Obesity and COVID-19

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Abstract

Background: Obesity is a recognized risk factor for severe COVID-19, possibly related to chronic inflammation that disrupts immune and thrombogenic responses to pathogens as well as to impaired lung function from excess weight. Obesity is a common metabolic disease; approximately two in three Iraqi adult participants were overweight/obese.

Aim of Study: The aim of this study is to investigate the association between COVID-19 disease severity and obesity in a sample of Iraqi patients.

Patient and method: The study included 609 patients with confirmed Covid-19 infection carried out in Azadi and alShifaa14 hospitals and on outpatient cases in Kirkuk city from 1st November2020 to 30 April 2021 through which BMI was calculated for each patient and correlated with severity.

Results: The study showed that majority of patients (77.9%) were overweight or obese., majority of patients (63.5%) were in sever condition, (24.5%) patients were in mild state, and only 2 patients were critical ill. The males gender was associated with more severe cases (p=0.018). Age was associated with more severity (p=0.0001). BMI showed an association with viral disease severity, in which over weight and obese categories were had more severe symptoms (p=0.0001).

Conclusions: BMI showed an association with COVID-19 Disease status, in which overweight and obese categories were had more severe symptoms (p=0.0001). The study revealed that males gender were associated with more severe cases of COVID-19 disease status (p=0.018).

Key word: Obesity, SARS-CoV-2, COVID-19, BMI

1. Introduction:

The Coronavirus Disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become one of the worst pandemics in this century. The World Health Organization (WHO) announced the confirmation of COVID-19 as a pandemic on March 11th, 2020.[1] As of July 20th, 2021, COVID-19 has affected over 190 million people worldwide, causing more than 4 million of fatalities.[2] The clinical outcomes of COVID-19 vary in severity from asymptomatic to lethal.[3] In addition to several degrees of pneumonia, COVID-19 may cause injury of many organs including liver, kidneys and heart.[4]

Obesity, defined as excessive accumulation of body fat, is generally determined by body mass index (BMI), calculated by body weight (kg) divided by height squared (m2).[5] The number of obese people is globally increasing. Adiposity affects adverse health outcomes such as coronary artery disease, cerebrovascular disease, insulin resistance, hypertension and fatty liver disease. Fat accumulation does not only affect mechanical-related health complications, but the abundant adipose tissue also releases many adipokines which play a role in the inflammatory process.[6] Nonetheless, the immune system is suppressed in obese people, especially in vulnerable people with multiple comorbidities.[7] Obese people may be more susceptible to SARS-CoV-2 infection.[8] A pathophysiology of COVID-19 is an immune response dysfunction resulting in damage to multiple organs, particularly the lower airways. Owing to similar pathogenesis, obesity could be correlated to adverse outcomes and severity of COVID-19.[9]

1.1. The Coronavirus Disease 2019:

The current coronavirus disease 2019 (COVID-19) outbreak is a worldwide emergency, as its rapid spread and high mortality rate has caused severe disruptions. [1] The number of people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, is rapidly increasing worldwide. Patients with COVID-19 can develop pneumonia,[10, 11] severe symptoms of acute respiratory distress syndrome (ARDS), and multiple organ failure.[12]

SARS-CoV-2 infection can activate innate and adaptive immune responses. However, uncontrolled inflammatory innate responses and impaired adaptive immune responses may lead to harmful tissue damage, both locally and systemically. In patients with severe COVID-19, but not in patients with mild disease, lymphopenia is a common feature, with drastically reduced numbers of CD4+ T cells, CD8+ T cells, B cells and natural killer (NK) cells,[13] as well as a reduced percentage of monocytes, eosinophils and basophils.[14] An increase in neutrophil count and in the neutrophil-to-lymphocyte ratio

usually indicates higher disease severity and poor clinical outcome5. In addition, exhaustion markers, such as NKG2A, on cytotoxic lymphocytes, including NK cells and CD8+ T cells, are upregulated in patients with COVID-19. In patients who have recovered or are convalescent, the numbers of CD4+ T cells, CD8+ T cells, B cells and NK cells and the markers of exhaustion on cytotoxic lymphocytes normalize. Moreover, SARS-CoV-2-specific antibodies can be detected.[15]

1.1.1. Transmission of infection

The transmission of infection is mainly person to person through respiratory droplets. Faecal–oral route is possible. The presence of the virus has been confirmed in sputum, pharyngeal swabs and faeces.[16] Vertical transmission of SARS-CoV-2 has been reported and confirmed by positive nasopharyngeal swab for COVID-19. The median incubation period of COVID-19 is 5.2 days; most patients will develop symptoms in 11.5 to 15.5 days. Therefore, it has been recommended to quarantine those exposed to infection for 14 days.[17]

1.1.2. The immunopathology of COVID-19

It has been shown that SARS-CoV-2 disrupts normal immune responses, leading to an impaired immune system and uncontrolled inflammatory responses in severe and critical patients with COVID-19. These patients exhibit lymphopenia, lymphocyte activation and dysfunction, granulocyte and monocyte abnormalities, high cytokine levels, and an increase in immunoglobulin G (IgG) and total antibodies.[18]

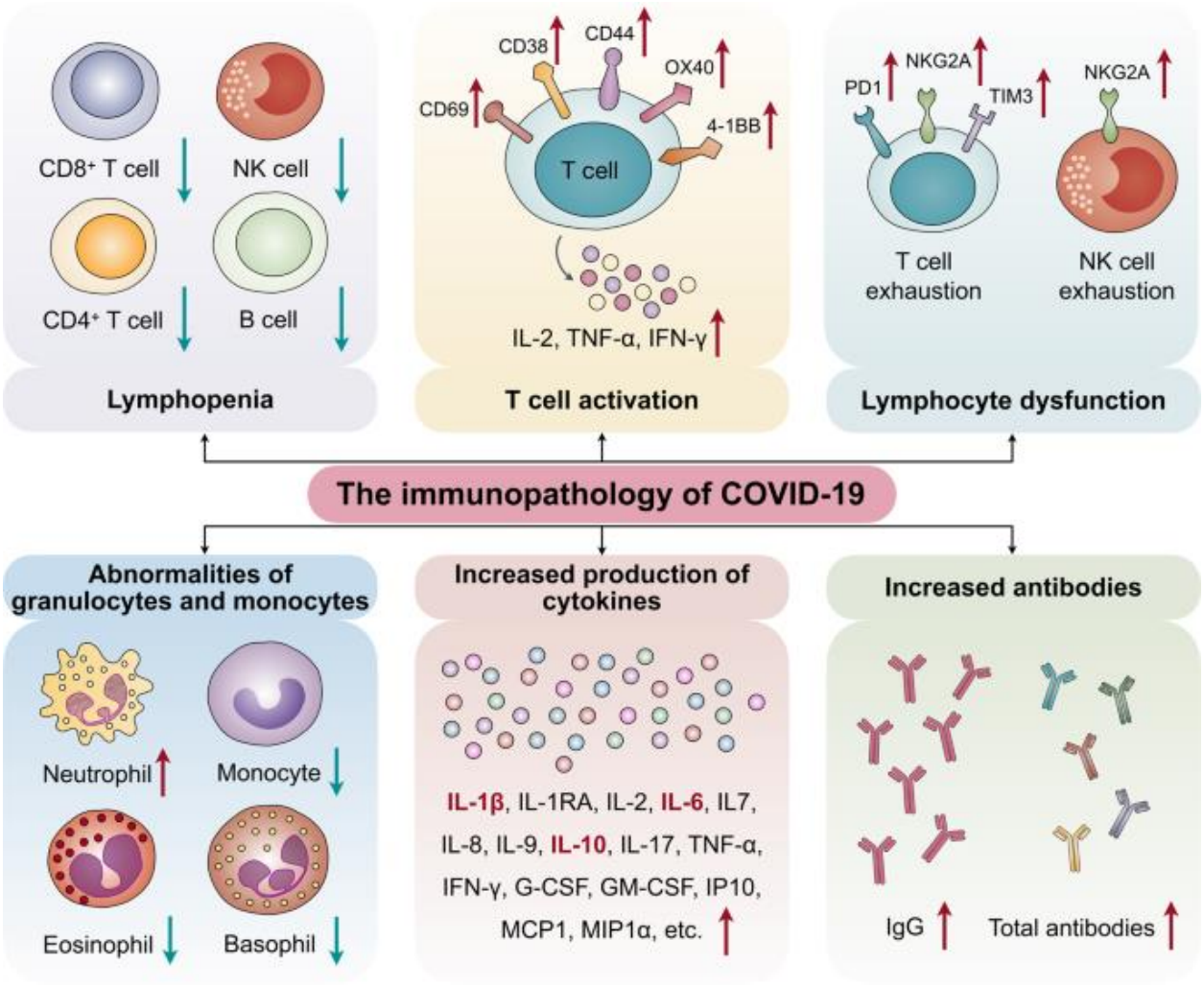

Figure 1. The immunopathology of COVID-19

The immune patterns of COVID-19 include lymphopenia, lymphocyte activation and dysfunction, abnormalities of granulocytes and monocytes, increased production of cytokines, and increased antibodies. Lymphopenia is a key feature of patients with COVID-19, especially in severe cases. CD69, CD38, and CD44 are highly expressed on CD4+ and CD8+ T cells of patients, and virus-specific T cells from severe cases exhibit a central memory phenotype with high levels of IFN-γ, TNF-α, and IL-2. However, lymphocytes show an exhaustion phenotype with programmed cell death protein-1 (PD1), T cell immunoglobulin domain and mucin domain-3 (TIM3), and killer cell lectin-like receptor subfamily C member 1 (NKG2A) upregulation. Neutrophil levels are significantly higher in severe patients, while the percentage of eosinophils, basophils, and monocytes are reduced. Increased cytokine production, especially of IL-1β, IL-6, and IL-10, is another key characteristic of severe COVID-19. IgG levels are also increased and there is a higher titer of total antibodies. [19]

1.1.3. Increased production of cytokines

Increased cytokine production is another key characteristic of severe COVID-19. Most severe COVID-19 cases exhibit an extreme increase in inflammatory cytokines, including IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interferon-inducible protein-10 (IP10), monocyte chemotactic protein 1 (MCP1), macrophage inflammation protein-1α, IFN-γ, and TNF-α, representing a "cytokine storm".[20]

1.1.4. Complications

Age and sex have been shown to affect the severity of complications of COVID-19. The rates of hospitalization and death are less than 0.1% in children but increase to 10% or more in older patients. Men are more likely to develop severe complications compared to women as a consequence of SARS-CoV-2 infection.[21] Patients with cancer and solid organ transplant recipients are at increased risk of severe COVID-19 complications because of their immunosuppressed status. [31]

The main complications reported in patients with SARS-CoV-2 may include:

- Coagulopathy, mainly disseminated intravascular coagulation, venous thromboembolism, elevated D-dimer and prolonged prothrombin time.[31]
- Laryngeal oedema and laryngitis in critically ill patients with COVID-19.
- Necrotizing pneumonia due to superinfection caused by Panton-Valentine leukocidin–secreting Staphylococcus aureus infection. This superinfection is usually fatal.[22]
- Cardiovascular complications, including acute pericarditis, left ventricular dysfunction, acute myocardial injury (associated with increased serum troponin), new or worsening arrhythmias and new or worsening heart failure.[32]
- Acute respiratory failure. Approximately 5% of COVID-19 patients require admittance to an intensive care unit because they develop severe disease complicated by acute respiratory distress syndrome.[23]
- Sepsis, septic shock and multiple organ failure.[33]
- Higher risk of death, particularly in male patients with severe disease, presence of heart injury and cardiac complications, hyperglycaemia and patients receiving high doses of corticosteroids.[24]
- Ventilation-associated pneumonia in up to 30% of patients requiring intensive mechanical ventilation.[34]
- Massive pulmonary embolism complicated by acute right-sided heart failure.[25]

1.2. Risk factors Associated with COVID-19:

The CDC has published a summary of evidence of comorbidities that are supported by meta-analysis/systematic review that have a significant association with risk of severe COVID-19 illness. These include the following conditions[26]:

- Cancer
- Cerebrovascular disease
- Chronic kidney disease
- COPD (chronic obstructive pulmonary disease)
- Diabetes mellitus, type 1 and type 2
- Heart conditions (eg, heart failure, coronary artery disease, cardiomyopathies)
- Immunocompromised state from solid organ transplant
- Obesity (BMI 30 kg/m ^{2} or greater)
- Pregnancy
- Smoking, current or former

1.3. Obesity with COVID-19:

Body Mass Index (BMI) is a simple toll used to calculate the person's weight based on height. The height and weight were measured using the standardized height and weight scale, The equation used for BMI is (BMI = Wight (kg) * (Height in Meter)^2.

BMI Categories:[27]

- Underweight = <18.5
- Normal weight = 18.5–24.9
- Overweight = 25–29.9
- Obesity = BMI of 30 or greater

Studies have shown that COVID-19 does not affect all population groups equally. The risk of severe COVID-19 increases as the number of underlying medical conditions increases in an individual.[28]

Obesity is a recognized risk factor for severe COVID-19, possibly related to chronic inflammation that disrupts immune and thrombogenic responses to pathogens as well as to impaired lung function from excess weight. Obesity is a common metabolic disease; approximately two in three Iraqi adult participants were overweight/obese.[29]

The Advisory Committee on Immunization Practices considers obesity to be a high-risk medical condition for COVID-19 vaccine prioritization.[30] Using data from the Premier Healthcare Database Special COVID-19 Release (PHD-SR), CDC assessed the association between body mass index (BMI) and risk for severe COVID-19 outcomes (i.e., hospitalization, intensive care unit [ICU] or

stepdown unit admission, invasive mechanical ventilation, and death). Among 148,494 adults who received a COVID-19 diagnosis during an emergency department (ED) or inpatient visit at 238 U.S. hospitals during March–December 2020, 28.3% had overweight and 50.8% had obesity. Overweight and obesity were risk factors for invasive mechanical ventilation, and obesity was a risk factor for hospitalization and death, particularly among adults aged <65 years. Risks for hospitalization, ICU admission, and death were lowest among patients with BMIs of 24.2 kg/m2, 25.9 kg/m2, and 23.7 kg/m2, respectively, and then increased sharply with higher BMIs. Risk for invasive mechanical ventilation increased over the full range of BMIs, from 15 kg/m2 to 60 kg/m2.[31]

How Obesity Affects the Pathogenesis of COVID-19:

Inflammation:

Obesity, characterized by adipose tissue expansion, affects the inflammatory response. Adipocytes secret pro-inflammatory cytokines, such as TNFa, interleukin (IL)-1, IL-6 and IL-10,[32] which results in elevated circulating levels of cytokines and chemokines in the plasma of obese patients.[33] Macrophages are the most abundant inflammatory cells in adipose tissue (AT). In such microenvironment, they tend to switch from an anti-inflammatory M2-polarized state to a proinflammatory M1 state of macrophages,[34] which leads to a low-grade inflammation situation.[35] "Cytokine storm", which is the hyperactivation of the inflammatory response with elevated interferon γ, IL-6, and other proinflammatory cytokines, also aggravates the severity of COVID-19.[36] In addition, a higher portion of CD14+CD16+ inflammatory monocytes was found in severe patients than non-severe patients,[37] which also suggests an elevated level of inflammation in severe COVID-19 patients.[38]

Immunity:

The function of various immune cells is also altered in obese patients, which significantly affects the immune system. Laboratory findings suggest that the number of lymphocytes including CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells are dramatically decreased in COVID-19 patients.[39] Unfortunately, obesity impairs both T and B cell responses, therefore retards the adaptive immune response to infection. The weakened immune system in obese patients may result in higher viral load, rapid viral replication and spreading. [53]

There is also considerable interaction between immunity and inflammation. Several studies reported that proinflammatory T and B cell phenotypes are involved in inflammation of adipose tissue.[40] For example, CD8+ T cells promote macrophage recruitment, while anti-inflammatory Th2

cells promoting macrophage differentiation into M2 reduce.[41] In the setting of obesity, pro-inflammatory T helper 1 (Th1) cells secret IFN-γ and increase the level of inflammation. Moreover, low-grade inflammation in obesity could also induce a dysfunctional immune system in the disease.[42]

Lipofibroblasts and Pulmonary Fibrosis:

There has been a positive correlation between the duration of SARS-CoV infection and the degree of interstitial lung fibrosis.[43] Extensive pulmonary fibrosis is one of the main reasons for pulmonary consolidation, due to excessive extracellular matrix components produced by activated myofibroblasts. This poses an obstacle to gas change. [45]

Pulmonary lipofibroblasts are a special type of adipocytes, which contain typical lipid droplets and reside close to type 2 alveolar epithelial cells in the alveolar interstitium.[44] Lipofibroblasts might be the result of ectopic fat deposition, and lipofibroblasts may be a vital role in the progress of COVID-19 in obese patients. When exposed to various stimulation such as hypoxia and infection,[45] pulmonary lipofibroblasts can transdifferentiate into a myogenic phenotype called "myofibroblasts" to induce pulmonary fibrosis.[46] Although there is a lack of direct evidence of how lipofibroblasts affect pulmonary fibrosis after SARS-Cov-2 infection, it is reasonable to speculate that the number of lipofibroblasts positively correlates with the severity pulmonary fibrosis. [43]

Lipid Metabolism

One of the reasons for obesity is the excessive lipid deposit in adipose tissue due to energy over-intake. Lipids have multiple functions in virus infection. In addition to being a source of energy, lipid droplets can be utilized as sites of virus assembly, such as hepatitis C virus.[47] It is reasonable to speculate that lipids accumulating in adipocytes in obese patients may facilitate the replication of SARS-COV-2 and ectopic fat depositing may contribute to organ injury during virus infection. [47]

Lipid rafts enriched with sphingolipids, cholesterol and proteins are microdomains of the cell membrane. Notably, lipid rafts were found co-localized with angiotensin-converting enzyme 2 (ACE2), the receptor of SARS-CoV. It is shown that lipid rafts facilitate the binding of the

2. Patients and Methods

2.1.1 Study design

A prospective observational cohort study done in Kirkuk city from 1st of November 2020 to 30th of April 2021.

2.1.2. Inclusion criteria:

The study was performed on 609 patients already infected with COVID19 virus; including outpatient cases, those who visited Azadi teaching hospital clinic, those who were admitted to, Al-Shifaa Hospital and Azadi teaching hospital for purpose of management.

2.2. Clinical presentation

The clinical spectrum of COVID-19 disease in this study was classified according to WHO Guidelines 2021 ranged from Mild to Critical.8

Mild	Moderate	Severe	Critical
• Symptomatic • No evedence of pneumonia or hypoxia	• Clinical signs of pneumonia • Spo2 >90%	• Signs of pneumonia and any of: 1.RR>30 b/m 2.severe respiratory distress 3.Spo2<90%	• ARDS • Sepsis • Septic shock

Results:

There were 609 patients diagnosed with COVID-19 have been included in this study.
Then mean age for all patients was 56.3 ± 17.9 years (range 11 – 91 years). Males were represented 59.11% of patients and females were represented 40.89% of patients.
Regarding patients' comorbidities, the DM was presented in (25.5%) of patients, hypertension in (35.3%), and other comorbidities was presented in (16.1%) of patients.

For the smoking status, there were (15.1%) of patients currently smoker.

Regarding BMI, the mean BMI was 28.4 ± 5.1 Kg/M^2 (range 13 – 46 Kg/M^2). The BMI categories showed, majority of patients (77.9%) were overweight or obese.

Table 3. comorbidities, and smoking status across patients

Variable	Frequency	Percentage
DM		
Diabetic	155	25.5
Not diabetic	454	74.5
Hypertension		
Hypertensive	215	35.3
Not hypertensive	394	64.7
Others(IHD,CKD,Asthma)		
Present	98	16.1
Not present	511	83.9
Smoking		
Current smoker	92	15.1
Non smoker	517	84.9
BMI categories		
Under weight	17	2.8

Normal	118	19.4
Overweight	272	44.7
Obese	202	33.2

Regarding the CBC, majority of patients were having lymphopenia (89.7%) and normal CBC was observed in 30 (4.9%) patients.

Table 4. CBC manifestation			
		Frequency	Percent
Valid	anemia	3	.5
	Increase PLT	5	.8
	leukocytosis	25	4.1
	lymphopenia	546	89.7
	Normal	30	4.9
	Total	609	100.0

Regarding the lung involvement by CT, there were (16.7%) of patients have less than 30% of lung involvement, and more than (59%) of patients have more than 50%.

Table 5. percentage of lung involvement by CT scan			
CT %		**Frequency**	**Percentage from total**
Valid	10 - 30	122	20.03
	31- 60	220	36.1
	> 60	122	20.03
	normal	145	23.8
	Total	**609**	**100.0**

Table 6. Association between CT involvement and BMI							
			BMI				Total
			Under weight	Normal	Over weight	Obese	
CT Involvement	<30 %	Count	0	16	60	26	102
		% within CT	0.0%	15.7%	58.8%	25.5%	100.0%
	≥30%	Count	5	43	163	151	362
		% within CT	1.4%	11.9%	45.0%	41.7%	100.0%
	Normal	Count	12	59	49	25	145
		% within CT	8.3%	40.7%	33.8%	17.2%	100.0%
Total		Count	17	118	272	202	609
		% within CT c	2.8%	19.4%	44.7%	33.2%	100.0%

After classification of patients based on severity, majority of patients (63.5%) were in sever condition, (24.5%) patients were in mild state, and only 2 patients were critical.

Table 7. Severity of COVID-19 infection			
		Frequency	Percent
COVID-19	Mild	149	24.5
	Moderate	71	11.7
	Severe	387	63.5
	Critical	2	.3
	Total	609	100.0

Factors associated with severity:

Gender:

The males gender were associated with more severe cases of COVID-19 status (p=0.018).

Table 8. Association between severity and gender						
		Mild N. (%)	Moderate N. (%)	Severe N. (%)	Critical N. (%)	Total N. (%)
Gender	Female	76 (51)	24 (33.8)	149 (38.5)	0 (0)	249 (40.8)
	Male	73 (49)	47 (66.2)	238 (61.5)	2 (100)	360 (59.1)
Total		149 (100)	71 (100)	387 (100)	2 (100)	609 (100)

Comorbidities:

The presence of DM, or hypertension, or other comorbidities were associated with more severe status of COVID-19 (p=0.0001

Table 10. Association between severity and Comorbidities						
		Mild N. (%)	Moderate N. (%)	Severe N. (%)	Critical N. (%)	P value
DM	Yes	0	11 (15.5)	144 (37.2)	0	**0.0001**
	No	149 (100)	60 (84.5)	243 (62.8)	2 (100)	
HTN	Yes	4 (2.7)	19 (26.8)	192 (49.6)	0	**0.0001**
	No	145 (97.3)	52 (73.2)	195 (50.4)	2 (100)	
Other	Yes	6 (4.0)	12 (16.9)	78 (20.2)	2	**0.0001**
	No	143 (96.0)	59 (83.1)	309 (79.8)	0 (100)	

Smoking:

The smoking status did not showed association with COVID-19 status (p=0.15).

Table 11. Association between severity and Smoking						
		Mild N. (%)	Moderate N. (%)	Severe N. (%)	Critical N. (%)	Total N. (%)
Smoking	No	128 (85.9)	66 (93.0)	321 (82.9)	2 (100)	517 (84.9)
	yes	21 (14.1)	5 (7.0)	66 (17.1)	0	92 (15.1)
Total		149(100)	71(100)	387(100)	2(100)	609(100)

Age: The age was associated with more sever status of COVID-19 (p=0.0001).

D-dimer: The level of D-dimer was significantly higher among patients with severe status of COVID-19 (p=0.0001).

CRP: The level of CRP was significantly higher among patients with severe status of COVID-19 (p=0.0001).

Body Mass Index

BMI showed an association with COVID-19 status, in which over weight and obese categories were had more severe symptoms (p=0.0001).

Table 13. Association between severity and BMI						
		Mild N. (%)	Moderate N. (%)	Severe N. (%)	Critical N. (%)	Total N. (%)
BMI	Under	12 (8.1)	0	5 (1.3)	0	17 (2.8)
	Normal	59 (36.6)	8 (11.2)	49 (12.7)	2 (100)	118 (19.4)
	Over	51 (34.2)	44 (62.0)	177 (45.7)	0	272 (44.7)
	Obese	27 (18.1)	19 (26.8)	156 (40.3)	0	202 (33.2)
Total		149(100)	71(100)	387(100)	2(100)	609(100)

Discussion:

Obesity is a recognized risk factor for severe COVID-19, possibly related to chronic inflammation that disrupts immune and thrombogenic responses to pathogens. [9]

In this study, there were 609 patients diagnosed with COVID-19 have been included to assess the association between obesity and severity of COVID-19…[9]

Regarding obesity, the prevalence overweight and obesity in this study was 2/3 of patients, in which it in line with general prevalence that showed in Iraq…[10]

Also, the result was comparable to prevalence of obesity among COVID-19, in which a large meta-analysis study showed that obesity prevalence was 34%. [11]

There were a slightly higher number of males in this study and this was comparable to a study conducted in China that showed there was an equal distribution in infection of COVID-19 between males and females. [12]

Regarding obesity, the prevalence overweight and obesity in this study was 2/3 of patients, in which it in line with general prevalence that showed in Iraq.Also, the result was comparable to prevalence of obesity among COVID-19, in which a large meta-analysis study showed that obesity prevalence was 34%. [11]

Factors associated with Severity of COVID-19 infection:

In this study, males' gender was associated with more severe cases of COVID-19 status. The same results were also reported by other studies that showed, men were more susceptible to severe disease than women were. The hormonal difference could play a role in increased of severity among males. .[13, 14, 15]

D-dimer and CRP, both were demonstrated to be associated with severity of COVID-19 infection, in which high level of D-dimer and CRP were significantly higher among patients with severe status of COVID-19. This results was in line with another study's results that showed a significant association of D-dimer and CRP with severity, also they reported that at time of admission could be simple available predictors for severe COVID-19 infection requiring ICU admission.[16, 17]

Obesity and Severity of COVID-19 infection

In this study, the obesity showed an association with COVID-19 status, in which over weight and obese categories were, had more severe symptoms. There are several reports evaluating the burden of obesity on the clinical course of COVID-19, in which pooled analyses showed that COVID-19 patients with obesity had a borderline higher risk for hospitalization. Obesity was related to significantly higher risk for ICU admission; however, obesity was not associated with increased risk for death in patients with COVID-19. Also, most of these meta-analyses indicated that in patients with COVID-19, obesity is significantly related to increased risk of severe disease and composite poor outcomes. [18, 19]

Obesity represents a major and urgent global health problem. It tends to increase with increasing age and is a known risk factor for the abovementioned comorbidities identified as predisposing factors for adverse outcomes in COVID-19. This association might relate to, Obesity is linked to impaired immune function, also, obesity decreases lung capacity and reserve and can make ventilation more difficult. [20, 21]

Conclusions:

BMI showed an association with COVID-19 status, in which overweight and obese categories were had more severe symptoms (p=0.0001). The study revealed that males gender were associated with more severe cases of COVID-19 status.

Recommendations:

- Special attention should be given for obese patients who get COVID-19 infection

- Early intervention and management for obese patients who get COVID-19 infection to decrease severity of infection.

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