Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Metabolism Clinical and Experimental 108 (2020) 154244

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

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

Keywords:
COVID-19
SARS-CoV-2
Obesity
MAFLD

Dear Sir,

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.

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 17, 2020 and February 11, 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 >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 were 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).

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 1, 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.

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 >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 are 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

https://doi.org/10.1016/j.metabol.2020.154244

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, $\times10^9$	4.9 (3.9–6.7)	4.8 (3.8–6.3)	5.0 (4.1–6.7)	0.495
$>10\times10^9$, n (%)	2 (3.0%)	0 (0.0%)	2 (4.4%)	0.511
$<4\times10^9$, n (%)	17 (25.8%)	7 (33.3%)	10 (22.2%)	
Lymphocyte count, $\times10^9$	1.2 (0.9–1.6)	1.4 (1.1–1.8)	1.1 (0.9–1.4)	0.040
$<1.5\times10^9$, 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, mmol/L	1.0 ± 0.3	1.1 ± 0.2	1.0 ± 0.3	0.255
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.

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.

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.

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.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2020.154244.

Declaration of competing interest

All authors declare no conflict of interests.

References

[1] WHO characterizes COVID-19 as a pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen; March 13, 2020, Accessed date: 18 March 2020.
[2] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2002032 In press.
[3] Eslam M, Newsome PN, Anstee QM, Targher G, Gomez MR, Zelber-Sagi S, et al. A new definition for metabolic associated fatty liver disease: an international expert consensus statement. J Hepatol 2020. https://doi.org/10.1016/j.jhep.2020.03.039.
[4] Arias-Loste MT, Fábrega E, López-Hoyos M, Crespo J. The crosstalk between hypoxia and innate immunity in the development of obesity-related nonalcoholic fatty liver disease. Biomed Res Int 2015;2015:319745.
[5] Lee CH, Choi SH, Chung GE, Park B, Kwak MS. Nonalcoholic fatty liver disease is associated with decreased lung function. Liver Int 2018;38:2091–100.
[6] Nseir WB, Mograbi JM, Amara AE, Abu Elheja OH, Mahamid MN. Non-alcoholic fatty liver disease and 30-day all-cause mortality in adult patients with community-acquired pneumonia. Qjm 2019;112:95–9.
[7] Peng TC, Kao TW, Wu LW, Chen YJ, Chang YW, Wang CC, et al. Association between pulmonary function and nonalcoholic fatty liver disease in the NHANES III Study. Medicine (Baltimore) 2015;94:e907.
[8] National Health Commission & State Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7); 2020 [EB/OL]. 2020.03.03.
[9] Goda A, Masuyama T. Obesity and overweight in Asian people. Circ J 2016;80:2425–6.
[10] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet Med 2006;23:469–80.
[11] Gao F, Zheng KI, Wang X-B, Sun Q-F, Pan K-H, Wang T-Y, et al. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care 2020.
[12] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
[13] Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, et al. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies. J Clin Transl Hepatol 2020;8(1):18–24.
[14] van der Poorten D, Milner KL, Hui J, Hodge A, Trenell MI, Kench JG, et al. Visceral fat: a key mediator of steatohepatitis in metabolic liver disease. Hepatology 2008;48:449–57.
[15] Chen F, Esmaili S, Rogers GB, Bugianesi E, Petta S, Marchesini G, et al. Lean NAFLD: a distinct entity shaped by differential metabolic adaptation. Hepatology 2019;71(4):1213–27.

Kenneth I. Zheng[1]
MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Feng Gao[1]
Department of Gastroenterology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Xiao-Bo Wang
Department of Critical Care Medicine, Wenzhou Central Hospital, Wenzhou, China

Qing-Feng Sun
Department of Infectious Diseases, Ruian People's Hospital, Wenzhou, China

Ke-Hua Pan
Department of Radiology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Ting-Yao Wang
Department of Nephrology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Yong-Ping Chen
MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Wen-Yue Liu
Department of Endocrinology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China

Jacob George*
Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Sydney, Australia
*Correspondence to: J. George, Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Westmead 2145, NSW, Australia.
E-mail address: jacob.george@sydney.edu.au.

Ming-Hua Zheng**
MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
Institute of Hepatology, Wenzhou Medical University, Wenzhou, China
Key Laboratory of Diagnosis and Treatment for The Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China
**Correspondence to: M.-H. Zheng, MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, No. 2 Fuxue Lane, Wenzhou 325000, China.
E-mail address: zhengmh@wmu.edu.cn.

2 April 2020

[1] Co-first author.