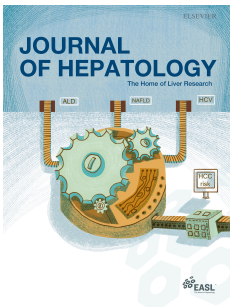
Journal Pre-proof



Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis

Yu-Jie Zhou, Kenneth I. Zheng, Xiao-Bo Wang, Hua-Dong Yan, Qing-Feng Sun, Ke-Hua Pan, Ting-Yao Wang, Hong-Lei Ma, Yong-Ping Chen, Jacob George, Ming-Hua Zheng

PII: S0168-8278(20)30271-3

DOI: https://doi.org/10.1016/j.jhep.2020.04.027

Reference: JHEPAT 7726

To appear in: *Journal of Hepatology*

Received Date: 14 April 2020

Revised Date: 16 April 2020

Accepted Date: 18 April 2020

Please cite this article as: Zhou YJ, Zheng KI, Wang XB, Yan HD, Sun QF, Pan KH, Wang TY, Ma HL, Chen YP, George J, Zheng MH, Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis, *Journal of Hepatology* (2020), doi: https://doi.org/10.1016/j.jhep.2020.04.027.

Title:

Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis

Yu-Jie Zhou[1,2#], Kenneth I. Zheng[1#], Xiao-Bo Wang[3], Hua-Dong Yan[4], Qing-Feng Sun[5], Ke-Hua Pan[6], Ting-Yao Wang[7], Hong-Lei Ma[1], Yong-Ping Chen[1], Jacob George[8*], and Ming-Hua Zheng[1,9,10*]

Institution:

[1] MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

[2] Division of Gastroenterology and Hepatology, Key Laboratory of Gastroenterology and Hepatology, Ministry of Health, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, Shanghai, China;

[3] Department of Critical Care Medicine, Wenzhou Central Hospital, Wenzhou, China;

[4] Department of Hepatology, Key Laboratory of Diagnosis and Treatment of Digestive System Tumors of Zhejiang Province, Hwamei Hospital, Ningbo No.2 Hospital, University of Chinese Academy of Sciences, Ningbo, China;

[5] Department of Infectious Diseases, Ruian People's Hospital, Wenzhou, China;

[6] Department of Radiology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

[7] Department of Nephrology, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China;

[8] Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Sydney, Australia;

[9] Institute of Hepatology, Wenzhou Medical University, Wenzhou, China;

[10] Key Laboratory of Diagnosis and Treatment for The Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China.

[#]**Co-first Author**: Yu-Jie Zhou and Kenneth I. Zheng

***Corresponding Author:**

Ming-Hua Zheng, MD, PhD

MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University; No. 2 Fuxue Lane, Wenzhou 325000, China.

E-mail: zhengmh@wmu.edu.cn; fax: (86) 577-55578522; tel: (86) 577-55579622.

Jacob George, MD, PhD

Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney; Westmead 2145, NSW, Australia.

Email: jacob.george@sydney.edu.au; tel: 61-2-88907705; fax: 61-2-96357582.

Electronic word count: 845

Number of figures and tables: 1

Author Contributions:

Study concept and design: Yu-Jie Zhou and Ming-Hua Zheng

Acquisition of data: Xiao-Bo Wang, Hua-Dong Yan, Qing-Feng Sun, Ke-Hua Pan, Ting-Yao Wang, Hong-Lei Ma, and Yong-Ping Chen

Analysis and interpretation of data: Yu-Jie Zhou

Drafting of the manuscript: Yu-Jie Zhou, and Kenneth I. Zheng

Critical revision of the manuscript for important intellectual content: Jacob George

Study supervision: Ming-Hua Zheng

Conflicts of interest: The authors disclose no conflicts

Acknowledgement: The authors would like to thank Xiaolong Qi, the chair of Chinese Portal Hypertension Diagnosis and Monitoring Study Group (CHESS) from the First Hospital of Lanzhou University, for his kindly technical assistance.

Funding sources:

This work was supported by grants from the National Natural Science Foundation of China (81500665), Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (2018ZD039), Ruian Science and Technology Bureau (2020023), High Level Creative Talents from Department of Public Health in Zhejiang Province, and Project of New Century 551 Talent Nurturing in Wenzhou.

To the Editor:

We read with great interest the article by Ji *et al.* on liver injury patterns and the clinical implications of metabolic associated fatty liver disease (MAFLD) in patients with Coronavirus Disease 2019 (COVID-19).[1] Metabolic and cardiovascular comorbidities like diabetes and hypertension aggravate the severity of COVID-19.[2] Another comorbidity, MAFLD, also affects COVID-19 severity, as pointed out by Ji *et al.*. Since excess liver fat is seen in up to a quarter of people,[3] we hypothesized that its impact on severity might be modulated by age. We considered that disease severity of older patients with a greater burden of cardiac and respiratory illness would more likely be impacted by their comorbid conditions, than the presence of liver fat. In this study, we investigated the effects of MAFLD on COVID-19 severity in older versus younger patients.

We consecutively recruited 327 adult patients (≥18 years old) with COVID-19 from four centers (the First Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital, Ningbo No.2 Hospital, and Ruian People's Hospital) in China, from 1st January 2020 to 29th February 2020. COVID-19 was diagnosed by high-throughput sequencing or RT-PCR assay of oropharyngeal swab specimens. Some of these patients were the subject of a previous report.[4] All subjects underwent screening for fatty liver by computed tomography. MAFLD was diagnosed based on the recent consensus criteria.[5, 6] Overweight was defined as body mass index (BMI) ≥23 kg/m^2, and obesity was defined as BMI ≥25 kg/m^2 in Asians.[7] Diabetes mellitus was

diagnosed based on the history or hemoglobin A1c ≥6.5%.[8] Hypertension was defined as blood pressure ≥130/85 mmHg or specific drug treatment. The requirement for written informed consent was waived by the ethics committees of all four centers due to the emergent epidemic and the anonymized retrospective nature of the analysis. All demographic and laboratory parameters were collected on the day of admission. COVID-19 severity was evaluated during hospitalization and divided into four subtypes namely mild, moderate, severe and critical illness in line with management guidelines in China. We defined mild and moderate COVID-19 subtypes as 'non-severe COVID-19', and severe and critically ill subtypes as 'severe COVID-19'. All subjects received standard medical treatment according to the COVID-19 management guidance (7^{th} edition).[9]

Seventy-four patients (22.6%) were elderly (i.e. more than 60 years of age) and 93 patients (28.4%) had MAFLD. In patients younger than 60 years, hypertension occurred in 45 (17.3%) patients, and diabetes were noted in 29 (11.2%) patients. In patients older than 60 years, there were 32 (43.2%) cases of hypertension and 18 (24.3%) of diabetes; this was significantly higher than in younger patients (P <0.001 and P=0.004, respectively). In contrast to the findings in younger patients (age <60 years), no significant difference in C-reactive protein, prevalence of diabetes and hypertension, or blood lipids was observed between non-MAFLD and MAFLD groups in elderly patients (all P >0.05). Moreover, an association between presence of MAFLD and COVID-19 severity was only observed in younger (Chi-square test P =

0.001), but not in elderly patients (Chi-square test $P = 0.66$).

MAFLD patients comprised 24.2% of the younger and 30.6% of the elderly cohort with non-severe COVID-19 (P=0.35), and 55.9% of the younger and 24% of the elderly patients with severe COVID-19 (P=0.01). Considering the effects of confounding bias, we performed multivariable logistic regression analyses (**Table 1**). In patients aged younger than 60 years, a more than two-fold higher prevalence of severe COVID-19 was observed in MAFLD patients compared to those without; this association remained significant after adjusting for age, sex, smoking status, overweight, diabetes, and hypertension (adjusted-OR 2.67, 95%CI 1.13-6.34, P=0.03). In contrast, MAFLD was not associated with disease severity in multivariable analysis in elderly patients (P >0.05). We performed sensitivity analysis by setting a cut-off point other than 60 years to define younger and elderly patients. Similar results were observed at cut-offs using 55 and 65 years.

This multi-center study (COVID-MAFLD-CHESS) establishes a synergistic effect of MAFLD for severe COVID-19 in patient aged less than 60 years. The exact mechanism(s) underlying the age-dependent relationship is uncertain. Previous research has noted cellular immune dysregulation in COVID-19.[10] Thus, it might be postulated that hepatic and systemic immune responses caused by MAFLD[11] contributes to the cytokine storm in younger patients with COVID-19. In the elderly however, other comorbidities like coronary heart disease and chronic obstructive

pulmonary disease are more prevalent and any association with MAFLD might be masked by their impact.[2]

A notable limitation of our study was the smaller sample size of the older cohort of patients, which might influence the validity of the results. When 60 years was set as the cut-off, there were only 53 non-MAFLD and 21 MAFLD in the older group for analysis. To remedy this shortcoming, we performed sensitivity analysis using 199 younger (including 56 MAFLD) vs. 128 older (including 37 MAFLD) patients with 55 years as a cut-off; the results remained insignificant in older patients. Further validation in a larger cohort from other ethnicities is warranted. COVID-19 as we show, is worse in younger patients with MAFLD and increases the likelihood of severe illness approximately three-fold after adjustment for confounders.

REFERENCES

[1] Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID-19: a preliminary analysis. Journal of hepatology 2020.

[2] Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. The European respiratory journal 2020.

[3] Younossi ZM. Non-alcoholic fatty liver disease - A global public health

perspective. Journal of hepatology 2019;70:531-544.

[4] Gao F, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, et al. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care 2020 (Accepted on 08 Apr 2020).

[5] Eslam M, Sanyal AJ, George J. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020.

[6] Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero□ Gomez M, et al. A new definition for metabolic associated fatty liver disease: an international expert consensus statement. Journal of hepatology 2020.

[7] Goda A, Masuyama T. Obesity and Overweight in Asian People. Circulation journal : official journal of the Japanese Circulation Society 2016;80:2425-2426.

[8] Sabanayagam C, Khoo EY, Lye WK, Ikram MK, Lamoureux EL, Cheng CY, et al. Diagnosis of diabetes mellitus using HbA1c in Asians: relationship between HbA1c and retinopathy in a multiethnic Asian population. The Journal of clinical endocrinology and metabolism 2015;100:689-696.

[9] 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.

[10] Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. J Clin Invest 2020.

[11] Narayanan S, Surette FA, Hahn YS. The Immune Landscape in Nonalcoholic

Steatohepatitis. Immune Netw 2016;16:147-158.

Table legends

Table 1. Association between the presence of MAFLD and COVID-19 severity in younger and older patients.

Table 1. Association between the presence of MAFLD and COVID-19 severity in younger and older patients.

	Younger patients			**Elderly patients**		
	OR	95% CI	*P*	OR	95% CI	*P*
60 years as the cut-off	n=253 [72(28.5%) MAFLD, 34(13.4%) severe cases]			n=74 [21(28.4%) MAFLD, 25(33.8%) severe cases]		
Unadjusted	3.97	1.89-8.35	< 0.001	0.72	0.24-2.15	0.55
Adjusted model I	3.25	1.47-7.16	0.003	0.75	0.25-2.28	0.61
Adjusted model II	2.49	1.04-5.96	0.04	0.45	0.13-1.59	0.22
Adjusted model III	2.67	1.13-6.34	0.03	0.61	0.18-2.03	0.42
55 years as the cut-off	n=199 [56(28.1%) MAFLD, 21(10.6%) severe cases]			n=128 [37(28.9%) MAFLD, 38(29.7%) severe cases]		
Unadjusted	6.48	2.45-17.1	< 0.001	1.00	0.44-2.31	0.99
Adjusted model I	5.02	1.81-13.90	0.002	1.02	0.44-2.39	0.96
Adjusted model II	3.10	1.01-9.56	0.05	0.77	0.30-1.99	0.60
Adjusted model III	3.63	1.20-10.95	0.02	0.91	0.37-2.28	0.85
65 years as the cut-off	n=276 [80(29.0%) MAFLD, 41(14.9%) severe cases]			n=51 [13(25.5%) MAFLD, 18(35.3%) severe cases]		
Unadjusted	3.13	1.59-6.18	0.001	0.76	0.20-2.94	0.69
Adjusted model I	2.69	1.31-5.53	0.01	0.75	0.19-2.94	0.68
Adjusted model II	2.22	1.02-4.86	0.04	0.33	0.07-1.69	0.19
Adjusted model III	2.41	1.12-5.22	0.03	0.59	0.13-2.64	0.49

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.

Model III: adjusted for age, sex, smoking, overweight, diabetes mellitus and hypertension.