obesity, chronic liver diseases and age and the outcome of COVID-19 in humans.[6]

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Conflict of interest
We declare no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
DJ, EQ, JX, and DZ treated the patients. DJ, GC, YW and GL processed statistical data and drafted the manuscript. DJ and GL had the idea for and designed the study.

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

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 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.*[1] 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 *vs.* younger patients.

We consecutively recruited 327 adult patients (≥18 years old) with COVID-19 from 4 centers (the First Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital, Ningbo No.2 Hospital, and Ruian People's Hospital) in China, from 17th January 2020 to 11th February 2020. COVID-19 was diagnosed by high-throughput sequencing or reverse-transcription PCR assays of oropharyngeal swab specimens. Some of these patients were the subject of a previous report.[4] All patients underwent screening for fatty liver by CT. 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

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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 4 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 4 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 patients received standard medical treatment according to the COVID-19 management guidance (7th 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 was 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 observed in younger patients (Chi-square test p = 0.001), but not in elderly patients (Chi-square test p = 0.66).

Patients with MAFLD 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 2-fold higher prevalence of severe COVID-19 was observed in those with MAFLD compared to those without; this association remained significant after adjusting for age, sex, smoking status, overweight, diabetes, and hypertension (adjusted odds ratio 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 multicenter 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] contribute 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 patients available for analysis in the older group. To remedy this shortcoming, we performed sensitivity analysis in 199 younger patients (including 56 with MAFLD) *vs.* 128 older patients (including 37 with MAFLD), using 55 years as a cut-off; the results remained insignificant in older patients. Further validation in a larger cohort including other ethnicities is warranted. COVID-19 as we show, is worse in younger patients with MAFLD and increases the likelihood of severe illness by approximately 3-fold after adjustment for confounders.

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 ORs and 95% 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.
MAFLD, metabolic-associated fatty liver disease; OR, odds ratio.

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Conflicts of interest
The authors disclose no conflicts.

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Authors' 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.

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