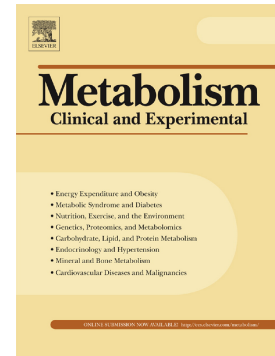# Journal Pre-proof

Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease

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Title:

Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease

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List of Abbreviations

BMI, body mass index; CI, confidence intervals; COVID-19, coronavirus

disease-2019; OR, odds ratio; IL-6, interleukin 6.

Number of tables and supplementary tables: 2/1

Number of figures: 0

Electronic word count: 920

Abstract

Background & Aims: Coronavirus disease 2019 (COVID-19) has been declared a pandemic in 2020. Patients with metabolic associated fatty liver disease (MAFLD) are often obese and have additional metabolic risk factors which may aggravate the severity of respiratory diseases and of COVID-19. This study aims to investigate the association between MAFLD and COVID-19 severity.

Methods: 214 patients with laboratory-confirmed COVID-19 aged between 18 and 75 years from three hospitals in Wenzhou, China were consecutively enrolled. Sixty-six patients with MAFLD were included in the final analysis. 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 was assessed during hospitalization and classified as severe and non-severe based on the current management guideline. All patients were screened for fatty liver by computed tomography and subsequently diagnosed as MAFLD according to a recent set of consensus diagnostic criteria. Obesity was defined as BMI greater than 25 kg/m^2.

Results: The presence of obesity in MAFLD patients was associated with a ~6-fold increased risk of severe COVID-19 illness (unadjusted-OR 5.77, 95% CI 1.19-27.91, p=0.029). Notably, this association with obesity and COVID-19 severity remained

significant (adjusted-OR 6.32, 95% CI 1.16-34.54, p=0.033) even after adjusting for age, sex, smoking, diabetes, hypertension, and dyslipidaemia.

Conclusions: Our data demonstrate that the risk of obesity to COVID-19 severity is greater in those with, than those without MAFLD.

Keywords:

COVID-19; SARS-CoV-2; obesity; MAFLD.

Introduction

Coronavirus disease 2019 (COVID-19) has been declared a pandemic in 2020.[1] Preliminary data suggests that obesity may aggravate the severity of respiratory diseases and of COVID-19.[2] Patients with metabolic associated fatty liver disease (MAFLD),[3] formerly known as non-alcoholic fatty liver disease, are often obese and have additional metabolic risk factors which may translate to a greater risk from respiratory diseases.[4-7] It is currently not known whether MALFD patients are also more likely to have greater COVID-19 severity of illness. This study investigated the association between MAFLD and COVID-19 severity.

Methods

We consecutively enrolled 214 patients with laboratory-confirmed COVID-19 aged between 18 and 75 years from three hospitals in Wenzhou, China (the First Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital, and Ruian People's Hospital) between January 1, 2020 and February 29, 2020. All patients were screened for fatty liver by computed tomography and subsequently diagnosed as MAFLD according to a recent set of consensus diagnostic criteria.[3] Sixty six COVID-19 patients with MAFLD were included in the analyses and were divided into two groups [those with obesity (n=45) and those without (n=21)]. All patients received standard treatment based on the COVID-19 Management Guidance (7th edition).[8] This study was approved by the local ethics review boards of all three hospitals. The requirement for written informed consent was waived for use of the

de-identified data.

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 was assessed during hospitalization and classified as severe and non-severe based on the management guideline.[8] Blood routine markers were analyzed at the central laboratory of respective hospital using standard methods by VITROS 5600 Integrated Immunodiagnostic System (VITROS 5600, Johnson, New Jersey, USA).

We collected demographic information and past medical history from all patients. Laboratory parameters were tested on the first day of hospital admission. Body weight and height were measured by trained examiners on admission. Body mass index (BMI) was calculated using the formula weight (kilograms) divided by height (meters) squared. Obesity was defined as BMI greater than 25 kg/m^2.[9] Diabetes, hypertension and dyslipidemia were diagnosed based on established criteria.[10] All patients denied a history of chronic obstructive or restrictive pulmonary disease.

Continuous variables are expressed as mean ± SD and compared using either the Student's t-test for normally distributed variables or the Mann-Whitney test for non-normally distributed variables. Continuous variables were tested for normality using the Shapiro-Wilk test. Differences between categorical variables was examined

with the chi-squared test or the Fisher's exact test as appropriate. The association

between obesity (as exposure) and COVID-19 severity (as the outcome) among

MAFLD patients was assessed by binary logistic regression. 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 enrolled patients was 47 years and 74.2% were female. **Table 1**

shows the main clinical and biochemical characteristics of COVID-19 patients with

MAFLD stratified by obesity status. Mean BMI for the non-obese and obese patients

were 22.7 ±2.1 kg/m^2 and 28.3 ±3.2 kg/m^2, respectively. Compared with the

non-obese group, obese patients had higher levels of aspartate aminotransferase,

fasting blood glucose and LDL-cholesterol, and lower lymphocyte counts. Notably,

MALFD patients that were obese had more severe COVID-19 disease (37.5% *vs.*

9.5%, p =0.021).

As shown in Supplementary Table, there were 47 (71.2%) patients with non-severe

COVID-19 and 19 (28.8%) with severe COVID-19. Compared to those with

non-severe COVID-19, patients with severe disease were more obese (89.5% *vs.*

59.6%, p =0.021). They were also more likely to be smokers (26.3% *vs.* 6.4%, p

=0.038), and had higher C-reactive protein concentrations (median 52.7 [IQR

33.5-74.9] *vs.* 18.3 [4.6-24.9], p <0.001) and lower lymphocyte counts (median 1.0

[IQR 0.8-1.2] *vs.* 1.4 [1.1-1.7], *p* =0.005).

As shown in Table 2, in the unadjusted logistic regression model with COVID-19 severity as the outcome, the presence of obesity in MAFLD patients was associated with a ~6-fold increased risk of severe COVID-19 illness (unadjusted OR 5.77, 95% CI 1.19-27.91, p=0.029). Notably, this association with obesity and COVID-19 severity remained significant (adjusted-OR 6.32, 95%CI 1.16-34.54, *p* =0.033) even after adjusting for age, sex, smoking, diabetes, hypertension, and dyslipidaemia.

Discussion

Our results show that in MAFLD patients with laboratory-confirmed COVID-19, the presence of obesity markedly increases the risk of having severe illness. This association remained significant after adjusting for likely confounders.

We reported previously that obesity is associated with a nearly 3-fold increased risk for severe COVID-19 with a dose-effect relationship between increasing BMI and the proportion of patients with severe illness.[11] In the current analysis, the risk of severe illness in MAFLD patients with co-existing obesity was more than 6-fold greater after adjustment for confounders. These findings are distinct, suggesting that the risk of obesity to COVID-19 severity is significantly greater in those with MAFLD. However, the virological and physiological mechanisms underlying the relationship we observed is not clarified by the present data. Systemic inflammatory

response syndrome, a common complication in severe COVID-19,[12] is promoted by the activation of CD14+ and CD16+ inflammatory monocytes producing a larger amount of interleukin (IL)-6 and other proinflammatory factors. This suggests IL-6 is a key proinflammatory factor that triggers the inflammatory "storm" in patients.[13] In MAFLD patients, particularly those with obesity, increased inflammatory activity in the liver and visceral fat is independently correlated with increased levels of IL-6,[14] which might have an additive/synergistic role in promoting greater severity of COVID-19. It is conceivable that the secretion of hepatokines for example, reduced adiponectin or the altered secretion of inflammatory lipid mediators in obese patients with MAFLD,[15] may also contribute to the current observations.

While this is the first multi-center study to investigate obesity as a possible risk factor for severe COVID-19 illness in patients with MAFLD, some limitations should be recognized. Patients included in our study did not undergo liver biopsy, thus COVID-19 severity in relation to liver histology could not be assessed. Waist circumference, a risk factor for MAFLD, was not measured in our patients, which precluded adjustment of this confounder. In addition, patients were of Asian ethnicity and thus the applicability of the results to other ethnic groups is uncertain. Additional studies will be needed to confirm these findings and to better understand the underlying mechanisms for why the association with obesity is greater in those with MAFLD.

In conclusion, our data demonstrate that the risk of obesity to COVID-19 severity is greater in those with, than those without MAFLD.

Authors Contributions

Study concept and design: Kenneth I. Zheng, Feng Gao and Ming-Hua Zheng

Acquisition of data: Xiao-Bo Wang, Qing-Feng Sun, Ke-Hua Pan, Ting-Yao Wang, Hong-Lei Ma

Analysis and interpretation of data: Fen Gao and Kenneth I. Zheng

Drafting of the manuscript: Kenneth I. Zheng, Feng Gao and Wen-Yue Liu

Critical revision of the manuscript for important intellectual content: Jacob George and Ming-Hua Zheng.

Study supervision: Ming-Hua Zheng

All authors contributed to the manuscript for important intellectual contents and approved the submission.

Funding

Conflict of interest statement

All authors declare no conflict of interests.

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Table legend

Table 1. Baseline characteristics of MAFLD patients with laboratory-confirmed

COVID-19 according to obesity status.

Table 2. Multivariable-adjusted association between obesity (as exposure) and

COVID-19 severity (as the outcome) in patients with MAFLD.

Supplementary Table. Baseline characteristics of MAFLD patients according to

COVID-19 severity.

Table 1. Baseline characteristics of MAFLD patients with laboratory-confirmed COVID-19 according to obesity status.

	Overall N=66	Without obesity N=21	With obesity N=45	*P* value
Demographics				
Age, years				
18-44 yrs, n (%)	39 (59.1%)	15 (71.43%)	24 (53.33%)	0.207
45-64 yrs, n (%)	22 (33.3%)	6 (28.57%)	16 (35.56%)	
≥65 yrs, n (%)	5 (7.6%)	0 (0.00%)	5 (11.11%)	
Female sex, n (%)	17 (25.8%)	4 (19.05%)	13 (28.89%)	0.548
Body mass index, kg/m^2	26.5 ± 3.9	22.7 ± 2.1	28.3 ± 3.2	<0.001
Coexisting disorders				
Current smoker, n (%)	8 (12.1%)	2 (9.5%)	6 (13.3%)	0.659
Type 2 diabetes, n (%)	16 (24.2%)	2 (9.5%)	14 (31.1%)	0.070
Hypertension, n (%)	19 (28.8%)	3 (14.3%)	16 (35.6%)	0.089
Dyslipidemia, n (%)	45 (68.2%)	14 (66.67%)	31 (68.89%)	0.857
Laboratory parameters				
White blood cell count, x10^9	4.9 (3.9-6.7)	4.8 (3.8-6.3)	5.0 (4.1-6.7)	0.495
>10 ×10^9, n (%)	2 (3.0%)	0 (0.0%)	2 (4.4%)	0.511
<4 ×10^9, n (%)	17 (25.8%)	7 (33.3%)	10 (22.2%)	
Lymphocyte count, x10^9	1.2 (0.9-1.6)	1.4 (1.1-1.8)	1.1 (0.9-1.4)	0.040
<1.5 ×10^9, n (%)	47 (71.2%)	11 (52.4%)	36 (80.0%)	0.021
C-reactive protein, mg/L	21.6 (8.1-47.3)	18.3 (5.8-24.5)	25.3 (11.3-53.5)	0.097
≥10 mg/L, n (%)	47 (71.2%)	13 (61.9%)	34 (75.6%)	0.382
Alanine aminotransferase, U/L	29.5 (24.0-62.5)	26.0 (20.0-45.0)	30.0 (24.0-65.0)	0.150
>40 U/L, n (%)	25 (37.9%)	6 (28.6%)	19 (42.2%)	0.415
Aspartate aminotransferase, U/L	31.5 (23.0-47.0)	25.0 (21.0-33.0)	35.0 (27.0-52.0)	0.010
>40 U/L, n (%)	20 (30.3%)	2 (9.5%)	18 (40.0%)	0.020
Total bilirubin, μmol/L	13.3 (9.3-17.1)	15.6 (11.8-19.3)	11.5 (8.8-16.7)	0.051
Creatinine, μmol/L	74.0 (65.5-83.0)	78.0 (67.0-87.0)	74.0 (65.0-82.0)	0.401
Fasting blood glucose, mmol/L	6.7 ± 2.3	5.8 ± 1.5	7.1 ± 2.6	0.047
HbA1c, %	1.5 ± 0.6	1.3 ± 0.6	1.5 ± 0.6	0.145
Triglycerides, mmol/L	3.9 ± 0.9	3.7 ± 0.9	4.1 ± 0.9	0.086
Total cholesterol,	1.0 ± 0.3	1.1 ± 0.2	1.0 ± 0.3	0.255

mmol/L				
HDL-cholesterol, mmol/L	2.3 ± 0.9	2.0 ± 0.9	2.4 ± 0.8	0.074
LDL-cholesterol, mmol/L	7.0 ± 1.1	5.7 ± 0.5	7.3 ± 1.1	0.032
COVID-19 severity, n (%)				0.021
Non-severe	47 (71.2%)	19 (90.5%)	28 (62.2%)	
Severe	19 (28.8%)	2 (9.5%)	17 (37.8%)	

Data are expressed as mean ± SD, medians and inter-quartile range or percentage.

Table 2. Multivariable-adjusted association between obesity (as exposure) and COVID-19 severity (as the outcome) in patients with MAFLD.

	OR	95% CI	*P* value
Unadjusted	5.77	1.19-27.91	0.029
Adjusted model I	6.25	1.23-31.71	0.027
Adjusted model II	6.32	1.16-34.54	0.033

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, smoking, type 2 diabetes, hypertension, and dyslipidemia.