286 | −1.82 (−2.8 to −1.0) | −2.61 (−3.1 to −1.9) | −0.68 (−1.4 to −0.2) | +0.26 (−0.03 to 1.6) | <0.005 |
| COVID-19 severity | | | | | <0.001 |
| Non-severe (%) | 88.4 | 86.4 | 63.9 | 57.1 | |
| Severe (%) | 11.6 | 13.6 | 36.1 | 42.9 | |

Sample size, n=310, except where indicated. Diabetes was diagnosed as self-reported history of disease and/or specific drug treatment. Obesity was diagnosed as BMI>25 kg/m². Data are expressed as mean±SD, medians and IQRs (in parentheses) or frequencies. Differences among the four groups of patients were tested by Fisher's exact test for categorical variables, one-way analysis of variance for normally distributed continuous variables or the Kruskal-Wallis test for not normally distributed continuous variables. For the sake of clarity, significant p values are highlighted in bold.

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease.

limitations, our study is the first to examine the impact of FIB-4 or NFS on COVID-19 severity in patients with imaging-defined MAFLD. These non-invasive fibrosis scores have been shown to predict histological fibrosis stage with reasonable accuracy in cohorts of patients with MAFLD,⁷ and are also associated with increased overall and disease-specific mortality in population-based studies.^{9,10} Our data demonstrate that patients with MAFLD with increased FIB-4 or NFS are at higher likelihood of having severe COVID-19 illness, irrespective of metabolic comorbidities. In the context of COVID-19, the presence of MAFLD with significant/advanced fibrosis might exacerbate the virus-induced cytokine 'storm', possibly through the hepatic release of multiple proinflammatory cytokines, thereby contributing mechanistically to severe COVID-19. Further research is needed to better understand the mechanistic link of advanced MAFLD to the viral disease process.

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of COVID-19 illness markedly increased among patients with MAFLD with intermediate or high FIB-4 scores.

The severity of COVID-19 illness was associated with intermediate (unadjusted OR 4.32, 95% CI 1.94 to 9.59) or high (unadjusted-OR 5.73, 95% CI 1.84 to 17.9) FIB4 scores among patients with MAFLD (table 2, model 1A). This association remained significant after adjusting for sex, obesity and diabetes (model 1B). We did not additionally adjust for age, because this variable was incorporated in the FIB-4 score. Similar to the main analysis, when the intermediate and high FIB-4 categories were combined, the risk of severe COVID-19 illness was increased with intermediate/high FIB-4 score in unadjusted (model 2A) and multivariate-adjusted analyses (model 2B).

Similarly, the intermediate/high NFS (unadjusted-OR 5.21, 95% CI 2.39 to 11.3) was associated with a higher risk of severe COVID-19 illness. This significant association persisted in multivariate-adjusted analyses after controlling for sex, obesity and diabetes (adjusted OR 2.91, 95% CI 1.20 to 7.06).

When we included FIB-4 or NFS as continuous measures in multivariable regression models, increasing FIB-4 (adjusted OR 1.90, 95% CI 1.33 to 2.72) or NFS (adjusted OR 2.57, 95% CI 1.73 to 3.82) were significantly associated with greater COVID-19 severity, even after adjusting for sex, obesity, diabetes and presence/absence of MAFLD.

Our study has some limitations, including the relatively modest sample size, the Asian ancestry of the cohort and the use of non-invasive fibrosis scores without a histological diagnosis of liver fibrosis. Despite these

Table 2 Association between imaging-defined MAFLD with increasing levels of FIB-4 score and risk of having severe illness associated with COVID-19

| Logistic regression analyses | ORs | 95% CI | P value |
|--|------|--------------|---------|
| Severity of COVID-19 illness (mild/moderate vs severe/critical) | | | |
| Unadjusted model 1A | | | |
| MAFLD/FIB-4 status | | | |
| No MAFLD (n=216) | Ref. | Ref. | |
| MAFLD with low FIB-4 (≤ 1.3 ; n=44) | 1.21 | 0.46 to 3.14 | 0.701 |
| MAFLD with intermediate FIB-4 (1.3–2.67, n=36) | 4.32 | 1.94 to 9.59 | <0.001 |
| MAFLD with high FIB-4 (>2.67, n=14) | 5.73 | 1.84 to 17.9 | <0.005 |
| Adjusted model 1B | | | |
| MAFLD/FIB-4 status | | | |
| No MAFLD (n=216) | Ref. | Ref. | |
| MAFLD with low FIB-4 (≤ 1.3 ; n=44) | 0.82 | 0.30 to 2.24 | 0.696 |
| MAFLD with intermediate FIB-4 (1.3–2.67, n=36) | 2.59 | 1.09 to 6.13 | 0.030 |
| MAFLD with high FIB-4 (>2.67, n=14) | 4.04 | 1.22 to 13.3 | 0.021 |
| Sex (men vs women) | 1.78 | 0.93 to 3.44 | 0.079 |
| Obesity (yes vs no) | 2.62 | 1.31 to 5.24 | <0.005 |
| Prior diabetes (yes vs no) | 1.04 | 0.40 to 2.80 | 0.928 |
| Unadjusted model 2A | | | |
| MAFLD/FIB-4 status | | | |
| No MAFLD (n=216) | Ref. | Ref. | |
| MAFLD with low FIB-4 (≤ 1.3 ; n=44) | 1.21 | 0.46 to 3.14 | 0.701 |
| MAFLD with intermediate/high FIB-4 (>1.3, n=50) | 4.68 | 2.31 to 9.49 | <0.001 |
| Adjusted model 2B | | | |
| MAFLD/FIB-4 status | | | |
| No MAFLD (n=216) | Ref. | Ref. | |
| MAFLD with low FIB-4 (≤ 1.3 ; n=44) | 0.82 | 0.30 to 2.24 | 0.696 |
| MAFLD with intermediate/high FIB-4 (>1.3, n=50) | 2.95 | 1.37 to 6.34 | <0.005 |
| Sex (men vs women) | 1.79 | 0.94 to 3.45 | 0.084 |
| Obesity (yes vs no) | 2.60 | 1.30 to 5.16 | <0.005 |
| Prior diabetes (yes vs no) | 1.09 | 0.41 to 2.89 | 0.862 |

Sample size, n=310. Data are expressed as ORs and 95% CI as tested by univariable (unadjusted) and multivariable (adjusted) logistic regression analysis. Diabetes was diagnosed as self-reported history of disease and/or specific drug treatment. Obesity was diagnosed as BMI > 25 kg/m². In the adjusted logistic regression models, we did not additionally adjust also for age, because this variable is already incorporated in the FIB-4 score. FIB-4, fibrosis-4; MAFLD, metabolic associated fatty liver disease; Ref, reference category.

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