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Correlation Between COVID-19 Severity, Body Mass Index and Radiological Hepatic Morphology

Correlación entre la Gravedad de COVID-19, el Índice de Masa Corporal y la Morfología Hepática Radiológica

Haitham Qandeel[1]; Raed Tayyem[1]; Jehad Fataftah[2]; Muhannad Qasem[3]; Rawan Sami[3]; Haneen Ashour[1]; Subreen Hasanat[1]; Rand Tayyem[1] & Rami Alqassieh4

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SUMMARY: Obesity and fatty liver steatosis are already considered metabolic risk factors which may aggravate the severity of COVID-19. This study aims to investigate the correlation between COVID-19 severity, obesity, and liver steatosis and fibrosis. 230 consecutive patients with laboratory-confirmed COVID-19 aged between 15 and 84?years, 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 admission to ICU. Obesity was assessed by Body Mass Index (BMI). CT-scan was used to check for the liver steatosis. Fibrosis-4 score was calculated. The study was conducted in March-May 2020. Obesity strongly and positively correlated with severe COVID-19 illness r: 0.760 (P<0.001). Hepatic steatosis had rather less of a correlation with COVID-19 severity r: 0.365 (P<0.001). Multivariable-adjusted association between hepatic steatosis or obesity, or both (as exposure) and COVID-19 severity (as the outcome) revealed increased risk of severe COVID-19 illness with obesity (Adjusted model I OR: 465.3, 95 % CI: 21.9–9873.3, P<0.001), with hepatic steatosis (Adjusted model I OR: 5.1, 95 % CI: 1.2–21.0, P<0.025), and with hepatic steatosis among obese patients (Adjusted model I OR: 132, 95 % CI: 10.3–1691.8, P<0.001). Obesity remained the most noticeable factor that strongly correlated with COVID-19 severity, more than liver steatosis. However, the risk to COVID-19 severity was greater in those with both factors: obesity and liver steatosis.

KEY WORDS: COVID-1; Obesity; Fatty liver; Body Mass Index; Hepatic Steatosis.

INTRODUCTION

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 (Petrilli *et al*., 2020). Nevertheless, it is appreciable that obesity is a risk factor for many COVID-19 complications, such as ICU admission, tracheal intubation, hospitalization and death.

The World Health Organization identifies non-communicable disorders such as obesity as a leading risk factor resulting in critical illness with COVID-19. 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 (Rebelos *et al*., 2020). There are numerous biochemical pathways by which COVID-19 can affect people with obesity, which is well reported to be pro-inflammatory condition (Caër *et al*., 2017). Some of these mechanisms are chronic inflammation and activation of ACE2-RAS system which are caused by excess adipose tissue in obese people.

With regard to the pathophysiological mechanism connecting obesity and COVID-19, evidence in subjects with H1N1 infection in a research, showed 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 a mechanism involved in the response to infection (Hagau *et al*., 2010).

[1] Surgery Department, Hashemite University, Zarqa'a, Jordan.
[2] Radiology Department, Hashemite University, Zarqa'a, Jordan.
[3] Surgery Department, Prince Hamza Hospital, Amman, Jordan.
[4] Anesthesia Department, Hashemite University, Zarqa'a, Jordan.

Fatty liver disease, which was formerly renamed Metabolic Associated Fatty Liver Disease (MAFLD), impacts 25 % of the world's population. 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 (Ji *et al*., 2020a) while the severity of the respiratory illness in obese patients without MAFLD increases by up to 3 fold (Zheng *et al*., 2020). There is also an increased risk of MAFLD progression to Non-Alcoholic SteatoHepatitis (NASH) in the long-term (Prins & Olinga, 2020). This study aims to examine the potential association between obesity, hepatic steatosis and the severity of COVID-19 illness.

MATERIAL AND METHOD

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. Ethical Permission for the study was granted by Faculty of Medicine at Hashemite University. Patients younger than 15years 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: Respiratory or cardiac arrests, respiratory rate ?40 or ?8 breaths/min, oxygen saturation < 90 % on 50 % oxygen, respiratory acidosis, pulse rate < 40 or >140 beats/min, Systolic blood pressure <90 mm Hg, sudden fall in level of consciousness and 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 (Sterling *et al*., 2006).

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 steatosis (Wells *et al*., 2016). Measurement of attenuation of liver only on unenhanced CT scans is best for prediction of pathologic fat content (Kodama *et al*., 2007).

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 % (Wells *et al*.).

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, sex, smoking, diabetes and hypertension was assessed by multinomial logistic regression analysis.

Statistical analyses were two-sided and significance was set at $p< 0.05$. All statistical tests were performed using SPSS version 23.0 (SPSS Inc., Chicago, USA).

Granted ethical Permission was obtained from Hashemite University-Jordan.

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. Tables I and II 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, sex, 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, sex 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, sex, smoking, diabetes and hypertension. Table III. The

association between hepatic steatosis or obesity, or both and COVID-19 illness severity.

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

Characteristic	Number of patients / total of 230 (%)	Correlation with ICU admission^ (P-value)
Sex	Females: 107/230 (47 %)	0.023 (< 0.001)
Age	Mean = 39 yrs (range 15-84 yrs)	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 II. 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 III. 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	

Model 1: adjusted for age and sex.

DISCUSSION

Jordanian health authority policy regarding management of COVID-19 pandemic was to admit and isolate every patient with positive PCR COVID-19 regardless of symptoms or clinical condition in early 2020. 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.

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 hospitalization (Chiappetta *et al*., 2020). 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 %).

Furthermore, 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 (Portincasa *et al*., 2020). 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 condition (Petrilli *et al*.). 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 death (Giacomelli *et al*., 2020). 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 (Palaiodimos *et al*., 2020). 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 obesity (Busetto *et al*., 2020).

A large study in UK assessed liver fat and liver fibro-inflammatory disease by MRI. The study concluded that hepatic steatosis, rather than underlying obesity, increases the risk of infection and hospitalization for COVID-19 (Zhu *et al*., 2021). Another study showed higher frequency of hepatic steatosis at CTscan among COVID-19-positive patients (Medeiros *et al*., 2020). Furthermore, a computed tomography study demonstrated that hepatic steatosis is an independent risk factor for severe disease in patients with COVID-19 (Palomar-Lever *et al*., 2020). On the contrary, a study concluded that the prevalence of steatosis and significant liver fibrosis was high in COVID-19 patients but was not associated with clinical outcomes (Sacks *et al*., 2018).

A study titled “Liver Fibrosis Index FIB-4 Is Associated with Mortality in COVID-19” illustrated that FIB-4 is associated with mortality in COVID-19, independent of underlying conditions including liver diseases. The study recommended FIB-4 as a simple and inexpensive approach to risk-stratify individuals with COVID-19 (Li *et al*., 2020).

Our study showed 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.

Several reports indicate that obesity may be a very significant consideration in younger people (Lighter *et al*., 2020; Klang *et al*., 2020). 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 age (Lighter *et al*.). 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 (Klang *et al*.).

This is similar to what is suggested by literature. Data suggests a viral shedding time 5 days longer and abnormal liver function x7 folds in patients with MAFLD. (Ji *et al*., 2020a) There is an increased risk of symptomatic infection in MALFD patients (Ji *et al*., 2020b).

Most patients in this cohort did not have symptoms and 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 response (Bouillon *et al*., 2019) 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 immunity (Rondanelli *et al*., 2018). Level of Vitamin D was not tested in patients in this study.

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.

QANDEEL, H.; TAYYEM, R.; FATAFTAH, J.; QASEM, M.; SAMI, R.; ASHOUR, H.; HASANAT, S.; TAYYEM, R. & ALQASSIEH, R. Correlación entre la gravedad de COVID-19, el índice de masa corporal y la morfología hepática radiológica. *Int. J. Morphol., 39(4)*:1096-1101, 2021.

RESUMEN: La obesidad y la esteatosis del hígado graso ya se consideran factores de riesgo metabólico que pueden empeorar la gravedad de la COVID-19. Este estudio tiene como objetivo investigar la correlación entre la gravedad de COVID-19, la obesidad y la esteatosis y fibrosis hepática. El estudio se realizó en 230 pacientes consecutivos entre 15 y 84 años con COVID-19 confirmado por laboratorio, ingresados en un hospital dedicado a pacientes con COVID-19. La gravedad de COVID-19 se clasificó como grave, versus no grave según el ingreso a la UCI. La obesidad se evaluó mediante el índice de masa corporal (IMC). Se utilizó una tomografía computarizada para verificar la esteatosis hepática. Se calculó la puntuación de Fibrosis-4. El estudio se realizó entre marzo-mayo de 2020. La obesidad se correlacionó fuerte y positivamente con la enfermedad grave de COVID-19 r: 0,760 (P <0,001). La esteatosis hepática tuvo una correlación bastante menor con la gravedad de COVID-19 r: 0.365 (P <0.001). La asociación ajustada multivariable entre la esteatosis hepática u obesidad, o ambas (como exposición) y la gravedad de COVID-19 (como resultado) reveló un mayor riesgo de enfermedad grave por COVID-19 con obesidad (OR del modelo ajustado I: 465,3, IC del 95 %: 21,9 –9873,3, P <0,001), con esteatosis hepática (OR del modelo I ajustado: 5,1, IC del 95 %: 1,2-21,0, P <0,025) y con esteatosis hepática entre los pacientes obesos (OR del modelo I ajustado: 132, IC del 95 % : 10,3-1691,8, P <0,001). La obesidad siguió siendo el factor más notable que se correlacionó significativamente con la gravedad de COVID-19, más que la esteatosis hepática. Sin embargo, el riesgo de gravedad de COVID-19 fue mayor en aquellos con ambos factores: la obesidad y esteatosis hepática.

PALABRAS CLAVE: COVID-19; Obesidad; Hígado graso; Indice de masa corporal; Esteatosis hepática.

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Corresponding Author:
Haitham Qandeel, FRCS Ass. Professor
Hashemite University
Department of Surgery
Zarqa'a
JORDAN

E-mail: hgbqandeel@yahoo.com

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