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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression – The debate continues

To the Editor:

We read with great interest the letter by Ji *et al.*[1] Obesity is a well-recognized risk factor for the development of non-alcoholic fatty liver disease (NAFLD) or metabolic dysfunction-associated liver disease (MAFLD) and is associated with adverse outcomes in COVID-19 patients.[2,3] Qatar's population has a high prevalence of obesity[4] and also has one of the highest rates of COVID-19 cases per million population, with one of the lowest mortality rates.[5] We hypothesized that NAFLD is an independent risk factor for worse outcomes in hospitalized COVID-19 patients in our population.

Methods

We studied 589 patients with confirmed symptomatic COVID-19 who were hospitalized from May 2020 to June 2020 to COVID-19 facilities in the state of Qatar. We categorized them into 2 groups; NAFLD and no NAFLD, based on the hepatic steatosis index (HSI).[6] People with an HSI index of 36 and above were considered as having NAFLD. The lowest aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values within the last 1 year before the COVID-19 diagnosis, and, when unavailable, the lowest values at the time of recovery were used for calculation of HSI index. The primary outcome was mortality, and secondary outcomes were disease severity on presentation, and disease progression, and liver injury. Development of acute respiratory distress syndrome (ARDS), requirement for intensive care unit (ICU) admission, and mechanical ventilation were regarded as markers of disease progression. Disease severity was defined using the WHO classification into severe and non-severe.[7] Liver injury was classified as borderline if ALT or AST were less than twice the upper limit of normal (ULN), mild if elevated 2–5×, moderate if 5–15×, and severe if more than 15× the ULN.[8] There were no patients with excessive use of alcohol in our study. The Medical Research Center of Hamad Medical Corporation approved the study (MRC-01-20-631).

Results

Univariate regression analysis showed that age, gender, diabetes mellitus, and increased BMI were significantly associated with mortality (Table 1). NAFLD was significantly associated with increased disease severity on admission, ICU admission, and requirement for mechanical ventilation (Table 1). We performed multivariate regression analysis using all the statistically significant variables. Age above 50 years was the only predictor of increased mortality (odds ratio [OR] 8.88; 95% CI 3.61–21.84; p <0.000*). For disease severity on presentation, only the presence of diabetes mellitus was a statistically significant predictor (OR 2.2; 95% CI 1.5–3.19; p <0.000). Age above 50 years and a BMI above 25 kg/m^2 were the only 2 significant predictors of all 3 markers of disease progression in our study: development of ARDS, ICU admission, and mechanical ventilation. Age was associated with increased risk of ARDS (OR 2.57; 95% CI 1.80–3.66; p <0.000*), ICU admission (OR 2.36; 95% CI 1.67–3.33; p <0.000*) and mechanical ventilation (OR 2.03; 95% CI 1.42–2.90; p <0.000*). Obesity was associated with increased risk of ARDS (OR 1.97; 95% CI 1.32–2.94; p = 0.001), ICU admission (OR 1.83; 95% CI 1.26–2.65; p = 0.001) and mechanical ventilation (OR 1.89; 95% CI 1.25–2.87; p = 0.002). The presence of NAFLD was not an independent predictor of increased mortality, disease severity on presentation, or disease progression. However, the presence of NAFLD was a predictor of the development of mild liver injury (OR 2.99; 95% CI 1.62–4.37; p = 0.000) and moderate liver injury (OR 5.104; 95% CI 3.21–6.99; p = 0.000).

Discussion

The presence of NAFLD has been associated with poor outcomes in patients with COVID-19.[1,3,9] However, our results conflict with these reports. We used similar inclusion criteria and used the HSI index as a surrogate marker for the presence of NAFLD like Ji *et al.*[1] We found that NAFLD is an independent predictor of the development of mild to moderate liver injury, like the authors described. However, when controlled for covariates in multivariate analysis, NAFLD was not a predictor of mortality, disease severity, or markers of disease progression in our study. We used the development of ARDS, ICU admission requirements, and the need for mechanical ventilation as surrogate markers of disease progression while the authors used the development of tachypnea and the requirement for supplemental oxygenation as surrogates of disease progression . Our observation was that in hospitalized patients using tachypnea and need for supplemental oxygen even once was quite common, so they are probably not the best markers for disease progression.

The difference in our results could be due to a much larger sample size of patients with NAFLD from heterogeneous ethnic populations in our study. Although the HSI index has a high specificity (93%) and positive predictive value (99%), it is affected by inflammation and potentially could overestimate the prevalence of NAFLD.[10] There is a need to study the outcomes in large scale studies with histologically confirmed cases of NAFLD and COVID-19.

Conclusion

The presence of NAFLD is an independent predictor of mild to moderate liver injury in hospitalized patients with COVID-19. However, NAFLD was not an independent predictor of mortality, disease severity on presentation, or disease progression in patients with COVID-19.

Keywords: COVID-19; Fatty liver; NAFLD; MAFLD; Mortality; Liver injury.
Received 2 September 2020; accepted 6 September 2020; available online 19 November 2020
https://doi.org/10.1016/j.jhep.2020.09.006

Table 1. Comparative results of patients with and without NAFLD on univariate analysis.

	No NAFLD (n = 269)	NAFLD (n = 320)	*p* value
Age (years) [±SD]	44.5 [13.85]	47.78 [13.4]	0.0073
Gender (male percentage)	242, (Male 89.6%)	257, (Male 80.8%)	0.016
Diabetes mellitus	75 (27.78%)	160 (50.3%)	0.000
Hypertension	70 (25.93)	135 (42.45%)	0.000
Smoking	31 (11.56%)	37 (11.86%)	0.764
BMI [±SD]	25.61 [7.47]	30.76 [4.9]	0.000
Coronary artery disease	19 (7.04%)	30 (9.43%)	0.224
Chronic kidney disease	17 (6.32%)	33 (10.38%)	0.062
Cirrhosis	7 (2.59%)	3 (0.95 %)	0.516
Malignancy	12 (4.46%)	4 (1.25%)	0.067
Lung disease	15 (5.56%)	25 (7.85%)	0.252
Use of Immunosuppressive drugs	11 (4.07%)	14 (4.39%)	0.556
Severe disease on presentation	60 (22.3%)	95 (29.87%)	0.041
ARDS	77 (28.9%)	128 (40.3%)	0.004
ICU admission	102 (38.64%)	157 (49.68%)	0.008
Mortality	15 (5.68%)	19 (6.01%)	0.866
Mechanical ventilation	70 (26.62%)	114 (36.31%)	0.013
Multiorgan failure	19 (7.04%)	29 (9.21%)	0.382
Liver failure	1 (0.38%)	6 (1.9%)	0.095
Liver injury	132 (49.4%)	186 (59%)	0.018
Borderline elevation (<2× ULN)	95 (35%)	121 (38.4%)	
Mild (2–5×)	30 (11.3%)	55 (17.4%)	
Moderate(5–15×)	5 (1.87%)	10 (3.1%)	
Severe (>15×)	2 (0.7%)	0 (0%)	

The continuous variables are normally distributed and expressed as mean ±SD, and were compared using Student's *t* test. normally distributed. The categorical variables were presented as numbers (percentage) and compared by the chi-square test or Fisher's exact test. ARDS, acute respiratory distress syndrome; BMI, body mass index; ICU, intensive care unit; NAFLD, non alcoholic fatty liver disease; ULN, upper limit of normal.

Financial support
Funding for publications costs are covered by Hamad Medical Corporation.

Conflict of interest
The authors declare no conflicts of interest that pertain to this work.

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

Authors' contribution
KM and MUK conceived and designed the study, did data analysis, literature review and manuscript writing. FI, DHA, HSC, FA, PI, KEN GB, MA, KA, SA, YMK did data collection, data analysis, manuscript writing and literature review. All authors verified the final version of the study.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.09.006.

References
Author names in bold designate shared co-first authorship

[1] **Ji D**, **Qin E**, Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. J Hepatol 2020;73(2):451–453.
[2] Eslam M, Sanyal AJ, George J, International Consensus Panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158(7):1999–2014.e1.
[3] Zhou YJ, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, et al. Metabolic-associated fatty liver disease is associated with severity of COVID-19. Liver Int 2020;40(9):2160–2163.
[4] Musaiger AO. Overweight and obesity in eastern mediterranean region: prevalence and possible causes. J Obes 2011;2011:407237.
[5] Coronavirus Update (Live): 23,277,088 Cases and 806,013 Deaths from COVID-19 Virus Pandemic - Worldometer [Internet]. Available at: https://www.worldometers.info/coronavirus/#countries. [Accessed 22 August 2020].
[6] Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42(7):503–508.
[7] Clinical Management of COVID-19 [Internet]. Available at: https://www.who.int/publications-detail-redirect/clinical-management-of-covid-19. [Accessed 22 August 2020].
[8] **Kwo PY**, **Cohen SM**, **Lim JK**. ACG Clinical Guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol 2017;112(1):18–35.
[9] Targher G, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QF, et al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. Gut 2020;69(8):1545–1547.
[10] **Fedchuk L**, **Nascimbeni F**, Pais R, Charlotte F, Housset C, Ratziu V, LIDO Study Group. Performance and limitations of steatosis biomarkers in patients with nonalcoholic fatty liver disease. Aliment Pharmacol Ther 2014;40(10):1209–1222
.

Kamran Mushtaq[1,2,*]
Muhammad Umair Khan[1,2]
Fatima Iqbal[2,3]
Deema Hussam Alsoub[4]
Hammad Shabir Chaudhry[4]
Fateen Ata[4]
Phool Iqbal[4]
Khaled Elfert[1]
Girisha Balaraju[1]
Muna Almaslamani[3,5]
Khalid Al-Ejji[1]
Saad AlKaabi[1]
Yasser Medhat Kamel[1]
[1]*Department of Gastroenterology and Hepatology, Hamad Medical Corporation*
[2]*Harvard T.H Chan School of Public Health, USA*

[3]Department of Infectious Disease, Communicable Disease Center, Doha, Qatar
[4]Department of Medicine, Hamad Medical Corporation, Doha, Qatar
[5]Weill Cornell Medicine, Qatar (WCM-Q), Doha, Qatar

*Corresponding author. Address: Department of Gastroenterology, Hamad Medical Corporation, P.O. Box 3050, Doha, Qatar. Tel.: +97466349759.
E-mail address: kmushtaq@hamad.qa (K. Mushtaq)

Reply to: "NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression – The debate continues"

To the Editor:

We read with interest the article by Mushtaq *et al.*[1] Both their study and ours[1,2] used similar inclusion criteria and the hepatic steatosis index as a surrogate marker for the presence of NAFLD. We found that NAFLD is an independent predictor of disease progression. However, their study showed that when controlled for covariates in multivariate analysis, NAFLD was not a predictor of mortality, disease severity, or markers of disease progression. Mushtaq *et al.* correctly pointed out the different conclusions may be due to the different criteria used to define COVID-19 disease progression, development of tachypnea and requirement of oxygen supplements in our study as opposed to development of acute respiratory distress syndrome, intensive care unit (ICU) admission, and the need for mechanical ventilation in their study. We chose a less stringent criteria for disease progression because our main purpose was to identify those patients who were absolutely safe to be managed at home or community facilities (no need for supplementary oxygen) as opposed to identifying patients that may require mechanical ventilation or ICU requirement. Zhou *et al.*, using a definition of severe COVID-19 similar to ours, also showed that metabolic dysfunction-associated fatty liver disease (MAFLD) was associated with severe COVID-19 in patients age <60.[3] Also, the prevalence of diabetes and hypertension in their NAFLD population were 50% and 42%, respectively, compared with 17.1% and 26.3%, respectively, in our and Zhou *et al.*'s studies. This may affect the impact of NAFLD in multivariate analysis. We agreed with the authors' suggestion that there is a need to study the outcomes in large scale studies with histologically confirmed cases of NAFLD and COVID-19 disease. Recently, Lax *et al.* reported hepatic steatosis, involving 50% to 60% of hepatocytes, in all 12 COVID-19 patients with pulmonary embolism on autopsy.[4] NAFLD patients had elevated plasma levels of von Willebrand factor and circulating plasminogen activator inhibitor type 1.[5] The liver is a frontline immune organ and increased production of pro-inflammatory cytokines by adipose cells and Kupffer cells has been reported in patients with NAFLD.[6] We had also observed that the mean admission and peak D-dimer levels were also significantly higher in COVID-19 patients with NAFLD than in those without NAFLD, 0.72 ± 1.10 ug/ml *vs.* 0.38 ± 0.46 ug/ml, p = 0.003 and 1.81 ± 4.1 mg/ml *vs.* 0.63 ± 0.41 mg/ml, p = 0.003 respectively. Therefore, the likelihood of activation of the coagulation cascade by pro-inflammatory cytokines, and subsequent thrombosis, may be higher in COVID-19 patients with underlying NAFLD. This NAFLD-associated hypercoagulable state may contribute to disease progression in COVID-19.

Received 21 October 2020; accepted 24 October 2020; available online 29 October 2020
https://doi.org/10.1016/j.jhep.2020.10.020

Financial support

This work is funded by the Capital Characteristic Clinic Project of Beijing Municipal Science and Technology Commission (Z181100001718034).

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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

Authors' contributions

DJ and GC wrote the manuscript; GL provided guidance and proof-read the manuscript; all authors revised and approved the final version.

Acknowledgments

We acknowledge all patients and health-care workers involved in the diagnosis and treatment of patients with COVID-19 in our hospitals.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.10.020.

References

Author names in bold designate shared co-first authorship

[1] Mushtaq K, Khan M, Iqbal F, Alsoub D, Chaudhry H, Ata F, et al. NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression – The debate continues. J Hepatol 2021;74(2):482–484.
[2] **Ji D**, **Qin E**, Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. J Hepatol 2020;73(2):451–453.
[3] **Zhou YJ**, **Zheng KI**, Wang XB, Yan HD, Sun QF, Pan KH, et al. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: a multicenter preliminary analysis. J Hepatol 2020;73(3):719–721.
[4] Lax S, Skok K, Zechner P, Kessler H, Kaufman F, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome:results from a prospective, single-center, clinicopathologic case series. Ann Intern Med 2020;173(5):350–361.