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BRIEF DEFINITIVE REPORT

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Metabolic-associated fatty liver disease is associated with severity of COVID-19

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Abstract

The Corona Virus Disease 2019 (COVID-19) pandemic has attracted increasing worldwide attention. While metabolic-associated fatty liver disease (MAFLD) affects a quarter of world population, its impact on COVID-19 severity has not been characterized. We identified 55 MAFLD patients with COVID-19, who were 1:1 matched by age, sex and obesity status to non-aged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-infected patients without MAFLD. Our results demonstrate that in patients aged less than 60 years with COVID-19, MAFLD is associated with an approximately fourfold increase (adjusted odds ratio 4.07, 95% confidence interval 1.20-13.79, P = .02) in the probability for severe disease, after adjusting for confounders. Healthcare professionals caring for patients with COVID-19 need to be aware that there is a positive association between MAFLD and severe illness with COVID-19.

Yu-Jie Zhou and Kenneth I. Zheng are co-first authors.

1 | INTRODUCTION

Respiratory disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has evolved into a global pandemic. Metabolic-associated fatty liver disease (MAFLD) affects about 20%-30% of people worldwide.[1] However, whether the co-existence of MAFLD affects COVID-19 severity is unknown. We explored the association between MAFLD and COVID-19 severity in non-aged patients with laboratory-proven SARS-CoV-2 infection.

2 | METHODS

The study cohort comprised 55 non-aged patients (<60 years old) with both COVID-19 and MAFLD from three major teaching hospitals (the First Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital and Ruian People's Hospital) in China. The patients were intended to be matched 1:1 by age (±5 years), sex and obesity status (body mass index ± 1 unit) to non-aged SARS-CoV-2-infected patients without MAFLD. Unfortunately, because of limitations in the number of patients with COVID-19, after matching for age and obesity, there were only 37 males in the non-MAFLD cohort and 45 in the MAFLD cohort (P = .08). All subjects were imaged by computed tomography (CT) for the detection of fatty liver. Detailed information on CT attenuation measurement and diagnosis of fatty liver can be referenced in subsection 1 of the Data S1.

MAFLD was diagnosed according to the recent consensus criteria.[1,2] Detailed diagnostic criteria for MAFLD are described in subsection 2 of the Data S1. Patients with viral hepatitis were excluded; patients with excess alcohol consumption (>20 g/d in females and 30 g/d in males) were excluded to the extent possible according to the clinical notes. Obesity was defined as body mass index (BMI) ≥ 25 kg/m^2 in Asians,[3] and diabetes mellitus was diagnosed according to the history or haemoglobin A1c ≥ 6.5%.[4] Hypertension and dyslipidaemia were diagnosed according to the literature.[5,6] Briefly, hypertension was defined as blood pressure ≥ 130/85 mmHg or specific drug treatment. Dyslipidaemia was defined as plasma triglycerides ≥ 1.70 mmol/L, or HDL cholesterol < 1.0 mmol/L for men and <1.3 mmol/L for women, or specific drug treatment. Laboratory parameters were measured on the day of admission. COVID-19 severity was assessed during hospitalization and classified into four clinical subtypes (mild, moderate, severe and critical), based on the Chinese management guideline (see subsection 3 of the Data S1). We defined mild and moderate COVID-19 subtypes as 'non-severe COVID-19', and severe and critical subtypes as 'severe COVID-19'. All patients received standard treatments according to the COVID-19 management guidance (7th edition).[7] All patients denied any history of active cancer, coronary heart disease or chronic obstructive or restrictive pulmonary disease. The study was approved by the ethics committees of the three hospitals.

Continuous variables are expressed as mean ± standard deviation or median [interquartile range] and compared using t test or Mann-Whitney U test, as appropriate. Categorical variables were compared using chi-squared test or Fisher exact test for non-ranked variables, and Kruskal-Wallis test for ranked data. Wilcoxon test (paired samples) was utilized to compare values of liver function tests at admission and during hospitalization. The association between MAFLD and severity of COVID-19 was determined by logistic regression. All statistical tests were two-sided and a value of P less than .05 was considered statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM Corporation).

3 | RESULTS

As shown in Table 1, among 110 non-aged subjects with SARS-CoV-2 infection, no significant difference was observed in age, sex and the proportion of obesity between MAFLD and non-MAFLD groups (all P > .05). Compared with the non-MAFLD group, MAFLD patients had higher levels of C-reactive protein, lactic dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), fasting blood glucose and triglycerides (all P < .05). After a median hospital stay of 19.5 days, all cases recovered and were discharged from hospital. The presence of MAFLD was associated with severity of COVID-19 (P = .002), and a trend to increased duration of hospital admission (with an insignificant P value of .09).

We then explored impacts of SARS-CoV-2 infection on liver function in 101 patients (49 MAFLD, 52 non-MAFLD) with available information. We compared peak values of aminotransferases, total bilirubin and GGT and minimum albumin value during hospitalization with their corresponding values at admission. We found that ALT, AST, AST/ALT ratio, total bilirubin and GGT were significantly elevated during hospitalization, while the albumin value was significantly decreased during hospitalization compared with that at the time of admission (all P < .001; Table S1).

MAFLD patients comprised 43.7% of non-severe COVID-19 and 73.9% of severe COVID-19 (P = .01). To adjust for confounding variables, we performed multivariable logistic regression analyses (Table 2). The association between MAFLD and the development of severe COVID-19 remained significant after adjusting for age, sex, smoking status, obesity, diabetes and hypertension (adjusted OR 4.07, 95% CI 1.20-13.79, P = .02).

4 | DISCUSSION

Our study demonstrates that in patients less than 60 years of age, the presence of MAFLD is independently associated with severe/critical COVID-19. In China, approximately 80% of deaths from COVID-19 occurred in patients aged 60 years or older.[8] In these patients, other co-morbid conditions including pre-existing respiratory or cardiac disease, and diabetes, may more severely impact the presentation and clinical course of COVID-19. To better define the impact of MAFLD on disease severity, we conducted this research in people aged <60 years.

Previous studies have shown that the angiotensin-converting enzyme 2 (ACE2)/Angiotensin-(1-7)/Mas axis plays a regulatory

TABLE 1 Baseline characteristics of COVID-19 patients stratified by the presence or absence of MAFLD

Variable	Overall (n = 110)	Non-MAFLD (n = 55)	MAFLD (n = 55)	*P* #
Demographics				
Age, y	42.1 ± 11.4	40.9 ± 11.9	43.4 ± 10.8	.25
Male, n (%)	82 (74.5%)	37 (67.3%)	45 (81.8%)	.08
Metabolic-associated factors				
Body mass index	25.6 ± 2.9	25.0 ± 2.7	26.1 ± 3.1	.07
Obesity, n (%)	68 (61.8%)	31 (56.4%)	37 (67.3%)	.24
Type 2 diabetes, n (%)	13 (11.8%)	2 (3.6%)	11 (20.0%)	.008
Hypertension, n (%)	24 (21.8%)	9 (16.4%)	15 (27.3%)	.17
Dyslipidaemia, n (%)	68 (61.8%)	23 (41.8%)	45 (81.8%)	<.001
Laboratory parameters				
White blood cell count, $\times 10^9$	4.9 [3.9, 6.2]	4.9 [3.9, 6.0]	4.9 [4.0, 6.5]	.55
Lymphocyte count, $\times 10^9$	1.3 [1, 1.6]	1.2 [1, 1.6]	1.3 [1, 1.7]	.57
C-reactive protein, mg/L	14.9 [3.6, 35.3]	7.1 [1.1, 24.4]	21.6 [6.3, 47.5]	.001
≥10 mg/L, n (%)	63 (57.3%)	24 (43.6%)	39 (70.9%)	.004
Lactic dehydrogenase, U/L	211.5 [181, 277]	203 [171, 248]	232 [196.5, 309.5]	.02
Total bilirubin, μmol/L	12.4 [9.7,16.7]	12.4 [10.1, 16.5]	12.3 [9.0, 16.7]	.88
Alanine aminotransferase, U/L	26 [17, 46]	18 [15, 35]	29 [24, 54.5]	<.001
Aspartate aminotransferase, U/L	25.5 [21, 35]	23 [19, 28]	31 [22.5, 45]	.001
Alkaline phosphatase, U/L	58 [50, 73]	57 [47.5, 75]	59 [50.5, 69]	.74
Gamma-glutamyl transferase, U/L	39 [22, 69.5]	28 [19, 50]	48 [26, 77]	.002
Fasting blood glucose, mmol/L	5.5 [5, 6.6]	5.3 [4.9, 5.9]	5.7 [5.3, 7]	.003
Triglycerides, mmol/L	1.2 [1, 1.7]	1.1 [0.8, 1.6]	1.5 [1, 1.8]	.01
Total cholesterol, mmol/L	3.9 [3.3, 4.5]	4.0 [3.4, 4.5]	3.8 [3.3, 4.5]	.49
HDL cholesterol, mmol/L	1.0 [0.9, 1.3]	1.2 [1, 1.4]	1.0 [0.9, 1.2]	.001
LDL cholesterol, mmol/L	2.1 [1.6, 2.8]	2.1 [1.7, 2.6]	2.2 [1.5, 3]	.73
Length of hospital stay, days	19.5 [14, 25]	18 [13, 21]	21 [16, 28]	.09
COVID-19 severity, n (%)				
Mild	8 (7.3%)	7 (12.7%)	1 (1.8%)	.002
Moderate	79 (71.8%)	42 (76.4%)	37 (67.3%)	
Severe	20 (18.2%)	5 (9.1%)	15 (27.3%)	
Critical	3 (2.7%)	1 (1.8%)	2 (3.6%)	

#*P* value was calculated by comparison between MAFLD and non-MAFLD groups.

role in insulin resistance and hepatic steatosis, and ACE2 gene expression in liver was increased in people with liver disease compared to those without.[9,10] However, whether ACE2 expression is elevated in patients with mild to moderate MAFLD compared with healthy controls has not been determined. The spike glycoprotein of SARS-CoV-2 binds to human ACE2 with high affinity, resulting in coronavirus recognition and infection.[11] This mechanism might possibly explain the association between MAFLD and COVID-19 disease severity. In this study, we found elevations in transaminase values in patients with COVID-19 during hospitalization, suggesting that SARS-Cov-2 infection or the stress of infection and hospitalization can impact liver function, as reported in a previous study.[12] However, in the context of COVID-19, hepatic and systemic immune and metabolic dysregulation in MAFLD[13] may exert negative impact on antiviral responses.

Our study has some limitations. Due to the infectious nature of COVID-19 and the emergent situation, fatty liver was detected by CT, rather than the 'gold standard' of liver biopsy or magnetic resonance proton density fat fraction (MR-PDFF). However, previous studies report that fatty liver can also be accurately and reliably diagnosed by

TABLE 2 Association between the presence of MAFLD and COVID-19 severity

	OR	95% CI	*P*
Unadjusted	3.65	1.31-10.16	.01
Adjusted model I	3.26	1.13-9.38	.03
Adjusted model II	4.07	1.20-13.79	.02

Note: Data are presented as odds ratios (ORs) and 95% confidence intervals (CIs) measured by univariable and multivariable logistic regression analyses.

Model I: adjusted for age and sex.

Model II: adjusted for age, sex, smoking, obesity, diabetes mellitus and hypertension.

CT scanning.[14,15] Additionally, although we matched non-MAFLD and MAFLD patients, patients were not matched according to the major outcome and selection bias or other biases might exist. Besides, in our study, COVID-19 severity was assessed during hospitalization, and treatment modalities during hospitalization can impact on the disease status. Moreover, the Asian ethnicity of the cohort, relatively smaller sample size, and the lack of detailed information on medication history might influence the generalizability of the results. Thus, it remains to be established whether the effect we observed of MAFLD on COVID-19 severity can be generalized to other ethnic groups, and whether patients with severe MAFLD (eg MAFLD with significant fibrosis) are more likely to have severe COVID-19 than those with mild MAFLD.

In sum, the results of this preliminary study suggest that the presence of MAFLD in Chinese patients is associated with increased odds of severe SARS-CoV-2 disease. In the context of our results, more care and active monitoring for disease progression are needed for MAFLD patients infected with SARS-CoV-2.

AUTHOR CONTRIBUTIONS

Yu-Jie Zhou and Ming-Hua Zheng involved in concept and design of the study. Xiao-Bo Wang, Qing-Feng Sun, Ke-Hua Pan, Ting-Yao Wang, Hong-Lei Ma and Yong-Ping Chen involved in data acquisition. Yu-Jie Zhou involved in data analysis and data interpretation. Yu-Jie Zhou and Kenneth I. Zheng drafted the manuscript. Jacob George involved in critical revision of the manuscript for important intellectual content. Ming-Hua Zheng supervised the study. All authors contributed to the manuscript for important intellectual content and approved the submission.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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