# Nonalcoholic fatty liver disease is associated with COVID-19 severity independently of metabolic syndrome: a retrospective case-control study

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**Aim** Coronavirus disease 2019 (COVID-19) is a recently encountered disease that was declared a pandemic by WHO in 2020. Obesity and other components of the metabolic syndrome may aggravate the severity of COVID-19. Nonalcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of metabolic syndrome. The aim of this study was to investigate a possible association between MAFLD and COVID-19 severity.

**Methods** We performed a retrospective, case-control study, enrolling 71 consecutive COVID-19 patients who were divided into two groups according to the presence or absence of fatty liver by computed tomography scan. All medical records of eligible patients were reviewed including demographic, clinical, laboratory parameters and data regarding the presence of NAFLD and COVID-19 severity.

**Results** NAFLD was identified in 22/71 (31%) of the study group. Out of 71, thirteen suffered from severe COVID-19. NAFLD patients had more severe COVID-19 compared with non-NAFLD subjects, 8/22 (36.3%) vs. 5/49(10.2%), ($P < 0.005$), respectively. Multiple logistic regression analysis showed that NAFLD subjects were more likely to have severe COVID-19 disease (odds ratio 3.57, 95% confidence interval: 1.22, 14.48, $P = 0.0031$).

**Conclusion** NAFLD represents a high risk for severe COVID-19 irrespective to gender, and independent of metabolic syndrome specifically in male gender. Moreover, obesity, hypertension and metabolic syndrome were also significantly associated with severe COVID-19. Eur J Gastroenterol Hepatol 33: 1578–1581


## Introduction

Coronavirus disease 2019 (COVID-19) is a recently encountered disease that has been declared a pandemic in 2020 by WHO. It became a global public health concern with rapid spreading worldwide [1]. The COVID-19 pandemic represents the major global public health crisis since the 1918 influenza pandemic that was the most severe pandemic in recent history [1].

Preliminary data suggest that obesity as well as other component of the metabolic syndrome may aggravate the severity of COVID-19, mainly the respiratory manifestations and complications of the disease [1,2]. Nonalcoholic fatty liver disease (NAFLD), which is the hepatic manifestation of the metabolic syndrome, represents a spectrum of disease ranging from hepatocellular steatosis through steatohepatitis to fibrosis and irreversible cirrhosis [3,4]. The prevalence of NAFLD has risen rapidly in parallel with the dramatic rise in obesity and diabetes, and is rapidly becoming the most common cause of liver disease in Western countries [5,6].

Recently, an association between NAFLD and infections was reported. Moreover, NAFLD was reported to be related with more severe infections such as community-acquired pneumonia and other infections [7,8].

However, a little is known whether NALFD patients are also more likely to have more severe COVID-19 illness. In this current study, we aim to investigate the interplay between MAFLD and COVID-19 severity.

## Methods

A retrospective, case-control study was conducted in Sharee Zedek Medical Center (SZMC), Jerusalem, Israel. Seventy-one consecutive patients with laboratory confirmed COVID-19 who met the inclusion and exclusion criteria of this study and who were hospitalized between 15 March 2020 and 30 April 2020 were enrolled in this study. We included hospitalized patients with confirmed COVID-19 infection, of both genders, aged ≥18-years-old, with computed tomography (CT) imaging data of the liver (within hospitalization or recently). We excluded patients with secondary causes of NAFLD (such as alcoholic liver

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disease, drug-induced liver injury, autoimmune hepatitis, viral hepatitis, cholestatic liver disease and metabolic/genetic liver disease).

COVID-19 positivity was defined as positive result by real-time reverse transcriptase-PCR assay of oropharyngeal and nasal swab specimens.

COVID-19 severity was assessed according to diagnosis and treatment protocol for novel Coronavirus pneumonia released by National Health Commission & State Administration of Traditional Chinese Medicine on 3 March 2020 (trial version 7) [9]. Patients who met any of the following criteria were considered to have severe COVID-19 disease: respiratory distress (equal or more than 30 breaths per minute), oxygen saturation equal or below 93% at rest, arterial partial pressure of oxygen $PaO_2$/fraction of inspired oxygen ($FiO_2$) equal or less than 300 mmHg.

All study group patients who underwent computer tomography during the current hospitalization were screened for NAFLD by revision of imaging study (computed tomography) and subsequently diagnosed as NAFLD according to the new definition for metabolic associated fatty liver disease: an international expert consensus statement from 2020 [10]. Subjects who do not underwent computer tomography during the hospitalization and who have documentation of NAFLD diagnosis in their history also were included.

Accordingly, the study population was divided into two groups: the first group included 22 (31%) COVID-9 subjects who have NAFLD, and the second group, control group, included 49 (69%) COVID-9 subjects without NAFLD.

All medical records of eligible patients from our liver clinic were reviewed and the following parameters were collected: demographic data (age, gender, BMI), background diseases (diabetes mellitus, ischemic heart disease, congestive heart failure, chronic renal failure, smoking and NAFLD), laboratory tests [alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, amylase and C-reactive protein (CRP)].

The current study received ethical approval from the hospital ethical committee and was done according to the Helsinki guidelines. The data were coded to keep anonymity of the patients. Informed consent was waived because of the retrospective noninterventional study design.

## Statistical analysis

For categorical variables, the $\chi^2$ test was performed and for continuous variables Student's *t*-test was used. According to CT data of the liver, we obtained two groups of patients with and without NAFLD. We compared between the groups in term of age, gender, BMI, comorbidities including hypertension, diabetes, smoking, glycated Hb, triglyceride, CRP, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and liver enzymes. Spearman rank correlation and univariate regression analysis statistics were used to compare patients with and without NAFLD. Data were reported as mean ± SD for quantitative continuous variables, and frequencies (percentages) for categorical variables. A parameter associated with a *P*-value <0.05 in univariate analysis was used for feature analysis. Multivariate logistic regression was used to estimate odds ratios (ORs) for variables on the severity of COVID-19. All analyses were carried out using the statistical analysis software (SAS Vs 9.4 Copyright (c) 2016 by SAS Institute Inc., Cary, NC, USA.)

## Results

Of 440 subjects with confirmed COVID-19 infection, 71 subjects met the inclusion and exclusion criteria and were included in final analysis. The mean age of enrolled patients was 51 ± 21.7 years. Fifty-one subjects (71.8%) were female. The study population of COVID-19 was divided into two groups: the first group constituted of 22 subjects (31%) who have NAFLD, and the second group constituted of 49 patients without NAFLD (Fig. 1).

Among the NAFLD group, in 13 patients (59%), the diagnosis of NAFLD was made by computer tomography performed during the hospitalization according to the new definition for metabolic-associated fatty liver disease: an international expert consensus statement from 2020 and in the rest nine patients (41%) according medical records documentation (with recent data of abdominal CT).

Regarding the baseline characteristics of the study participants, compared with the non-NAFLD group, subjects with NAFLD were statistically more obese, with higher glycated HB, higher serum liver function test, as well as more dyslipidemia and lower lymphocytes count. Moreover, NAFLD patients had more severe COVID-19 vs. non-NAFLD 39.7% vs. 11.7% ($P < 0.005$), and lower absolute lymphocyte count. Baseline characteristics of the study groups are presented in (Table 1).

Overall, in our study cohort were 58 patients (81.7%) with nonsevere COVID-19 and 13 (18.3%) with severe disease. Subjects with severe COVID-19 were more obese (BMI > 30 $Kg/m^2$) 91.7% vs. 56.4% ($P = 0.019$); more likely to be active and/or former smokers 27.1% vs. 7.2% ($P = 0.34$) and 5.2% vs. 1.1% ($P = 0.037$), respectively. They were also more likely to show higher CRP levels 4.9 ± 2.7 vs. 1.5 ± 2.3 ($P < 0.001$), higher AST levels 151.43 ± 29.36 vs. 83.16 ± 31.76 ($P < 0.001$), higher ALT levels 93.8 ± 42.7 vs. 73.2 ± 20.5 ($P < 0.001$), higher GGT levels 152.8 ± 53.8 vs. 112.7 ± 45.2 ($P < 0.05$) and lower lymphocyte count 1.1 ± 0.9 vs. 1.4 ± 1.2 ($P < 0.001$) (Table 2).

Regarding the relationship between NAFLD and COVID-19 severity, the unadjusted logistic model with COVID-19 severity as the outcome, NAFLD subjects were more likely to have severe COVID-19 disease [unadjusted OR 3.57, 95% confidence interval (CI): 1.22, 14.48, $P = 0.0031$].

The adjusted ORs for NAFLD in both genders were calculated. After adjusting for age, smoking, BMI and metabolic syndrome components, the logistic regression analysis indicates that NAFLD (men: OR 3.29, 95% CI: 3.28, 3.58, $P = 0.001$; women: OR 3.25, 95% CI: 3.09, 3.47, $P = 0.002$), obesity (men: OR 2.35, 95% CI: 2.19, 2.61, $P < 0.001$; women: OR 3.32, 95% CI: 3.09, 3.55, $P = 0.012$), metabolic syndrome (men: OR 3.32, 95% CI: 3.2, 3.61, $P = 0.001$; women: OR 3.28, 95% CI: 3.16, 3.42, $P = 0.002$) were associated with severe COVID-19.

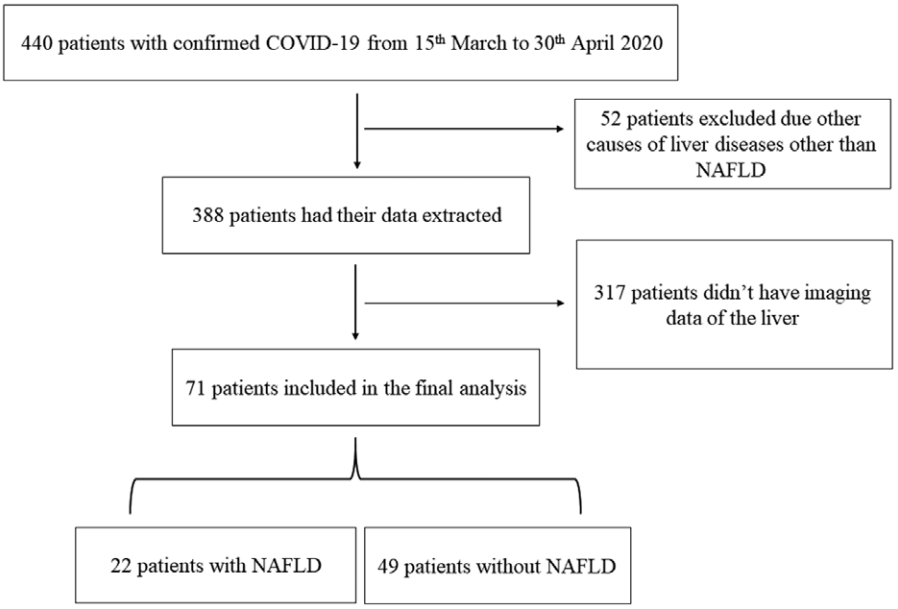


**Fig. 1.** Demonstrating the flow chart of our study cohort.

**Table 1.** Baseline characteristics of COVID-19 subjects with and without fatty liver disease

| Variable | Total (n = 71) | With NAFLD (n = 22) | Without NAFLD (n = 49) | *P* value |
|---|---|---|---|---|
| Female sex | 51 (71.8) | 15 (68.2) | 33 (67.3) | 0.056 |
| Age (years) | 51.0 ± 21.7 | 53.7 ± 19.9 | 56.2 ± 20.0 | <0.05 |
| BMI (kg/m$^2$) | 25 ± 3.2 | 29.2 ± 4.3 | 26.1 ± 4.1 | <0.05 |
| Hypertension (%) | 36 (50.7) | 13 (59.1) | 24 (48.9) | <0.05 |
| Diabetes (%) | 21 (29.5) | 8 (36.3) | 19 (38.8) | <0.05 |
| Smoking (%) | 17 (23.9) | 6 (27.2) | 11 (22.4) | <0.05 |
| Metabolic syndrome (%) | 18(25.3) | 9 (40.1) | 9(18.3) | <0.05 |
| Glycated hemoglobin (%) | 6.1 ± 0.6 | 6.9 ± 0.8 | 6.5 ± 0.4 | <0.05 |
| Triglyceride (mg/dl) | 173.4 ± 63.2 | 199.6 ± 69.2 | 162.1 ± 60.8 | <0.05 |
| CRP (mg/l) | 1.8 ± 3.8 | 5.2 ± 2.1 | 3.2 ± 1.7 | <0.05 |
| HDL-C (mg/dl) | 51.2 ± 14.1 | 45.9 ± 11.4 | 56.5 ± 12.4 | <0.05 |
| LDL-C (mg/dl) | 121.2 ± 41.1 | 132.1 ± 31.1 | 117.9 ± 31.1 | <0.05 |
| AST (U/l) | 132.9 ± 22.1 | 167 ± 31.2 | 138.2 ± 27.1 | <0.05 |
| ALT (U/l) | 136.3 ± 20.2 | 151.3 ± 25.4 | 141.3 ± 26.2 | <0.05 |
| Lymphopenia (%) | 12 (16.9) | 4 (18.1) | 8 (6.3) | 0.67 |
| ACE inhibitors (%) | 30 (42.2) | 9 (40.9) | 21(42.8) | 0.78 |
| Severe COVID-19 cases (%) | 13 (18.3) | 8 (36.3) | 5 (10.2) | <0.005 |

ACE, angiotensin converting enzyme; ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease.

**Table 2.** Baseline characteristics of severe and nonsevere COVID-19 subjects

| Variable | Severe COVID-19 (N = 13) | Nonsevere COVID-19 (N = 58) | |
|---|---|---|---|
| Male gender (%) | 6 (75) | 14 (24) | 0.002 |
| Age (years) | 56 ± 19 | 57 ± 18 | 0.06 |
| BMI >30 kg/m$^2$ (%) | 12 (92.3) | 27 (46.5) | 0.019 |
| Diabetes (%) | 9 (69.2) | 12 (20.6) | 0.04 |
| Metabolic syndrome | 8 (61.5) | 10 (17.2) | 0.038 |
| Active smoking | 7 (53.8) | 8 (13.7) | 0.031 |
| Former smoking | 1 (7.7) | 1 (1.7) | 0.037 |
| CRP (mg/l) | 4.9 ± 2.7 | 1.5 ± 2.3 | <0.001 |
| AST (U/l) | 151.43 ± 29.36 | 83.16 ± 31.76 | <0.001 |
| ALT (U/l) | 93.8 ± 42.7 | 73.2 ± 20.5 | <0.001 |
| GGT (U/l) | 152.8 ± 53.8 | 112.7 ± 45.2 | <0.05 |
| Lymphocyte x 10$^3$/µl | 1.1 ± 0.9 | 1.4 ± 1.2 | <0.001 |

ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase.

Smoking were only associated with severe COVID-19 in men (OR 2.26, 95% CI: 2.09, 2.42, $P = 0.010$; $P < 0.001$) (Table 3).

## Discussion

Our findings confirm the result of the single previously published study by Kenneth *et al*. that there is a statistically significant association between NAFLD and the severity of COVID-19 [11], and the mentioned study focused on obesity and patients with metabolic syndrome-associated fatty liver disease, while our study showed an independent link between the severity of COVID-19 and NAFLD regardless of the metabolic syndrome or/and his components [11].

Previously published data also suggested that patients suffering from obesity are at increased risk for severe COVID-19 disease compared with nonobese patients [2,11], taking this finding together with the results of our study, we can conclude that the presence of both factors, obesity and NAFLD can increase significantly the risk of severe COVID-19; but also NAFLD in the absence of obesity and/or metabolic syndrome still play as a significant risk factor in aggravation and or severe COVID-19 illness.

**Table 3.** The adjusted odds ratio for severe COVID-19 in both genders by nonalcoholic fatty liver disease, obesity, hypertension, metabolic syndrome diabetes and smoking

| Variable | Men OR | Men CI | *P*-value | Women OR | Women CI | *P*-value |
|---|---|---|---|---|---|---|
| NAFLD | 3.29 | 3.28–3.58 | 0.001 | 3.25 | 3.09–3.47 | 0.002 |
| Obesity | 2.35 | 2.19–2.61 | <0.001 | 3.32 | 3.09–3.55 | 0.012 |
| Metabolic syndrome | 3.32 | 3.20–3.561 | 0.001 | 3.28 | 3.16–3.42 | 0.002 |
| Diabetes | 3.27 | 3.07–3.52 | 0.010 | 3.01 | 3.07–3.18 | 0.052 |
| Smoking | 2.26 | 2.09–2.42 | <0.001 | 1.09 | 1.04–1.14 | 0.061 |

CI, confidence interval; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio.

Our study was designed to assess the possible association between NAFLD and COVID-19 severity as well as other components of metabolic syndrome that can be in correlation with COVID-19 severity. As noted, previous published data reported that NAFLD is closely related to several components of the metabolic syndrome [12] and it represents the hepatic manifestation of the metabolic syndrome. All components of metabolic syndrome mainly obesity as well as hypertension and diabetes were associated with severe COVID-19 [13], as subjects with NAFLD had worse metabolic syndrome parameters with higher metabolic syndrome prevalence [12].

In this study, we evaluated the adjusted ORs of NAFLD concerning the severity of COVID for each gender. The impact of gender of metabolic syndrome patients on metabolic cardiovascular and metabolic complications is unclear. We examined the contribution of gender, and found that men with NAFLD have increased risk than women for severe COVID-19.

To the best of our knowledge, there are no data in the English medical literature regarding the association between severity of COVID-19 and NAFLD per se independently to metabolic syndrome. In our study, the prevalence of severe COVID-19 among NAFLD patients is more common than non-NAFLD patients, 39.7% vs. 11.7% ($P < 0.005$). Furthermore, this association persisted even after full adjustments.

Our study has several limitations; the main limitation is the retrospective and case-control design with the drawback of selection bias, which afflicts all case-control studies of this kind. Hence, we were unable to reassess diagnosis and prevalence of NAFLD/NASH on a later time, thus follow-up and natural history learning were unfeasible. Second, self-reported viral hepatitis and/or other liver diseases may have introduced recall bias. Finally, the small number of COVID-19 patients underwent computer tomography to diagnose NAFLD coexistence.

In conclusion, patients with NAFLD have an increased risk of severe COVID-19 in both genders, in men specifically; NAFLD, obesity, hypertension and metabolic syndrome were significantly associated with severe COVID-19. The potential role of NAFLD and metabolic syndrome components in the development of severe COVID-19 remains to be elucidated by large prospective future studies.

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Author contributions: Mahmud Mahamud and Eran Goldin contributed to the design of the article. All authors contributed to data collection and analysis. Wiliam Nseir and Wisam Sbeit contributed wrote the initial draft. Tawfik Khoury, Wiliam Nseir and Wisam Sbeit revised the article for intellectual contents. All authors approved the final version to be published.

### *Conflicts of interest*

There are no conflicts of interest.

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