

Correlation Between COVID-19 Severity, Body Mass Index and Hepatic Steatosis: A Retrograde Cohort Study

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Abstract

Background

Obesity and fatty liver steatosis are already considered metabolic risk factors that may aggravate the severity of COVID-19. This study aims to investigate the correlation between COVID-19 severity, body mass index, and hepatic steatosis.

Methods

Consecutive patients with laboratory-confirmed COVID-19, admitted to a hospital devoted to COVID-19 patients, were enrolled in the study. COVID-19 severity was classified as severe versus non-severe based on the condition at time of admission to ICU. Obesity was assessed by Body Mass Index (BMI). CT-scan of the patient liver was used to check for the hepatic steatosis. Fibrosis-4 score was calculated.

Results

230 patients were enrolled in this study. Obesity strongly and positively correlated with severe COVID-19 illness. Hepatic steatosis had rather less of a correlation with COVID-19 severity. Multivariable-adjusted association between hepatic steatosis or obesity, or both (as exposure) and COVID-19 severity (as the outcome) revealed an increased risk of severe COVID-19 illness with obesity, with hepatic steatosis, and with hepatic steatosis among obese patients.

Conclusions

BMI remained the most noticeable factor that strongly correlated with COVID-19 severity. Obesity even in the absence of hepatic steatosis greatly increased the risk of severe COVID-19. This association remained significant after adjusting for likely confounders. The presence of liver steatosis even in non-obese patients increased the risk of severe COVID-19 but to a much lesser degree compared to obesity. The risk of steatosis to COVID-19 severity was greater in those with than those without obesity. This association also remained significant after adjusting for likely confounders

Key Points

- Obesity and fatty liver steatosis are already considered metabolic risk factors which may aggravate the severity of COVID-19.
- BMI remained the most noticeable factor that strongly correlated with COVID-19 severity.
- Obesity even in the absence of hepatic steatosis greatly increased the risk of severe COVID-19.

Background

Evidence from different studies have supported the notion that obesity increases the severity and mortality rate of COVID-19 patients. The co-morbidities associated with COVID-19 hospital admission are

fairly similar to those associated with many other serious infectious illnesses that require hospital admission or ICU level care ¹. Nevertheless, it is particularly significant that obesity is a risk factor for death, ICU admission, tracheal intubation, and hospitalization related to COVID-19 ².

The World Health Organization identifies non-communicable disorders such as obesity as a leading risk factor resulting in critical illness with COVID-19 ³. Obesity is a significant potential risk factor that was not illustrated in initial Chinese reports on COVID-19 patients circumstances which could probably explain why COVID-19 mortality rate is much higher in countries with higher obesity prevalence, such as Italy, relative to China and Japan ^{4;5}.

There are numerous biochemical pathways by which COVID-19 can affect people with obesity, which is well reported to be pro-inflammatory condition ^{6;7}. Some of these mechanisms are chronic inflammation and activation of ACE2-RAS system which are caused by excess adipose tissue in obese people.

By analogy with other respiratory infections, high body mass index (BMI) and obesity were predictors of poor results and deaths related to H1N1 ⁸. With regard to The pathophysiological mechanism connecting obesity and COVID-19, relevant evidence has been observed from other research carried out in subjects with H1N1 infection, showing that individuals with obesity have a more intense release of IL-8, compared to individuals with normal body weight, which is an important chemokine for the activation and migration of neutrophils to tissues, a mechanism involved in the response to infection ^{9;10}.

Fatty liver disease, which was formerly renamed Metabolic Associated Fatty Liver Disease (MAFLD), impacts 25% of the world's population ¹¹. Recent studies showed that MAFLD patients with SARS-CoV-2 infection increases the severity of COVID-19 respiratory illness by up to 4–6 fold ^{12–17}, while the severity of the respiratory illness in obese patients without (MAFLD) increases by up to 3 fold ¹³. There is also an increased risk of MAFLD progression to Non-Alcoholic SteatoHepatitis (NASH) in the long-term ¹⁸.

This study aims to examine the potential association between obesity, hepatic steatosis and the severity of COVID-19 illness.

Methods

Data was collected for consecutive laboratory-confirmed COVID-19 patients admitted at the hospital devoted completely by Jordanian Government to isolate and treat COVID-19 patients (Prince Hamza Hospital - PHH) between March and May 2020. Patients younger than 15 years were excluded. COVID-19 was diagnosed as a positive result by polymerase chain reaction (PCR) assay of oropharyngeal swab specimens.

Demographic information and past medical history were obtained and blood samples were tested on the first day of hospital admission. A case was considered as a 'Severe COVID-19' case if the patient was

admitted to the Intensive Care Unit (ICU). Hospital policy for admitting COVID-19 patients to the ICU included the following indications:

1. Respiratory or cardiac arrests
2. Respiratory rate ≥ 40 or ≤ 8 breaths/min
3. Oxygen saturation $< 90\%$ on $\geq 50\%$ oxygen
4. Respiratory acidosis
5. Pulse rate < 40 or > 140 beats/min
6. Systolic blood pressure < 90 mm Hg
7. Sudden fall in level of consciousness
8. Two or more organ failures

Obesity was assessed by Body mass index (BMI). Patients with BMI ≥ 30 were considered obese. The presence of hepatic steatosis was confirmed by a liver CT scan. The Fibrosis-4 score was calculated to estimate the degree of fibrosis in the liver by a formula that incorporated values for age, Liver enzymes (AST, ALT) and platelet count.¹⁹

The liver CT scan used in this study was non-enhanced, which has been found to be better at measuring the hepatic Hounsfield unit and presence of steatosis²⁰. Measurement of attenuation of liver only on unenhanced CT scans is best for prediction of pathologic fat content.²¹

CT scan diagnostic criteria for steatosis are liver attenuation of at least 10 Hounsfield Units (HU) less than that of the spleen or absolute liver attenuation of less than 40 HU. Unenhanced CT scans have a sensitivity for steatosis ranging from 43 to 95% and a specificity of 90–100%.²⁰

Continuous variables were expressed as mean (range). Differences between categorical variables were examined with the chi-squared test or the Fisher's exact test as appropriate.

The association between exposure factors such as obesity, liver steatosis and liver steatosis among obese patient vs. the outcome of COVID-19 severity was assessed by using the Spearman bivariate correlation coefficient with significance at 0.05% level (2 tailed).

The Odds Ratio (OR) between exposure factors such as obesity, liver steatosis and liver steatosis among obese patient vs. the outcome of our interest (COVID-19 severity) was assessed by using the binary logistic regression. The Odds Ratio adjusted for covariates such as age, gender, smoking, diabetes and hypertension was assessed by multinomial logistic regression analysis.

Statistical analyses were two-sided and significance was set at $p < .05$. All statistical tests were performed using SPSS version 23.0 (SPSS Inc., Chicago, USA).

Results

Data was collected for 302 patients. 72 patients younger than 15 years were excluded. 230 patients aged between 15 and 84 years were enrolled in this study. Table-1 and table-2 show their characteristic.

The presence of obesity was associated with an around 290 fold increased risk of severe COVID-19 illness. This association remained significant even after adjusting for age, gender, smoking, diabetes and hypertension. The presence of hepatic steatosis was associated with an around 17 fold increased risk of severe COVID-19 illness. This association remained significant even after adjusting for age, gender but not for smoking, diabetes and hypertension. The presence of both obesity and liver steatosis together was associated with an over 300 fold increased risk of severe COVID-19 illness. This association remained significant even after adjusting for age, gender, smoking, diabetes and hypertension. Table-3 summarizes the association between hepatic steatosis or obesity, or both and COVID-19 illness severity.

Table 1
Demographic data, co morbidities, ICU admissions and mortality.

Characteristic	Number of patients / total of 230 (%)	Correlation with ICU admission [^] (P-value)
Gender	Females: 107/230 (47%)	0.023 (< 0.001)
Age	Mean = 39 year (range 15–84 year)	0.407 (< 0.001)
15-40yr	130/230 (57%)	
41-60yr	79/230 (34%)	
61-85yr	21/230 (9%)	
DM	25/230 (11%)	0.358 (< 0.001)
HTN	40/230 (17%)	0.511 (< 0.001)
Cardiac	13/230 (6%)	0.385 (< 0.001)
Respiratory	41/230 (18%)	0.197 (0.003)
Smoking	82/230 (36%)	0.070 (0.289)
BMI (obese vs. non-obese)	Mean = 28 (range 15–51)	0.760 (< 0.001)
Number of patients with BMI >= 30	19/230 (8%) (11 admitted to ICU)	
BMI of ICU patients	Mean = 33.5 (range 30–39)	
ICU admission	12/230 (5%)	
Mortality	9/230 (4%)	
[^] : Spearman correlation coefficient		
ICU = intensive care unit, DM = diabetes mellitus, HTN = hypertension, BMI = body mass index		

Table 2
Biochemical and radiological findings and ICU admissions.

Characteristic	Number of patients / total of 230 (%)	Correlation with ICU admission [^] (P-value)
WBC	Abnormal in 50/230 (22%)	0.113 (0.086)
NLR	Abnormal in 6/230 (3%)	0.280 (0.026)
CRP	Abnormal in 54/230 (23%)	0.415 (< 0.001)
LDH	Abnormal in 29/230 (13%)	0.500 (< 0.001)
ALT	Abnormal in 13/230 (6%)	0.015 (0.842)
AST	Abnormal in 12/230 (5%)	0.110 (0.133)
Fibrosis-4 score (FIB-4)	Abnormal in 30/230 (13%)	0.331 (< 0.001)
FIB-4 < 1.45	200/230 (87%)	
FIB-4 = 1.46–3.24	28/230 (12%)	
FIB-4 > 3.24	2/230 (1%)	
Steatosis on CT scan liver	11/230 (5%)	0.352 (< 0.001)
Hepatic steatosis among obese patients	8/19 (42%)	0.702 (< 0.001)
[^] : Spearman correlation coefficient ICU = intensive care unit, WBC= white blood cell, NLR = Neutrophils : Lymphocytes Ratio, CRP = C-reactive protein, LDH = Lactate dehydrogenase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CT = computed tomography		

Table 3
Multivariable-adjusted association between hepatic steatosis or obesity, or both (as exposure) and COVID-19 severity (as the outcome).

	OR	95% CI	P value
Obesity vs. Severe COVID-19			
Unadjusted	288.8	33.1–2517.5	<0.001
Adjusted model I	465.3	21.9–9873.3	<0.001
Adjusted model II	174.0	11.0–2759.8	<0.001
Hepatic steatosis vs. Severe COVID-19			
Unadjusted	17.0	4.7–60.7	<0.001
Adjusted model I	5.1	1.2–21.0	0.025
Adjusted model II	3.7	0.9–15.9	0.079
Hepatic steatosis among obese patient vs. Severe COVID-19			
Unadjusted	303.8	31.2–2955.7	<0.001
Adjusted model I	132	10.3–1691.8	<0.001
Adjusted model II	38.0	3.7–390.4	.002
Model 1: adjusted for age and sex.			
Model 2: adjusted for smoking, type 2 diabetes and hypertension.			

Discussion

Jordanian health authority policy regarding management of COVID-19 pandemic was to admit every patient with positive PCR COVID-19 regardless of symptoms or clinical condition. Many individuals were tested for COVID-19 only because they were in close contact with COVID-19 patients. Therefore most patients were asymptomatic. This also explains why the laboratory tests on admission for most patients were within normal range. Most patients did not require more than paracetamol as treatment. This is different from other countries such as China and Italy.

Wuhan's results demonstrate that hypertension (30%), diabetes (22%), and coronary artery disease (22%), all of which are more prevalent in people with obesity, were the most common co morbidities in patients needing hospitalization²². The percentage of these co-morbidities was lower by about 50% in our cohort of patients: with hypertension (17%), diabetes (11%), cardiac disease (6%). However, the ICU patient prevalence of the above mentioned co-morbidities was higher: hypertension (100%), diabetic (58%) and cardiac disease (42%).

BMI positively and strongly correlates with ICU admission increasing the risk of severe COVID-19 illness to around 300 folds. This is consistent with other published results^{23–25}. Additionally, the presence of hepatic steatosis increased the risk of severe COVID-19 illness to around 17 folds. The presence of hepatic steatosis among obese patient increased the risk to over 300 folds.

A large New York City cohort report revealed that obesity (BMI 30–40) is strongly correlated with a progression to serious illness with a relatively increased odds ratio than any cardiovascular or pulmonary condition⁴. Another study in the early days of the Italian epidemic demonstrated that the Case-fatality rate of patients hospitalized with COVID-19 was about 20%. Older age, obesity and disease severity upon admission were factors related with increased risk of death²⁶.

Even after adjustment for other possibly confounding factors such as age, gender, race and troponin levels, obesity was reported to be associated with significantly higher levels of ICU admission and mortality in hospitals^{27–30}. Higher demand for assisted ventilation beyond pure oxygen support (Invasive Mechanical Ventilation or Non-Invasive Ventilation) and increased admission to intensive or semi-intensive care units has been identified in patients in overweight and obesity³¹.

While other literature does not provide data about steatosis and its correlation with severity of COVID-19, our study provides valuable evidence about this correlation. On the other hand, there was rather a weak correlation between FIB-4 and ICU admission. Additional studies are needed to confirm these findings and to better understand the underlying mechanisms for why the association is greater in those with obesity.

The total number of COVID-19 positive patients in Jordan from March until July 2020 was about 1200 and only 10 of them died (0.8%). Our cohort (230 patients) represents about 19% of the total COVID-19 patients in Jordan. Our cohort contained 9 of the 10 patients who died and 90% of all patients admitted to ICU. Most mortalities occurred in the first cohort of patients (300) that were diagnosed in Jordan. Only one mortality occurred in the following cohort of patients (900) that were not included in our study.

Several reports indicate that obesity may be a very significant consideration in younger people^{32–34}. A report of 3,615 New York patients revealed that obesity was strongly correlated with hospital and ICU admittance for patients under 60 years of age³². Another study showed that hospitalized patients younger than 50 with morbid obesity are more likely to die from COVID-19. This is particularly relevant in the western world where obesity rates are high. In the same context, the findings of another study found a greater prevalence of obesity in younger hospitalized patients^{33;34}.

This is similar to what is suggested by literature. data suggests a longer viral shedding time + 5 days & abnormal liver function x7 folds in patients with (MAFLD)^{12;16}. There is an increased risk of symptomatic infection in MALFD patients³⁵.

No mortalities occurred among children in Jordan. The youngest patient who died was 44 years old and had hypertension, diabetes and cardiac disease.

The Hashemite kingdom of Jordan managed to keep the COVID-19 pandemic under control. Jordan followed an early and strict lockdown strategy and all infected cases were admitted to hospital regardless of symptoms. COVID-19 did not widely spread in Jordan, which has a population of about 10 million. COVID-19 was only found in 1200 patients over 4 months, which is (0.012%).

Most Jordanian patients did not have symptoms. Most patients did not require treatment or antiviral medication. Therefore this could be the reason for the generally unaltered liver function enzymes.

Some limitations of this study should be recognized. While the liver was assessed by CT scan for severe steatosis, patients included in our study did not undergo liver biopsy, thus COVID-19 severity in relation to liver histology could not be assessed.

Another common characteristic of obesity is vitamin D deficiency, which raises the risk of bacterial infections and impairs the immunity response³⁶. Vitamin D has several mechanisms by which it eliminates the chance of microbial infection and death according to an analysis of the role of vitamin D in lowering the risk of common cold, which divides these mechanisms into three groups: physical barrier, cellular natural immunity and adaptive immunity³⁷. Level of Vitamin D was not tested in patients in this study.

In addition, patients were mostly of Arab ethnicity and thus the applicability of the results to other ethnic groups is uncertain.

Conclusions

BMI remained the most noticeable factor that strongly correlated with COVID-19 severity. Obesity even in the absence of hepatic steatosis greatly increased the risk for severe COVID-19. This association remained significant after adjusting for likely confounders. The presence of liver steatosis even in non-obese patients increased the risk for severe COVID-19 but to a much lesser degree compared to obesity. The risk of steatosis to COVID-19 severity was greater in those with, than those without obesity. This association also remained significant after adjusting for likely confounders.

Abbreviations

BMI

body mass index

MAFLD

Metabolic Associated Fatty Liver Disease

NASH

Non-Alcoholic Steatohepatitis

PCR

polymerase chain reaction

ICU

Intensive Care Unit
OR
Odds Ratio
DM
diabetes mellitus
HTN
hypertension
WBC
white blood cell
NLR
Neutrophils Lymphocytes Ratio
CRP
C-reactive protein
LDH
Lactate dehydrogenase
ALT
alanine aminotransferase,
AST
aspartate aminotransferase
CT
computed tomography

Declarations

Ethics approval and consent to participate

Ethics approved from Hashemite University Faculty of Medicine and no consent is needed for this retrospective anonymous data.

Consent for publication

Consent was obtained from Hashemite University Faculty of Medicine.

Availability of data and materials

Data available upon request from the authors.

Competing of Interest Declaration

The authors declare that they have no competing interests.

Funding State

None

Authors' contributions

-Haitham Qandeel supervised all other co-authors.

-Haitham Qandeel and Raed Tayyem were the head of this research.

-Haitham Qandeel, Raed Tayyem, and Rand Tayyem conceived, designed and perform the statistical analysis of the data.

-Jehad Fataftah performed and analyzed the liver CT scans.

-Muhannad Qasem and Rawan Sami collected the data.

-Rami Alqassieh participated in writing this manuscript and went through the manuscript for revision.

-Haneen Ashour and Subreen Hasanat read page proofs, conduct the literature review, managed the references and communicate with journals about submissions.

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