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Metabolic associated fatty liver disease increases coronavirus disease 2019 disease severity in nondiabetic patients

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Author contribution: Study concept and design was provided by Feng Gao, Kenneth I. Zheng, and Ming-Hua Zheng. Xiao-Bo Wang, Hua-Dong Yan, Qing-Feng Sun, Ke-Hua Pan, Ting-Yao Wang, and Yong-Ping Chen acquired the data. Fen Gao and Kenneth I. Zheng analyzed and interpreted the data. Feng Gao and Kenneth I. Zheng drafted the manuscript. Critical revision of the manuscript for important intellectual content was carried out by Jacob George.

Abstract

Background and Aim: Coronavirus disease 2019 (COVID-19) has attracted increasing worldwide attention. While diabetes is known to aggravate COVID-19 severity, it is not known whether nondiabetic patients with metabolic dysfunction are also more prone to more severe disease. The association of metabolic associated fatty liver disease (MAFLD) with COVID-19 severity in nondiabetic patients was investigated here.
Methods: The study cohort comprised 65 patients with (i.e. cases) and 65 patients without MAFLD (i.e. controls). Each case was randomly matched with one control by sex (1:1) and age (±5 years). The association between the presence of MAFLD (as exposure) and COVID-19 severity (as the outcome) was assessed by binary logistic regression analysis.
Results: In nondiabetic patients with COVID-19, the presence of MAFLD was associated with a four-fold increased risk of severe COVID-19; the risk increased with increasing numbers of metabolic risk factors. The association with COVID-19 severity persisted after adjusting for age, sex, and coexisting morbid conditions.
Conclusion: Health-care professionals caring for nondiabetic patients with COVID-19 should be cognizant of the increased likelihood of severe COVID-19 in patients with MAFLD.

Ming-Hua Zheng supervised the study. All authors contributed to the manuscript for important intellectual contents and approved the submission.

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Introduction

The outbreak of coronavirus disease 2019 (COVID-19) has attracted increasing worldwide attention.[1] Diabetes commonly aggravates the severity of COVID-19,[2] but it is currently not known whether nondiabetic patients with metabolic dysfunction are also more likely to have greater COVID-19 severity. Metabolic associated fatty liver disease (MAFLD) is a common cause of chronic liver disease that affects a quarter of the population worldwide.[3,4] MAFLD is considered a sensitive and important indicator of metabolic dysfunction.[3] We investigated the association between MAFLD and COVID-19 severity among nondiabetic patients with laboratory-confirmed COVID-19.

Methods

Study population and design. Patient data were collected from the electronic medical records of four hospitals in China (The First Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital, Ningbo No. 2 Hospital, and Ruian People's Hospital) between January 17 and February 11, 2020. All records of COVID-19 patients aged between 18 and 75 years were accessed for possible inclusion in the study. We excluded patients for the following reasons: (i) presence of diabetes; (ii) presence of active cancer, chronic obstructive or restrictive pulmonary diseases, or other end-stage diseases; and (iii) incomplete data on an abdominal computed tomography (CT) scan. As result, 65 COVID-19 patients with MAFLD (i.e. cases) and 201 patients without MAFLD (i.e. controls) were included. We then matched 65 COVID-19 patients with MAFLD (i.e. cases) 1:1 to a randomly selected group of COVID-19 patients without MAFLD (i.e. controls) by sex (1:1) and age (±5 years). The cohort thus comprised 130 nondiabetic patients with COVID-19. Some of these patients were the subjects of a previous study.[5] The study was approved by the local ethics committees of all four hospitals. The requirement for written informed consent was waived owing to the retrospective and anonymous nature of the study.

Clinical and laboratory data. Anthropometric and biochemical parameters were measured on the first day of hospital admission. COVID-19 was diagnosed as a positive result by high-throughput sequencing or real-time reverse transcriptase–polymerase chain reaction assay of oropharyngeal swab specimens. COVID-19 severity of illness was assessed during hospitalization and classified into four clinical subtypes (i.e. mild, moderate, severe, and critically ill) on the basis of management guidelines (Table S1).[2] Patients were diagnosed as having fatty liver by CT (Table S2) and subsequently diagnosed as MAFLD according to a recent set of consensus diagnostic criteria.[4] The criteria are based on evidence of hepatic steatosis, in addition to one of the following criteria, namely, overweight (body mass index $\geq$ 23 kg/m^2 in Asian populations), presence of type 2 diabetes mellitus, or presence of metabolic dysregulation. Metabolic dysregulation is defined by the presence of at least two metabolic risk abnormalities ([i] blood pressure $\geq$ 130/85 mmHg or specific drug treatment; [ii] plasma triglycerides $\geq$ 1.70 mmol/L or specific drug treatment; [iii] plasma high-density lipoprotein [HDL]-cholesterol $<$ 1.0 mmol/L for men and $<$ 1.3 mmol/L for women or specific drug treatment; and [iv] fasting glucose levels 5.6 to 6.9 mmol/L or HbA1c 5.7% to 6.4%). More detailed information about the MAFLD definition is presented in Table S3.

All included patients had undergone an abdominal CT scan during hospitalization. We retrieved images from the archived scans in the four hospitals for central reading. All images were read by an experienced radiologist (Pan K.), blinded to clinical data. Detailed information about CT attenuation measurement and diagnosis of fatty liver is presented in Table S2.

Obesity was defined as a body mass index $\geq$ 25 kg/m^2 in this Asian population. Hypertension and dyslipidemia were diagnosed as past medical history of these diseases, use of specific drugs, or abnormal biochemical parameters, on the basis of established criteria.[6] Patients received standard treatment according to the Chinese COVID-19 management guidance (7th edition)[2] and were discharged alive from the hospital.

Statistical analysis. Continuous variables are expressed as means ± SD or medians and interquartile ranges (IQRs) and compared using either the Student *t*-test (for normally distributed variables) or the Mann–Whitney test (for non-normally distributed variables). Differences between categorical variables are expressed as percentages and compared using the chi-squared test or the Fisher exact test as appropriate. For the purpose of further analysis, COVID-19 patients were categorized according to disease severity as non-severe (mild and moderate disease, combined) and severe (severe and critical, combined). The association between presence of MAFLD and COVID-19 severity (as the outcome) was assessed by binary logistic regression analysis. Statistical analyses were two-sided, and significance was set at $P < 0.05$. All statistical tests were performed using SPSS version 23.0 (SPSS Inc., Chicago, USA).

Results

The mean age of patients was 46 years, and 36.9% were female. As shown in Table 1, compared with those without MAFLD, patients with imaging-defined MAFLD were more likely to be obese (60.0% vs. 36.9%, $P = 0.008$) and overweight (84.6% vs. 61.5%, $P = 0.003$); have a higher proportion of dyslipidemia (75.4% vs. 53.8%, $P = 0.010$) and metabolic dysregulation (84.6% vs. 63.1%, $P = 0.005$); and have higher levels of C-reactive protein (median 21.9 [IQR 8.5–47.3] vs. 11.2 [2.5–32.4] mg/L; $P = 0.023$), alanine aminotransferase (median 29 [IQR 22–48] vs. 22 [15–32] U/L; $P = 0.001$), aspartate aminotransferase (median 30 [IQR 22–39] vs. 23 [18–29] U/L; $P = 0.001$), and creatinine (median 74.5 [IQR 67.0–83.8] vs. 66.0 [60.0–79.0] μmol/L; $P = 0.016$) and lower levels of HDL-cholesterol (median 1.0 [IQR 0.9–1.2] vs. 1.1 [1.0–1.4] mmol/L; $P = 0.003$) at hospital admission. Notably, they also had more severe COVID-19 disease (requiring intensive care in those with critical illness, $P = 0.003$).

As shown in Table 2, the presence of MAFLD was associated with an approximately four-fold increased risk of severe COVID-19 (unadjusted odds ratio 4.22, 95% confidence interval 1.45–12.22), as compared with patients without MAFLD. Notably, the association between MAFLD and COVID-19 severity remained significant even after adjusting for age, sex, smoking status, obesity, hypertension, and dyslipidemia (Model 3, adjusted odds ratio 4.07, 95% confidence interval 1.10–15.09). We further divided patients into three groups (No-MAFLD; MAFLD but with only one diagnostic criteria [either overweight or metabolic dysregulation]; and MAFLD with both diagnostic criteria [both overweight and metabolic dysregulation]). In this analysis, there was a significant increase in COVID-19 severity from those without MAFLD to those meeting both the diagnostic criteria (P for trend = 0.025, Table 2).

Discussion

This multicenter study demonstrates a synergistic effect of MAFLD and metabolic risk factors for severe COVID-19 in nondiabetic patients.

Table 1 Baseline characteristics of COVID-19 patients stratified by MAFLD status

	Overall *n* = 130	Without MAFLD *n* = 65	With MAFLD *n* = 65	*P* value[†]
Demographics				
Age, years	46 ± 13	47 ± 13	46 ± 13	0.530 (matched)
18–39 years, *n* (%)	36 (27.7%)	18 (27.7%)	18 (27.7%)	0.999 (matched)
40–59 years, *n* (%)	72 (55.4%)	36 (55.4%)	36 (55.4%)	
60–75 years, *n* (%)	22 (16.9%)	11 (16.9%)	11 (16.9%)	
Female sex, *n* (%)	48 (36.9%)	24 (36.9%)	24 (36.9%)	0.999 (matched)
Body mass index, kg/m^2	25.0 ± 3.8	23.7 ± 3.2	26.2 ± 3.9	<0.001
Comorbid conditions				
Current smoking, *n* (%)	15 (11.5%)	11 (16.9%)	4 (6.2%)	0.097
Hypertension, *n* (%)	25 (19.2%)	11 (16.9%)	14 (21.5%)	0.504
Dyslipidemia, *n* (%)	84 (64.6%)	35 (53.8%)	49 (75.4%)	0.010
Obesity, *n* (%)	63 (48.5%)	24 (36.9%)	39 (60.0%)	0.008
Overweight, *n* (%)	95 (73.1%)	40 (61.5%)	55 (84.6%)	0.003
Metabolic dysregulation, *n* (%)	96 (73.8%)	41 (63.1%)	55 (84.6%)	0.005
Both overweight and metabolic dysregulation, *n* (%)	75 (57.7%)	30 (46.2%)	45 (69.2%)	0.008
Fatty liver, *n* (%)	66 (50.8%)	1 (1.5%)	65 (100%)	<0.001
Laboratory parameters				
White blood cell count, $\times 10^9$	4.8 (3.8–6.2)	4.7 (3.7–5.9)	4.8 (3.9–6.6)	0.656
Lymphocyte count, $\times 10^9$	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.2 (0.9–1.6)	0.922
C-reactive protein, mg/L	19.2 (4.1–41.2)	11.2 (2.5–32.4)	21.9 (8.5–47.3)	0.023
Fasting glucose, mmol/L	5.5 ± 1.3	5.4 ± 1.4	5.5 ± 1.2	0.528
HbA1c, %	6.0 ± 0.4	5.8 ± 0.3	6.0 ± 0.4	0.368
Triglycerides, mmol/L	1.3 (0.9–1.8)	1.2 (0.9–1.6)	1.5 (1.0–1.8)	0.169
Total cholesterol, mmol/L	4.0 (3.4–4.4)	4.0 (3.5–4.5)	3.9 (3.3–4.4)	0.306
HDL-cholesterol, mmol/L	1.0 (0.9–1.2)	1.1 (1.0–1.4)	1.0 (0.9–1.2)	0.003
LDL-cholesterol, mmol/L	2.3 (1.8–2.7)	2.3 (1.8–2.8)	2.3 (1.7–2.7)	0.710
Alanine aminotransferase, U/L	26 (18–38)	22 (15–32)	29 (22–48)	0.001
Aspartate aminotransferase, U/L	26 (20–35)	23 (18–29)	30 (22–39)	0.001
Albumin, g/L	41 ± 5	42 ± 7	41 ± 4	0.428
Total bilirubin, μmol/L	11.6 (8.8–16.5)	10.7 (8.3–16.3)	13.6 (8.9–16.7)	0.270
Creatinine, μmol/L	73.0 (61.5–82.0)	66.0 (60.0–79.0)	74.5 (67.0–83.8)	0.016
COVID-19 severity, *n* (%)				0.003
Mild	6 (4.6%)	6 (9.2%)	0 (0.0%)	
Moderate	102 (78.5%)	54 (83.1%)	48 (73.8%)	
Severe	19 (14.6%)	5 (7.7%)	14 (21.5%)	
Critical	3 (2.3%)	0 (0.0%)	3 (4.6%)	

Data are expressed as means ± SD, medians (IQR), and number (percentages).
[†]Statistical difference between those with and those without MAFLD.
COVID-19, coronavirus disease 2019; MAFLD, metabolic associated fatty liver disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 Association between presence of MAFLD and COVID-19 severity (as the outcome) among nondiabetic patients

	Prevalence	Model 1	Model 2	Model 3
MAFLD (yes vs. no)	17/65 (26.2%) vs. 5/65 (7.7%)	4.22 (1.45–12.22)	4.35 (1.46, 13.01)	4.07 (1.10, 15.09)
Non-MAFLD	5/65 (7.7%)	Ref	Ref	Ref
MAFLD meets 1 criteria[†]	3/20 (15.0%)	2.19 (0.47, 10.09)	2.35 (0.49, 11.24)	2.60 (0.47, 14.42)
MAFLD meets 2 criteria[‡]	14/45 (31.1%)	5.26 (1.74, 15.88)	5.34 (1.71, 16.68)	5.25 (1.23, 22.33)
P for trend		0.003	0.004	0.025

Data are expressed as odds ratio (OR) and 95% confidence intervals (CI) tested by univariable and multivariable logistic regression analyses.
Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, smoking status, obesity, hypertension, and dyslipidemia.
[†]Either overweight/obesity or metabolic dysregulation;
[‡]Both overweight/obesity and metabolic dysregulation.
MAFLD, metabolic associated fatty liver disease; COVID-19, coronavirus disease 2019; Ref, reference.

The mechanisms underlying the strong relationship however are poorly understood. Previous studies have found that in adults, chronically elevated insulin levels (as frequently observed in patients with MAFLD) are associated with reduced lung function in patients irrespective of a diabetes diagnosis.[7] In addition, changes in adipokines (leptin and adiponectin) could play a role in how metabolic abnormalities adversely impact lung function.[7] Finally, pro-inflammatory mediators such as tumor necrosis factor-alpha and interleukin-6 may contribute to the observed association between MAFLD and the severity of COVID-19, and further mechanistic studies are warranted.[8]

Health-care professionals caring for nondiabetic patients with COVID-19 should be cognizant of the increased likelihood of severe COVID-19 in patients with metabolic risk factors. In particular, the presence of MAFLD increases the risk of severe illness approximately four-fold; this risk increases with increasing numbers of metabolic risk factors.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Clinical subtypes (mild, moderate, severe, and critical) of COVID-19 severity, according to the Chinese management guidelines.

Table S2. CT attenuation measurement and diagnosis of fatty liver.

Table S3. Metabolic associated fatty liver disease definition.