LETTER

Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores

A recent study reported that patients with severe COVID-19 were more likely to have non-alcoholic fatty liver disease (NAFLD) compared with those with non-severe COVID-19 illness.[1] However, the prognosis of NAFLD (recently renamed metabolic dysfunction-associated fatty liver disease (MAFLD)[2]) is determined by the severity of liver fibrosis.[3 4] We therefore postulated that patients with MAFLD with increased non-invasive liver fibrosis scores are at higher risk of severe illness from COVID-19.

We studied 310 patients with laboratory-confirmed COVID-19 who were consecutively hospitalised at four sites in Zhejiang Province, China, between January and February 2020. Some of these patients (n=150) have been included in a prior study examining the association between obesity and COVID-19 severity.[5] Patients with viral hepatitis, excessive alcohol consumption, chronic pulmonary diseases or active cancers were excluded. Clinical and laboratory data were collected at hospital admission. All patients were screened for hepatic steatosis by computed tomography and subsequently diagnosed as MAFLD.[6] The originally validated cut-points for fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS) were used to categorise liver fibrosis probability as low, intermediate or high.[7] COVID-19 severity was classified as severe and non-severe.[8] The study protocol was approved by the local ethics committees of the four hospitals.

In our cohort of 310 confirmed cases of COVID-19, 94 (30.3%) patients had MAFLD. As shown in table 1, patients with MAFLD with intermediate or high FIB-4 scores were more likely to be older, obese, have diabetes and have higher NFS, higher liver enzymes, higher C reactive protein, as well as lower levels of lymphocyte count, platelet count, triglycerides and high-density lipoprotein cholesterol compared with their counterparts with low FIB-4 score or those without MAFLD. Notably, the severity of COVID-19 illness markedly increased among patients with MAFLD with intermediate or high FIB-4 scores.

The severity of COVID-19 illness was associated with intermediate (unadjusted OR 4.32, 95% CI 1.94 to 9.59) or high (unadjusted-OR 5.73, 95% CI 1.84 to 17.9) FIB4 scores among patients with MAFLD (table 2, model 1A). This association remained significant after adjusting for sex, obesity and diabetes (model 1B). We did not additionally adjust for age, because this variable was incorporated in the FIB-4 score. Similar to the main analysis, when the intermediate and high FIB-4 categories were combined, the risk of severe COVID-19 illness was increased with intermediate/high FIB-4 score in unadjusted (model 2A) and multivariate-adjusted analyses (model 2B).

Similarly, the intermediate/high NFS (unadjusted-OR 5.21, 95% CI 2.39 to 11.3) was associated with a higher risk of severe COVID-19 illness. This significant association persisted in multivariate-adjusted analyses after controlling for sex, obesity and diabetes (adjusted OR 2.91, 95% CI 1.20 to 7.06).

When we included FIB-4 or NFS as continuous measures in multivariable regression models, increasing FIB-4 (adjusted OR 1.90, 95% CI 1.33 to 2.72) or NFS (adjusted OR 2.57, 95% CI 1.73 to 3.82) were significantly associated with greater COVID-19 severity, even after adjusting for sex, obesity, diabetes and presence/absence of MAFLD.

Our study has some limitations, including the relatively modest sample size, the Asian ancestry of the cohort and the use of non-invasive fibrosis scores without a histological diagnosis of liver fibrosis. Despite these limitations, our study is the first to examine the impact of FIB-4 or NFS on COVID-19 severity in patients with imaging-defined

Table 1 Main clinical and biochemical characteristics of patients with laboratory-confirmed COVID-19, stratified by the presence or absence of imaging-defined MAFLD with increasing levels of FIB-4 score

	No MAFLD	MAFLD with low FIB-4 (≤1.3)	MAFLD with intermediate FIB-4 (1.3–2.67)	MAFLD with high FIB-4 (>2.67)	P value
N	216	44	36	14	
Age (years)	45.9±15.4	41.2±14.2	54.2±10.8	59.9±9.1	**<0.001**
Male sex (%)	43.5	54.6	63.9	57.1	0.086
BMI (kg/m^2)	23.0±3.2	26.5±4.7	26.6±3.2	26.1±2.8	**<0.001**
Obesity (%)	25.9	61.4	75.0	64.3	**<0.001**
Current smokers (%)	8.8	2.3	11.1	7.1	0.768
Systolic blood pressure (mm Hg)	130±17	136±15	136±16	136±14	**0.047**
Diastolic blood pressure (mm Hg)	80±11	84±11	82±11	79±8	0.117
Prior diabetes (%)	7.4	20.4	13.9	28.6	**0.010**
White blood count (×10^9/L)	4.90 (3.9–6.2)	5.35 (4.5–6.7)	4.69 (3.8–6.6)	4.90 (3.2–5.8)	0.254
Neutrophil count (×10^9/L)	3.05 (2.2–4.1)	3.49 (2.6–4.2)	3.0 (2.4–4.7)	3.20 (1.9–4.5)	0.759
Lymphocyte count (×10^9/L)	1.20 (0.9–1.6)	1.40 (1.2–2.0)	1.10 (0.7–1.3)	0.92 (0.7–1.14)	**<0.001**
Haemoglobin (g/L)	132.4±16	136.6±15	135.5±12	135.8±17	0.305
Platelet count (×100 000/mm^3)	211±72	246±75	183±64	125±24	**<0.001**
Prothrombin time (s), n=211	12.1±1.3	11.9±2.3	12.2±1.2	12.3±1.1	0.754
APTT (s), n=211	31.5±3.8	32.7±5.4	32.8±3.7	35.3±7.4	**0.026**
D-dimer (mg/L), n=183	0.18 (0.11–0.29)	0.21 (0.1–0.5)	0.21 (0.1–0.4)	0.27 (0.1–0.4)	0.432
C reactive protein (mg/L)	7.9 (1.9–24.9)	8.6 (2.9–23.6)	25.4 (8.7–53.3)	25.5 (8.7–53.4)	**<0.001**
Procalcitonin (ng/mL), n=190	0.05 (0.03–0.25)	0.08 (0.04–0.25)	0.06 (0.04–0.10)	0.20 (0.08–0.25)	**0.077**
Albumin (g/L), n=286	41.4 (38.0–44.5)	42.3 (37.3–44.6)	41.0 (36.9–43.1)	38.6 (37.7–42.8)	0.348
Total bilirubin (µmol/L)	10.5 (7.0–15.5)	10.1 (7.5–15.6)	12.0 (9.5–16.6)	15.3 (11.8–17.3)	**0.025**
AST (IU/L)	22 (17–27)	23 (19–32)	32 (26–50)	44 (29–83)	**<0.001**
ALT (IU/L)	18 (13–27)	30 (22–52)	28 (22–48)	27 (16–82)	**<0.001**
GGT (IU/L)	21 (14–33)	31 (22–54)	51 (24–81)	49 (32–102)	**<0.001**
Elevated AST>40 IU/L (%)	7.9	9.1	27.8	57.1	**<0.001**
Elevated ALT >40 IU/L (%)	13.0	29.6	30.6	42.9	**<0.001**
Total cholesterol (mmol/L)	3.98±0.8	4.11±0.9	3.73±0.7	3.82±1.0	0.217
Triglycerides (mmol/L)	1.15 (0.9–1.7)	1.61 (1.0–2.1)	1.48 (1.1–1.8)	1.11 (0.9–1.6)	**<0.005**
HDL cholesterol (mmol/L)	1.18±0.4	0.96±0.2	1.06±0.2	1.09±0.4	**<0.005**
LDL cholesterol (mmol/L)	2.23±0.7	2.54±0.8	2.10±0.7	2.20±0.8	0.116
Hospital stay (days)	18 (13–24)	18 (13–22)	22 (16–29)	17 (6–23)	0.122
NAFLD fibrosis score, n=286	−1.82 (−2.8 to −1.0)	−2.61 (−3.1 to −1.9)	−0.68 (−1.4 to −0.2)	+0.26 (−0.03 to 1.6)	**<0.005**
COVID-19 severity					**<0.001**
Non-severe (%)	88.4	86.4	63.9	57.1	
Severe (%)	11.6	13.6	36.1	42.9	

Sample size, n=310, except where indicated. Diabetes was diagnosed as self-reported history of disease and/or specific drug treatment. Obesity was diagnosed as BMI>25 kg/m^2. Data are expressed as means±SD, medians and IQRs (in parentheses) or frequencies. Differences among the four groups of patients were tested by Fisher's exact test for categorical variables, one-way analysis of variance for normally distributed continuous variables or the Kruskal-Wallis test for not normally distributed continuous variables. For the sake of clarity, significant p values are highlighted in bold.
ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; GGT, gamma-glutamyltransferase; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease.

Table 2 Association between imaging-defined MAFLD with increasing levels of FIB-4 score and risk of having severe illness associated with COVID-19

Logistic regression analyses	ORs	95% CI	P value
Severity of COVID-19 illness (mild/moderate vs severe/critical)			
Unadjusted model 1A			
MAFLD/FIB-4 status			
No MAFLD (n=216)	Ref.	Ref.	
MAFLD with low FIB-4 (≤1.3; n=44)	1.21	0.46 to 3.14	0.701
MAFLD with intermediate FIB-4 (1.3–2.67, n=36)	4.32	1.94 to 9.59	**<0.001**
MAFLD with high FIB-4 (>2.67, n=14)	5.73	1.84 to 17.9	**<0.005**
Adjusted model 1B			
MAFLD/FIB-4 status			
No MAFLD (n=216)	Ref.	Ref.	
MAFLD with low FIB-4 (≤1.3, n=44)	0.82	0.30 to 2.24	0.696
MAFLD with intermediate FIB-4 (1.3–2.67, n=36)	2.59	1.09 to 6.13	**0.030**
MAFLD with high FIB-4 (>2.67, n=14)	4.04	1.22 to 13.3	**0.021**
Sex (men vs women)	1.78	0.93 to 3.44	0.079
Obesity (yes vs no)	2.62	1.31 to 5.24	**<0.005**
Prior diabetes (yes vs no)	1.04	0.40 to 2.80	0.928
Unadjusted model 2A			
MAFLD/FIB-4 status			
No MAFLD (n=216)	Ref.	Ref.	
MAFLD with low FIB-4 (≤1.3, n=44)	1.21	0.46 to 3.14	0.701
MAFLD with intermediate/high FIB-4 (>1.3, n=50)	4.68	2.31 to 9.49	**<0.001**
Adjusted model 2B			
MAFLD/FIB-4 status			
No MAFLD (n=216)	Ref.	Ref.	
MAFLD with low FIB-4 (≤1.3, n=44)	0.82	0.30 to 2.24	0.696
MAFLD with intermediate/high FIB-4 (>1.3, n=50)	2.95	1.37 to 6.34	**<0.005**
Sex (men vs women)	1.79	0.94 to 3.45	0.084
Obesity (yes vs no)	2.60	1.30 to 5.16	**<0.005**
Prior diabetes (yes vs no)	1.09	0.41 to 2.89	0.862

Sample size, n=310. Data are expressed as ORs and 95% CI as tested by univariable (unadjusted) and multivariable (adjusted) logistic regression analysis. Diabetes was diagnosed as self-reported history of disease and/or specific drug treatment. Obesity was diagnosed as BMI>25 kg/m^2.
In the adjusted logistic regression models, we did not additionally adjust also for age, because this variable is already incorporated in the FIB-4 score.
FIB-4, fibrosis-4; MAFLD, metabolic associated fatty liver disease; Ref, reference category.

MAFLD. These non-invasive fibrosis scores have been shown to predict histological fibrosis stage with reasonable accuracy in cohorts of patients with MAFLD,[7] and are also associated with increased overall and disease-specific mortality in population-based studies.[9 10] Our data demonstrate that patients with MAFLD with increased FIB-4 or NFS are at higher likelihood of having severe COVID-19 illness, irrespective of metabolic comorbidities. In the context of COVID-19, the presence of MAFLD with significant/advanced fibrosis might exacerbate the virus-induced cytokine 'storm', possibly through the hepatic release of multiple proinflammatory cytokines, thereby contributing mechanistically to severe COVID-19. Further research is needed to better understand the mechanistic link of advanced MAFLD to the viral disease process.

Giovanni Targher ,[1] **Alessandro Mantovani,**[1] **Christopher D Byrne,**[2] **Xiao-Bo Wang,**[3] **Hua-Dong Yan,**[4] **Qing-Feng Sun,**[5] **Ke-Hua Pan,**[5] **Kenneth I Zheng** ,[6] **Yong-Ping Chen,**[7] **Mohammed Eslam,**[8] **Jacob George** ,[8] **Ming-Hua Zheng** [6,9]

[1]Department of Medicine, Endocrinology and Metabolism, University of Verona, Verona, Veneto, Italy
[2]Southampton National Institute for Health Research Biomedical Research Centre, Southampton General Hospital, Southampton, Hampshire, UK
[3]Department of Critical Care Medicine, Wenzhou Medical College First Affiliated Hospital, Wenzhou, Zhejiang, China
[4]Department of Hepatology, Ningbo No 2 Hospital, Ningbo, Zhejiang, China
[5]Department of Radiology, Wenzhou Medical University First Affiliated Hospital, Wenzhou, Zhejiang, China
[6]NAFLD Research Center, Department of Hepatology, Wenzhou Medical College First Affiliated Hospital, Wenzhou, Zhejiang, China
[7]Department of Infection and Liver Diseases, Liver Research Center, Wenzhou Medical College First Affiliated Hospital, Wenzhou, Zhejiang, China
[8]Storr Liver Centre, Westmead Institute for Medical Research, Westmead, New South Wales, Australia
[9]Institute of Hepatology, Wenzhou Medical University, Wenzhou, Zhejiang, China

Correspondence to Professor Giovanni Targher, Department of Medicine, Endocrinology and Metabolism, University of Verona, Verona 37126, Italy; giovanni.targher@univr.it

Contributors Concept and design: M-HZ. Acquisition of data: X-BW, H-dY, Q-FS, K-HP, KIZ and Y-PC. Analysis and interpretation of data: GT and AM. Drafting of the manuscript: GT. Critical revision of the manuscript for important intellectual content: AM, CDB, ME and JG. Study supervision: M-HZ

Funding M-HZ is supported by grants from the National Natural Science Foundation of China (81500665). CDB is supported in part by the Southampton NIHR Biomedical Research Centre (IS-BRC-20004), UK. GT is supported in part by grants from the School of Medicine, University of Verona, Verona, Italy.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Targher G, Mantovani A, Byrne CD, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2020-321611

Received 28 April 2020
Revised 4 May 2020
Accepted 6 May 2020

Gut 2020;**0**:1–2. doi:10.1136/gutjnl-2020-321611

ORCID iDs
Giovanni Targher http://orcid.org/0000-0002-4325-3900
Kenneth I Zheng http://orcid.org/0000-0002-1726-9298
Jacob George http://orcid.org/0000-0002-8421-5476
Ming-Hua Zheng http://orcid.org/0000-0003-4984-2631

REFERENCES

1 Ji D, Qin E, Xu J, *et al*. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020:S0168-8278(20)30206-3.
2 Eslam M, Sanyal AJ, George J, *et al*. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology* 2020;158:1999–2014.
3 Younossi ZM. Non-alcoholic fatty liver disease - A global public health perspective. *J Hepatol* 2019;70:531–44.
4 Taylor RS, Taylor RJ, Bayliss S, *et al*. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology* 2020;158:1611–25.
5 Gao F, Zheng KI, Wang XB, *et al*. Obesity as a risk factor for greater severity of COVID-19. *Diabetes Care* 2020.
6 Eslam M, Newsome PN, Sarin SK, *et al*. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. *J Hepatol* 2020. doi:10.1016/j.jhep.2020.03.039. [Epub ahead of print: 08 Apr 2020].
7 Vilar-Gomez E, Chalasani N. Non-invasive assessment of non-alcoholic fatty liver disease: clinical prediction rules and blood-based biomarkers. *J Hepatol* 2018;68:305–15.
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.
9 Unalp-Arida A, Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. *Hepatology* 2017;66:84–95.
10 Sung Ki-Chul, Johnston MP, Lee MY, *et al*. Non-invasive liver fibrosis scores are strongly associated with liver cancer mortality in general population without liver disease. *Liver Int* 2020;59