Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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ORIGINAL RESEARCH

Association Between Obesity and COVID-19 Disease Severity in Saudi Population

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Background: The persistent coronavirus disease 2019 (COVID-19) outbreak has placed a significant burden on the scientific and medical professions. The study examined the association between body mass index (BMI), stratified by category, and severe form of COVID-19, and to explore the influence of demographic characteristics and other known risk factors.

Methods: This was a retrospective analysis based on COVID-19 data from the Saudi Arabian Ministry of Health. Data were collected for all patients admitted to three main hospitals in Riyadh region between March 1st and July 30, 2020. The effects of BMI, demographic characteristics, clinical presentation, and comorbidities on infection severity were investigated.

Results: A total of 950 patients were included in the study (70% male, 85% aged younger than 60 years old). A total of 55 (5.8%) patients were underweight, 263 (27.7%) were normal weight, 351 (37%) were overweight, 161 (17%) were obese class I, 76 (8%) were obese class II, and 44 (4.6%) were obese class III. Cough, fever, and shortness of breath were the most common symptoms among overweight patients. According to the findings of a bivariate logistic regression study, class III obesity was significantly associated with a more severe form of COVID-19 (odds ratio, 2.874; 95% confidence interval, 1.344–6.149).

Conclusion: This study revealed that patients with a BMI ≥40 kg/m^2 had a higher risk of severe COVID-19 than those with normal weight. This suggests that obesity is a risk factor for severe COVID-19 and influences disease presentation.

Keywords: COVID-19, body mass index, obesity, severe COVID-19

Introduction

In March 2019, the World Health Organization declared the latest pandemic in human history caused by a novel strain of coronavirus.[1] As of December 25, 2021, the new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), officially known as COVID-19, infected more than 279 million cases with over 5,395,856 deaths.[2] Approximately 14% of patients admitted with COVID-19 developed severe pneumonia and meet the criteria for acute respiratory distress syndrome.[3]

Several factors have been linked to COVID-19 disease severity and mortality. These include advanced age; male sex; and comorbid diabetes mellitus, cardiovascular disease, respiratory disease, kidney, and liver disorders.[4,5] Obesity also emerged as one of the risk factors linked to unfavorable disease course and was a significant contributor to poor health outcomes, including higher incidence of ICU admissions and need for mechanical ventilation.[6–8] Patients with body mass index (BMI) ≥30 kg/m^2 represent a substantial proportion of hospitalized patients with COVID-19.[2] Two other studies found that obesity was a risk factor for invasive mechanical ventilation.[9,10] A case control study of 179,288 patients admitted in the periods before the pandemic[11,12] (149,098 patients) and (30,190 patients) during the pandemic found that

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patients with BMI >40kg/m^2 has higher odds for increased mortality during the COVID-19 compared to pre-pandemic odds.[13]

Pre-dating the COVID-19 era, the association between obesity and markers of inflammation is well established. Indeed, during the 2009 H1N1 influenza pandemic obese patients had twice the risk of admission to ICU and death.[14] Moreover, the main characteristics observed in severe COVID-19 is the overwhelming triggering of the body inflammatory responses with dysregulation of innate and adaptive immunity.[15] Likewise, there is a wealth of literature describing the role of inflammatory, immunological and coagulopathic processes in obese patients leading to increased risk of cardiometabolic diseases, severity of illnesses and hospitalization.[16] Hence, for obese patient, a coinfection with COVID-19 infection is a double whammy[17–19] independent of the age and comorbidities.[20] Recent literatures with data from various countries highlighted the severity of illness in COVID-19 in obese individuals[21–24] in different population and ethnicity. Conversely, several studies demonstrated no difference in disease severity in obese patients.[25] In Saudi Arabia, the country recorded 552,406 COVID-19 cases, with 8870 deaths.[2] Obesity was reported to be prevalent in 35.6% of Saudi individuals according to a national survey done between 1995 and 2000.[26] In 2013, nationwide research revealed a prevalence rate of 28.7%.[27] However, to the best of our knowledge, a limited number of national studies has investigated the association between obesity and COVID-19. Therefore, this study aims to characterize the association between BMI, stratified by category, and the severe form of COVID-19, and to investigate interactions with demographic characteristics and other known risk factors.

Method

Study Design and Population

This is a retrospective study utilizing Ministry of Health databases linked to three main hospitals in Riyadh region. Patients with COVID-19 admitted from March 1, 2020 to July 30, 2020 were included in this study. The Institutional Review Board of the Ministry of Health approved the study protocol and methodology (IRB-20222E-RC20.239.R). Informed consent was obtained from all patients before participating in the study. The study was conducted in accordance with the hospital management guidelines and MoH regulations. Our research was in compliance with the Helsinki Declaration.

Data Measures

The demographics, clinical presentations, comorbidities, BMI, severity, and outcome of COVID-19 were obtained and recorded. All patients have documentation of COVID-19 diagnosis using nucleic acid test (real-time reverse transcriptase polymerase chain reaction assay [RT-PCR] for SARS-CoV-2).[28] Parent or legal guardian of patients under 18 years of age provided informed consent. Patients were stratified into different groups according to BMI as follows: underweight (≤18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), class I obesity (30–34.9 kg/m^2), class II obesity (35–39.9 kg/m^2), and class III obesity (≥40 kg/m^2).[29]

For COVID-19 disease severity classification, WHO guidance on COVID-19 guidance was adopted.[30] The absence of clinical symptoms of COVID-19 infections with a positive RT-PCR result was defined as asymptomatic infections. Mild COVID-19 illness was defined as the absence of respiratory distress and imaging indications of pneumonia, as well as the presence of mild clinical symptoms. Moderate disease was defined as observable fever, respiratory symptoms, and pneumonia on CT. Severe disease was defined as the presence of at least one of the following three conditions: respiratory distress, a respiratory rate equal to or more than 30 beats per minute, oxygen saturation in the resting state ≤93%, or arterial blood oxygen partial pressure/oxygen concentration ≤300 mmHg (1 mmHg = 0.133 kPa). Critical illness was defined as when patients had respiratory failure requiring mechanical ventilation, shock, or combined organ failure necessitating intensive care unit (ICU) monitoring and treatment.

Statistical Analysis

Descriptive statistics were utilized, and significance was assessed using the chi-squared test and parametric or non-parametric binomial tests when appropriate, and multivariate binary logistic regression was used to determine the association of obesity with severe or critical COVID-19 patients' disease. Statistical analyses were performed using IBM SPSS version 25 software (IBM Corp., Armonk, NY, USA). The level of significance was set at 0.05 for all tests ($P < 0.05$).

Results

A total of 951 patients were diagnosed with COVID-19 between March 1 and July 30, 2020. Table 1 shows the demographic and clinical features of patients stratified by the BMI standard classification. Men accounted for 70% (664) and Saudi Nationals accounted for 53% (498) of the cases. BMI significantly increased with age from 21 to 60 years ($p < 0.05$). BMI distribution was as follows: overweight (351, 37%), class I obesity (161, 17%), class II obesity (76, 8%), and class III obesity (44, 4.6%). The majority of patients with COVID-19 patients had mild disease (602, 63%); 167 (17.6%) had moderate disease, 102 (10.7%) had severe disease, and only 63 (6.6%) were classified as critically ill (Table 1). Notably, BMI was significantly higher in patients with severe and critical disease ($p < 0.05$).

The most prevalent symptoms among patients with COVID-19 were fever, cough, and shortness of breath, and these symptoms were significantly associated with overweight patients ($p < 0.05$) (Table 2). A total of 3.8% of patients were asymptomatic.

Diabetes mellitus was found in 20% of patients with COVID-19, hypertension in 10%, immunocompromise in 5.4%, chronic kidney disease in 4.3%, asthma in 4.23%, and coronary heart disease in 3% (Table 3). A significant association was observed between diabetes mellitus and chronic liver disease in overweight patients ($p < 0.05$). Almost 2.5% of patients had travelled abroad before getting infected, while 20% of patients were in contact with positive cases. Management protocol employed and patient outcomes are summarized in Table 4. Antibiotics, bronchodilators, anti-malaria, and corticosteroids were prescribed in 30%, 24.6%, 6.6%, and 2.5% of cases, respectively (Table 4). These medications were administered significantly more to overweight patients. Symptom's improvement was seen in 45% of the cases with an average hospital stay of 10.02 ± 5.91 days and 2% of patients died from COVID-19 and they were all critical cases. The results of the bivariate logistic regression analysis are demonstrated in Table 5; class III obesity (odds ratio [OR] = 2.874; 95% confidence interval [CI], 1.344–6.149) and diabetes mellitus (OR = 5.385; 95% CI, 3.622–8.005) were significantly and independently associated ($p < 0.05$) with severe COVID-19.

Discussion

The focus of this study was to characterize the relationship between BMI, stratified by category, and severity of COVID-19, as well as to explore the interplay between demographic parameters and other recognized risk factors. In consistent with other studies, our findings demonstrated that overweight and obese patients were more likely to present with symptomatic disease with history of fever, cough, and shortness of breath.[31] The multivariable analysis conducted in our study showed that the severity of COVID-19 increased significantly in patients with a BMI $\geq$40 kg/m^2. This is consistent with the earlier findings of others in which patients with BMI >35 kg/m^2 were found to require mechanical ventilation more than those with BMI <25 kg/m^2.[9,32,33] The association between obesity and worse outcomes in patients with COVID-19 is expected. Thus, obese patients are associated with rapid progression of the disease. Similar findings were observed in obese patients who were infected with H1N1, a novel influenza A strain that emerged in 2009, and their weight had affected their risk of hospitalization, mechanical ventilation, and death, regardless of their other comorbidities.[34,35]

Pulmonary complications are known to be more common in obese patients because of upper respiratory illnesses caused by a reduction in lung volume, hypoventilation, congestive heart failure, and acute respiratory distress syndrome.[36] Moreover, recent studies have shown that COVID-19 infection leads to a hypercoagulable state, hence, elevated risk of pulmonary embolism, stroke, and arterial thrombosis.[37] Furthermore, a systemic inflammatory response initiated by the activation of CD4+ T lymphocytes into T-helper 1 cells that produce cytokines is thought to contribute to the adverse respiratory outcomes observed in COVID-19 patients. This leads to massive production of inflammatory cytokines, causing a cytokine storm that results in apoptosis, vascular leakage, poor virus clearance, altered tissue homeostasis, acute lung injury, cardiac dysfunction, and subsequent acute respiratory distress syndrome.[38,39] Therefore, elevation of inflammatory biomarkers, including ferritin, lactate dehydrogenase, D-dimer, and C-reactive protein, has

Table 1 Distribution of Patients with COVID-19 According to Demographic Characteristics, N = 951, Saudi Arabia

		Class of Obesity						Total	P-value
		Underweight ($\le$18.5 kg/m^2)	**Normal (18.5–24.9 kg/m^2)**	**Overweight (25.0–29.9 kg/m^2)**	**Class 1 Obesity (30–34.9 kg/m^2)**	**Class 2 Obesity (35–39.9 kg/m^2)**	**Class 3 Obesity ($\ge$40 kg/m^2)**		
Sex	Male	37 (5.6%)	195 (29.4%)	253 (38.1%)	117 (17.6%)	39 (5.9%)	23 (3.5%)	664 (70%)	<0.05
	Female	18 (6.3%)	68 (23.8%)	98 (34.3%)	44 (15.4%)	37 (12.9%)	21 (7.3%)	286 (30%)	
Nationality	Saudi	52 (10.4%)	122 (24.5%)	159 (31.9%)	78 (15.7%)	55 (11%)	32 (6.4%)	498 (52.9%)	<0.05
	Non-Saudi	4 (0.9%)	141 (31.1%)	192 (42.4%)	83 (18.3%)	21 (4.6%)	12 (2.6%)	453 (47.6%)	
Age	0–2.5 years	9 (69.2%)	4 (30.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13 (1.4%)	<0.05
	2.6–5 years	9 (81.8%)	1 (9.1%)	0 (0%)	0 (0%)	0 (0%)	1 (9.1%)	11 (1.16%)	
	6–20 years	25 (30.1%)	29 (34.9%)	13 (15.7%)	8 (9.6%)	4 (4.8%)	4 (4.8%)	83 (10%)	
	21–40 years	10 (2.6%)	126 (32.9%)	148 (38.6%)	64 (16.7%)	21 (5.5%)	14 (3.7%)	383 (40%)	
	41–60 years	1 (0.3%)	76 (22.9%)	141 (42.5%)	62 (18.7%)	33 (9.9%)	19 (5.7%)	332 (30%)	
	>61 years	2 (1.6%)	27 (21.1%)	48 (37.5%)	27 (21.1%)	18 (14.1%)	6 (4.7%)	128 (10%)	
Severity of illness	Mild	51 (8.5%)	170 (28.2%)	208 (34.6%)	97 (16.1%)	48 (8%)	28 (4.7%)	602 (63%)	<0.05
	Moderate	3 (1.8%)	49 (29.3%)	78 (46.7%)	25 (15%)	9 (5.4%)	3 (1.8%)	167 (17.6%)	
	Severe	0 (0%)	26 (25.5%)	35 (34.3%)	22 (21.6%)	11 (10.8%)	8 (7.8%)	102 (10.7%)	
	Critical	2 (3.2%)	15 (23.8%)	24 (38.1%)	12 (19%)	5 (7.9%)	5 (7.9%)	63 (6.6%)	
Site of admission	ICU	0 (0%)	14 (23.3%)	30 (50%)	13 (21.7%)	2 (3.3%)	1 (1.7%)	60 (10%)	<0.05
	General ward	20 (4%)	158 (31.7%)	194 (39%)	82 (16.5%)	29 (5.8%)	15 (3%)	498 (50%)	
	Unknown	26 (10.8%)	51 (21.2%)	71 (29.5%)	44 (18.3%)	31 (12.9%)	18 (7.5%)	241 (30%)	

Table 2 Distribution of Confirmed Cases of COVID-19 According to Symptoms, N=951

Symptoms	Class of Obesity						Total	P-value
	Underweight (≤18.5 kg/m^2)	Normal (18.5–24.9 kg/m^2)	Overweight (25.0–29.9 kg/m^2)	Class I Obesity (30–34.9 kg/m^2)	Class II Obesity (35–39.9 kg/m^2)	Class III Obesity (≥40 kg/m^2)		
Cough	2 (0.7%)	85 (29.1%)	126 (43.2%)	59 (20.2%)	12 (4.1%)	8 (2.7%)	292 (30%)	<0.05
Fever	4 (1.4%)	81 (27.7%)	131 (44.9%)	58 (19.9%)	12 (4.1%)	6 (2.1%)	292 (30%)	<0.05
Sore throat	0 (0%)	10 (32.3%)	11 (35.5%)	5 (16.1%)	4 (12.9%)	1 (3.2%)	31 (3.30%)	0.65
Shortness of breath	1 (0.5%)	59 (30.6%)	75 (38.9%)	42 (21.8%)	8 (4.1%)	8 (4.1%)	193 (20%)	<0.05
Diarrhoea	0 (0%)	19 (40.4%)	16 (34%)	9 (19.1%)	1 (2.1%)	2 (4.3%)	47 (5%)	0.14
Vomiting	0 (0%)	4 (40%)	3 (30%)	1 (10%)	1 (10%)	1 (10%)	10 (1%)	0.81
Nausea	0 (0%)	6 (50%)	3 (25%)	2 (16.7%)	0 (0%)	1 (8.3%)	12 (13%)	0.45
Asymptomatic	2 (6.3%)	14 (43.8%)	9 (28.1%)	5 (15.6%)	2 (6.3%)	0 (0%)	32 (3.4%)	0.35

Table 3 Distribution of Confirmed Cases of COVID-19 According to Comorbidities, N=951

Comorbidities	Class of Obesity						Total	P-value
	Underweight (≤18.5 kg/m^2)	Normal (18.5–24.9 kg/m^2)	Overweight (25.0–29.9 kg/m^2)	Class I Obesity (30–34.9 kg/m^2)	Class II Obesity (35–39.9 kg/m^2)	Class III Obesity (≥40 kg/m^2)		
Hypertension	0 (0%)	25 (26.6%)	37 (39.4%)	21 (22.3%)	7 (7.4%)	4 (4.3%)	94 (10%)	0.14
Diabetes mellitus	1 (0.7%)	46 (31.1%)	56 (37.8%)	30 (20.3%)	11 (7.4%)	4 (2.7%)	148 (20%)	<0.05
Asthma	0 (0%)	10 (25%)	15 (37.5%)	11 (27.5%)	4 (10%)	0 (0%)	40 (4.23%)	0.18
COPD	0 (0%)	1 (7.1%)	7 (50%)	3 (21.4%)	3 (21.4%)	0 (0%)	14 (1.5%)	0.17
Coronary heart disease	0 (0%)	8 (28.6%)	12 (42.9%)	3 (10.7%)	3 (10.7%)	2 (7.1%)	28 (3%)	0.66
Heart failure	0 (0%)	6 (27.3%)	9 (40.9%)	4 (18.2%)	2 (9.1%)	1 (4.5%)	22 (2.33%)	0.91
Stroke	1 (8.3%)	3 (25%)	5 (41.7%)	0 (0%)	3 (25%)	0 (0%)	12 (1.3%)	0.21
Malignancy	0 (0%)	4 (26.7%)	8 (53.3%)	0 (0%)	2 (13.3%)	1 (6.7%)	15 (1.6%)	0.39
Chronic kidney disease	0 (0%)	12 (35.3%)	16 (47.1%)	4 (11.8%)	2 (5.9%)	0 (0%)	34 (4.3%)	0.44
Chronic liver disease	0 (0%)	2 (16.7%)	3 (25%)	3 (25%)	4 (33.3%)	0 (0%)	12 (1.8%)	<0.05
Immunocompromised disease	3 (8.8%)	10 (29.4%)	15 (44.1%)	3 (8.8%)	2 (5.9%)	1 (2.9%)	34 (5.4%)	0.45
Organ transplant	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)	0.88

been reported in patients with severe COVID-19.[40] In patients with obesity, there is chronic subclinical inflammation, which includes an increase in the same inflammatory markers that are involved in cytokine storm.[41,42] In obesity, both hypercoagulable and hyperinflammatory states exist, which may increase the risk of COVID-19 infection severity.

Table 4 Outcome of Clinical Management in Patients with COVID-19

Category	Class of Obesity							P-value
	Underweight (≤18.5 kg/m^2)	Normal (18.5–24.9 kg/m^2)	Overweight (25.0–29.9 kg/m^2)	Class I Obesity (30–34.9 kg/m^2)	Class II Obesity (35–39.9 kg/m^2)	Class III Obesity (≥40 kg/m^2)	N (%)	
Medications								
Antibiotics	4 (1.3%)	94 (30.1%)	132 (42.3%)	58 (18.6%)	16 (5.1%)	8 (2.6%)	312 (30%)	<0.05
Antimalaria	0 (0%)	19 (30.2%)	27 (42.9%)	13 (20.6%)	4 (6.3%)	0 (0%)	63 (6.6%)	<0.05
Bronchodilator	3 (2.9%)	28 (27.2%)	50 (48.5%)	17 (16.5%)	3 (2.9%)	2 (1.9%)	103 (10%)	<0.05
Corticosteroid	-	8 (33.3%)	10 (41.7%)	5 (20.8%)	1 (4.2%)	-	24 (2.5%)	<0.05
Response to medications								
Symptoms improving	7 (1.6%)	141 (32.6%)	179 (41.4%)	77 (17.8%)	18 (4.2%)	10 (2.3%)	432 (50%)	0.87
Clinical outcome								
Death	0 (0%)	2 (15.4%)	5 (38.5%)	1 (7.7%)	2 (15.4%)	3 (23.1%)	13 (2%)	<0.05
Hospital admission period in days (Mean ± SD)	10.14 ± 4.74	9.62 ± 5.86	10.37 ± 6.37	10.16 ± 5.61	9.57 ± 4.01	9.5 ± 4.37	10.02 ± 5.91	0.94

Table 5 Association of BMI and Diabetes Mellitus with Severe/Critical COVID-19

Risk Factor	B	S.E.	Wald	df	P value	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Underweight (≤18.5 kg/m^2)	−1.258	0.747	2.840	1	0.09	0.284	0.066	1.228
Overweight (25.0–29.9 kg/m^2)	0.142	0.233	0.369	1	0.54	1.152	0.730	1.820
Class I obesity (30–34.9 kg/m^2)	0.410	0.272	2.278	1	0.13	1.507	0.885	2.569
Class II obesity (35–39.9 kg/m^2)	0.491	0.347	2.002	1	0.15	1.634	0.828	3.226
Class III obesity (≥40 kg/m^2)	1.056	0.388	7.408	1	<0.05	2.874	1.344	6.149
History of diabetes mellitus	1.684	0.202	69.270	1	<0.05	5.385	3.622	8.005

Alterations in immunological function, particularly complement activation, thrombosis likelihood, and alterations in lung function are all possible causes of a worsened disease course in obese patients. An earlier study reported that obese patients, in comparison to those with normal weight, have altered immune cell activity.[43] Such disturbances in host defense in obese patients could increase the risk of COVID-19 complications. The observed inflammation, platelet activation, and endothelial dysfunction observed in COVID-19 increase the risk of thrombotic illness in both the venous and arterial circulation.[44] Thrombotic diseases, such as pulmonary embolism, are regarded as another manifestation of severe disease that contributes to the need for ICU admission and an increase in mortality, although it was not investigated in our study. As reported in a previous report,[45] obesity is associated with a higher risk of thrombosis due to increased platelet activation and increased production of prothrombotic factors. This prothrombotic condition may predispose obese patients with COVID-19 to thrombotic incidents, which are associated with greater disease severity and poor prognosis.[46]

Having a high BMI has adverse consequences on lung function, lowering the forced expiratory volume and forced vital capacity.[47] The ability of a patient to sustain adequate oxygenation is directly affected by changes in the respiratory mechanics. This might explain the higher rate of cough and shortness of breath observed in our study in overweight patients than in patients with normal BMI.

In the current study, the prevalence of cardiometabolic disorders such as diabetes, hypertension, and coronary artery disease did not increase as BMI increased. However, diabetes mellitus was found to be associated with severe COVID-19, as revealed by multivariable regression analysis conducted in our study, which corroborates previous findings.[48–50] This implies that these diseases contribute to poor COVID-19 outcomes, regardless of BMI.

Limitations of the study include the retrospective nature of this study and the limited number of patients included. Other factors may contribute to the severity of COVID-19 in obese patients, which could become significant in future studies involving larger sample sizes. Moreover, due to the small number of deaths recorded in our study, we were unable to investigate the effect of BMI on death rates.

Conclusion

In conclusion, the results of the current study collectively revealed that the severity of COVID-19 was significantly higher in patients with a BMI ≥40 kg/m^2. This study highlights obesity as a serious health problem, particularly regarding its association with severe COVID-19 infection and emphasizes the importance of addressing obesity as a public health issue in Saudi Arabia.

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Disclosure

The authors report no conflicts of interest in this work.

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