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Increased Severity of COVID-19 In Obese Patients: A Meta-analysis

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Abstract

The purpose of this research is to investigate the role of obesity in the pathogenesis of severe COVID-19 infection. The relation between obesity and severe COVID-19 has not been completely recorded. PUBMED, Cochrane Clinical trials database, Google Scholar and MEDLINE were used to search for literature. Comprehensive Meta-analysis software and Excel were used to analyze data. The retrospective cohort study examined the correlation between BMI and in patients accepted in intensive care for COVID-19. Nine studies were chosen with a total of 340,811 patients were selected. Patients with a severe COVID-19 cases had varying pooled odds ratios based on BMI; for BMI of 25-29.9 kg/m^2 1.24 (random; 95% CI: 1.03-1.48; p = 0.374; I2 =0.000), for BMI of 30-34.9 kg/m^2 2.01 (random; 95% CI: 1.41-2.88; p = 0.041; I2 = 59.942) and for BMI of ≥35 kg/m^2 2.16 (random; 95% CI: 1.61-2.89; p = 0.172; I2 = 43.242). These studies also showed a linear increase in percentage of severe COVID-19 cases based on increasing BMI. The present study indicates a high frequency of obesity among patients accepted in intensive care for COVID-19. Disease severity escalates with Body mass index (BMI). Obesity is a risk factor for COVID-19 severity. Awareness of this severity is needed to be spread widely so as to curtail overweight or obesity.

Keywords: Obesity; BMI; COVID-19; severity; ventilator; ICU.

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1. Introduction

The coronavirus disease 2019 (COVID-19) is the cause of a speedily progressing pandemic. It originates from a viral respiratory disease known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The rapid spread of this virus led to the public announcement of a pandemic by the World Health Organization on the 11th March 2020[1]. Researchers believe that patients at risk for severe acute respiratory syndrome COVID-19 have been marked as having preexisting diseases, such as cardiovascular disease, high blood pressure, obesity, chronic lung disease, diabetes or heart disease, chronic respiratory disease, or cancer while others singled out an increase in BMI with few other comorbidities as the major risk factors for COVID-19[2]. Obesity is considered as an unusual or excessive fat collection that presents a risk to health and predisposes the body with risk of other diseases and health problems, such as heart disease, diabetes and COVID-19[3,4]. A body mass index (BMI) is a criterion used to identify one as obese. If BMI is less than 18.5 kg/m^2, it is considered as underweight. But if it within 18.5 to 24 kg/m^2, is considered normal and if it is from 25 to 29 kg/m^2, is seen as overweight[5]. Obesity has different grades, for example: if BMI is measured from 30 to 34 kg/m^2, is considered as obese class I. While from 35 to 39 kg/m^2, is seen as obese class II and finally if it is greater than 40 kg/m^2, is considered as obese class III or extreme obesity[6]. Our research will be concentrating on BMI from 25 kg/m^2 upwards. The purpose of this research, firstly, is to establish the fact that obesity plays a severe role in the pathogenesis of COVID-19 infection. This is so, considering the fact, obese persons secrete excess free fatty acids which will induce lipo-toxicity that cause damage to many organs including the respiratory system and thus, contribute to worsening of COVID-19. Obesity induces cytokines release such as tumor necrosis factor alpha, monocyte chemoattractant protein-1, and interleukin-6 that causes hypertension via renin-angiotensin-aldosterone system activation. These cytokines will cause damage to vascular endothelium and induce symptoms such as fatigue or confusion, chest pain, difficulty breathing or irregular heartbeat often seen in COVID-19 patients[7]. Secondly, to let the general population be aware of danger of obesity and also to trigger the minds of many scholars and researches to pay more attention on obesity without other comorbidities as a risk factor in the severity of COVID-19. This urgency is needed, considering the fact that over two-thirds of Westernized society are overweight or obese[8]. These findings can have a significant impact on the evaluation of patients and implications for policy. Therefore, obese patients are amongst groups at high risk and should be advised to take preventive precautions such as hand hygiene and social distancing to prevent being contaminated by coronavirus disease. It is also vital to engage in regular exercise, and avoid high calorie diets which contributes to weight gain[3].

2. Method

The present study seeks to demonstrate a relationship between individuals with obesity and severity of COVID-19. “Severe COVID-19 case” was defined as patients that tested positive for COVID-19 and required ICU and/or assisted ventilation. With this in mind, a search through databases were made. PUBMED, Cochrane Clinical trials database, Google Scholar and MEDLINE were the main databases used to search for literature. Key subject searches included “obesity and COVID19”, “obesity and severe COVID19”, “obesity ventilator and COVID19” and “obesity ICU and COVID19”. Initially, there was a manual literature search screening title headings and abstracts. This initial search was based on the inclusion and exclusion criteria shown in Figure 1.

Furthermore, the references of included articles were searched to identify other potentially relevant studies. The search was focused on studies published in English during 2020. After the selection of certain studies, a more thorough inclusion/exclusion process was conducted by reading each study in its entirety. The studies that met all criteria were included in the meta-analysis (Figure 2).

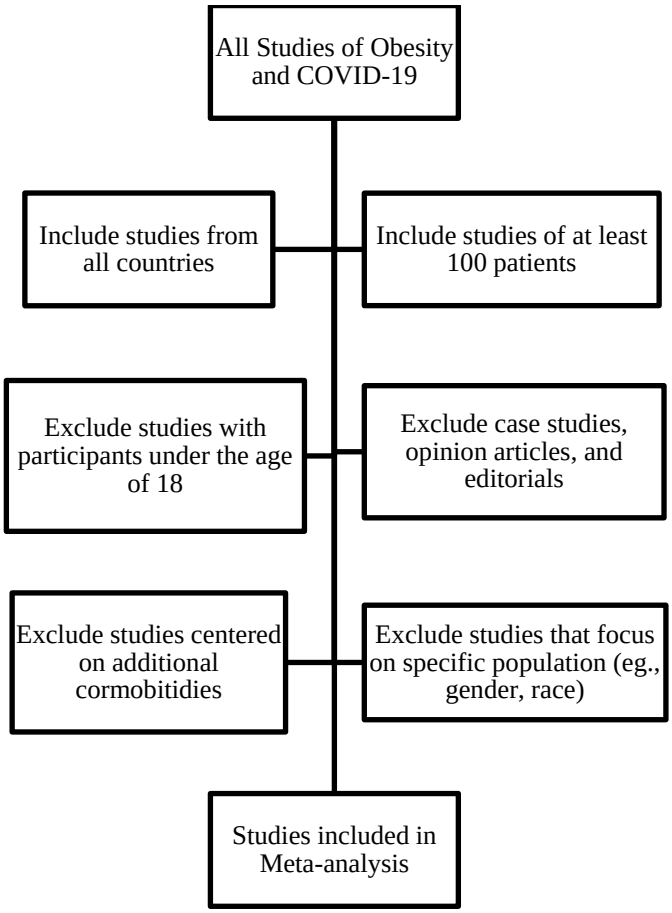


Figure 1: Flow chart showing selection process of literature.

For data analysis of odds ratios Comprehensive Meta-analysis software was used. Graphical representation of percentage of severe COVID-19 cases based on BMI compared to non-severe cases, was completed through Excel.

3. Results

Of the 57 studies identified, 9 studies were included that met all inclusion criteria (Figure 2). The following data was extracted: location, study dates, study design, sample size, odds ratios, hazard ratio, confidence intervals, p-values, and prevalence of severe cases by BMI (%). There was a total of 340, 811 patients from these 9 selected studies. Description of these studies are included in Table 1. All 9 studies overlap in time based on study dates.

Table 1: Characteristics of studies that met criteria

Study	Study Dates	Country	Study Design	Population
Hammer and colleagues	Mar 16 – Apr 26	UK	Retrospective Cohort	334, 329
Simonnet and colleagues	Feb 27 – Apr 5	France	Retrospective Cohort	124
Caussy and colleagues	Mar 27*	France	Retrospective Cohort	1210
Lighter and colleagues	Mar 3 – Apr 4	USA	Retrospective Cohort	3615
Pettit and colleagues	Mar 1 – Apr 18	USA	Retrospective Cohort	238
Cai and colleagues	Jan 11– Mar 26	China	Prospective Cohort	383
Kalligeros and colleagues	Feb 17 – Apr 5	USA	Retrospective Cohort	103
Nakeshbandi and colleagues	Mar 10 – Apr 3	USA	Retrospective Cohort	504
Frank and colleagues	Mar 13 – Apr 3	USA	Retrospective Cohort	305

*Start date was not included

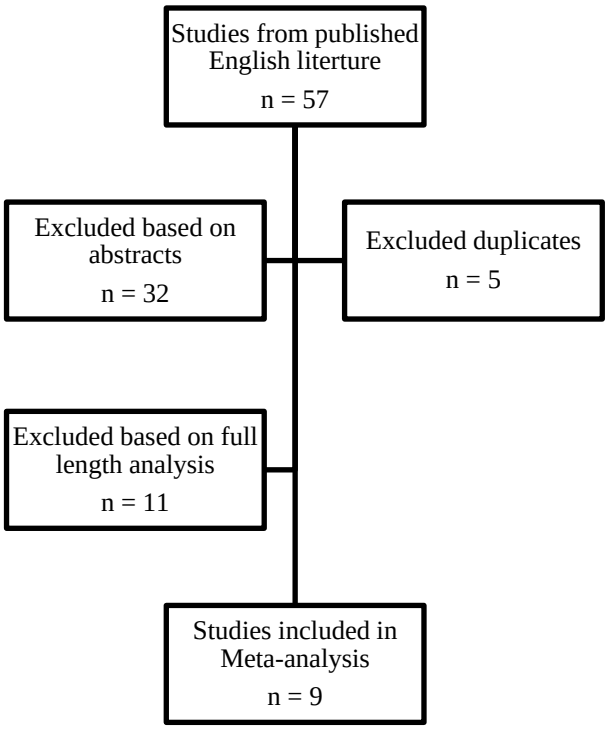


Figure 2: Flow chart showing number of studies excluded and included during selection process of literature

Of the 9 selected studies, 6 included data of percent severity of COVID-19 based on four BMI brackets: <25 kg/m^2, 25-29.9 kg/m^2, 30-34.9 kg/m^2, and ≥35 kg/m^2. These 6 studies were used to show the general trend of percentage of severe cases as BMI increased. The results show a linear increase in percentage of severe COVID-19 cases based on increasing BMI (Table 2, Figure 3). All studies show an increase in percentage of severe

cases as BMI increases with the exception of Pettit and colleagues and Kalligeros and colleagues studies[6,7]. In both studies the only results that do not follow this trend is seen between BMI of 25-29.9 kg/m^2 showing a higher percentage of cases compared to 30-34.9 kg/m^2.

Table 2: Percent of severe COVID-19 cases based on BMI compared to non-severe cases

Study	<25 kg/m^2 (%)	25-29.9 kg/m^2 (%)	30-34.9 kg/m^2 (%)	≥35 kg/m^2 (%)	p-value
Frank and colleagues	30	38	52	51	0.006
Pettit and colleagues	23.30	34	25.40	53.50	0.77
Cai and colleagues	19.20	29.30	39	39	0.001
Simmonet and colleagues	47.10	60.40	75	85.70	0.01
Kalligeros and colleagues	11.30	31.80	25	31.80	-
Nakeshbandi and colleagues	12	24	38	38	0.002

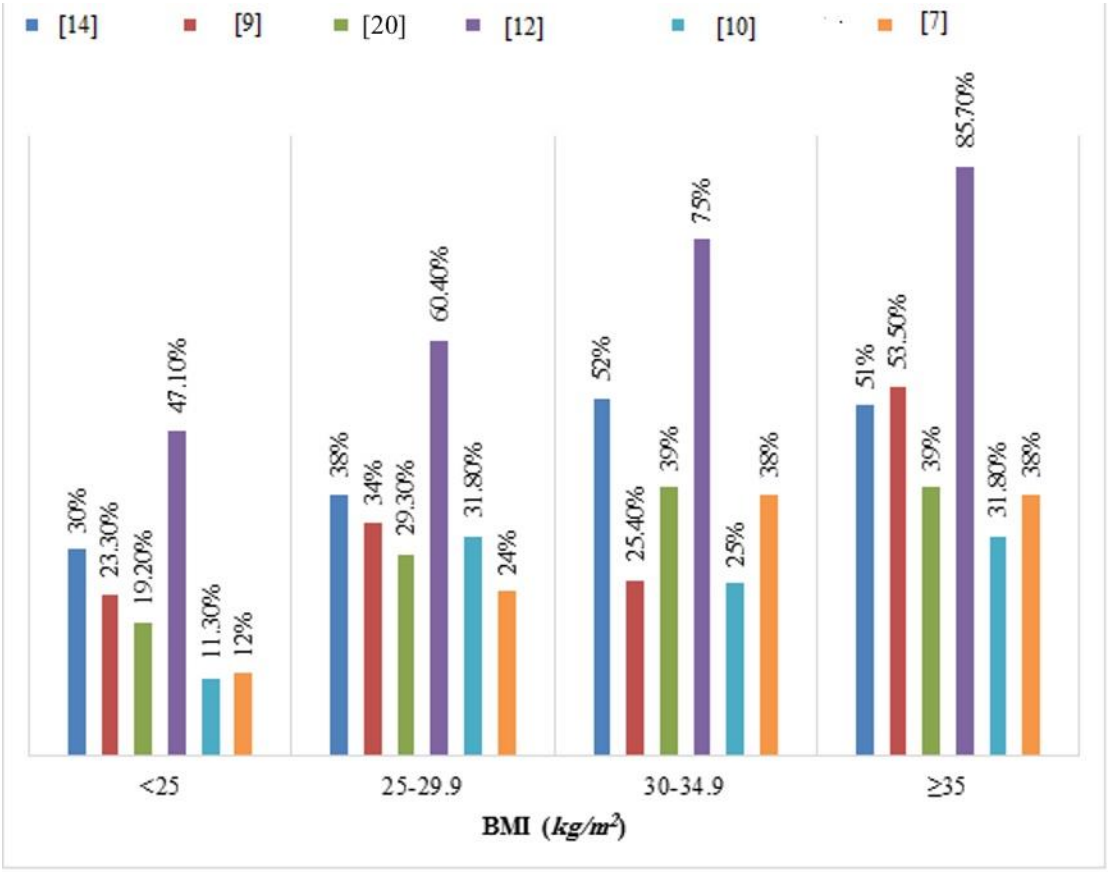
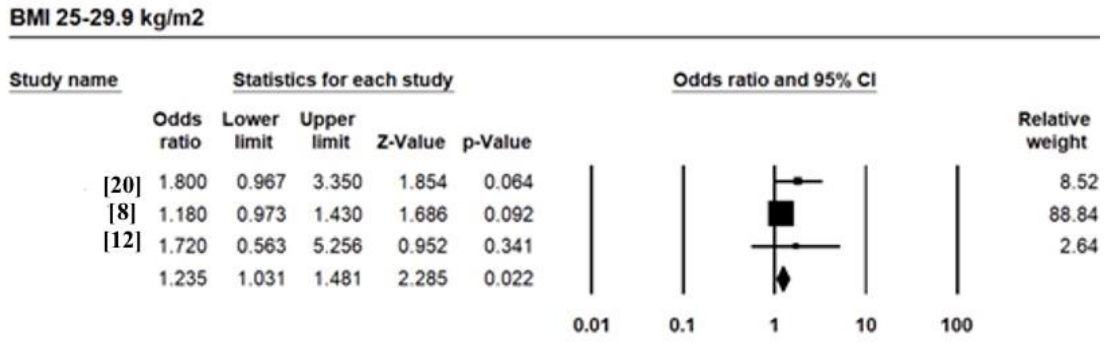


Figure 3: Percentage of severe COVID-19 cases based on BMI compared to non-severe cases

Odds ratios were included in 5 of the 9 studies, based on the following BMI brackets: 25-29.9 kg/m^2, 30-34.9 kg/m^2, and ≥35 kg/m^2. These findings are presented in the forest plots in Figure 4. Three studies that

provided odds ratios of patients with a BMI of 25-29.9 kg/m^2 showed an overall pooled odds ratio of 1.24 (random; 95% CI: 1.03-1.48) and a low heterogeneity (p = 0.374; I^2 =0.000). Five studies with odds ratios of patients with a BMI of 30-34.9 kg/m^2 had overall pooled odds ratio of 2.01 (random; 95% CI: 1.41-2.88) and a moderate heterogeneity (p = 0.041; I^2 = 59.942). Three studies that provided odds ratios of patients with a BMI of ≥ 35 kg/m^2 showed an overall pooled odds ratio of 2.16 (random; 95% CI: 1.61-2.89) and a moderate heterogeneity (p = 0.172; I^2 = 43.242). These results suggest a significant association between COVID-19 severity and obesity in all three groups of BMIs.

A



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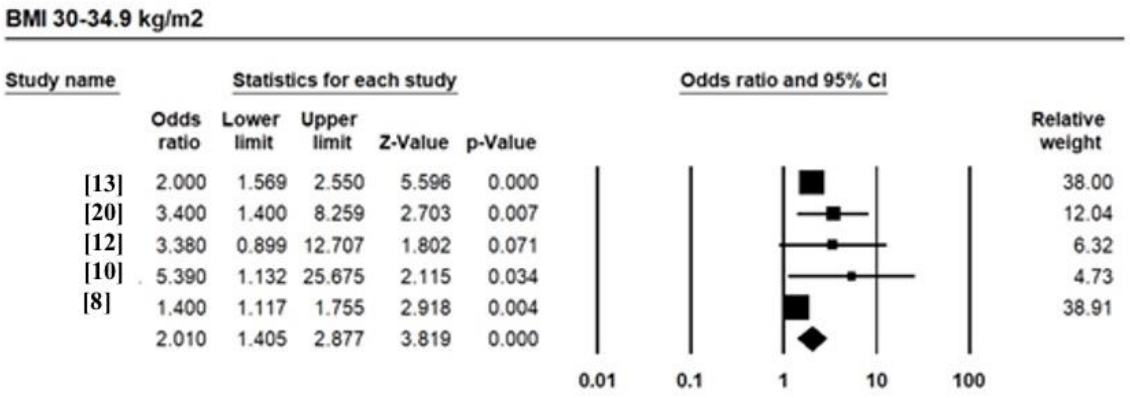

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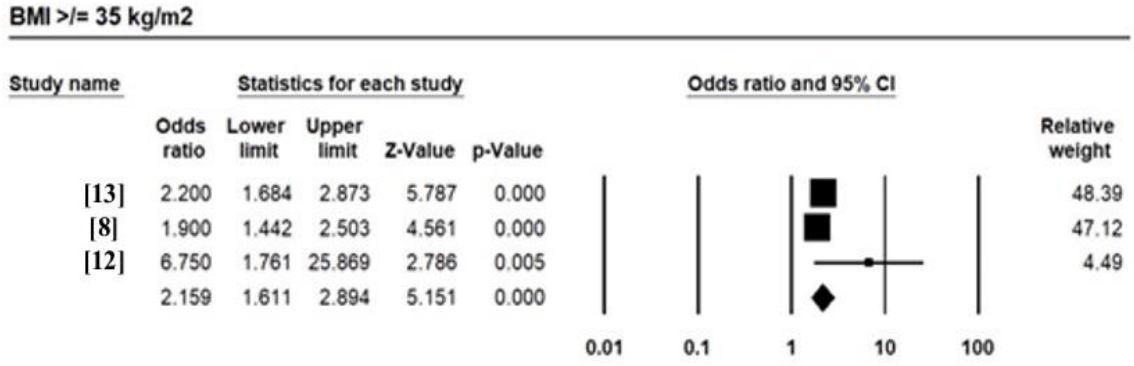

Figure 4: Forest plots of severe COVID-19 cases based on BMI of (A) 25-29.9 kg/m^2 (B) 30-34.9 kg/m^2 (C) ≥35 kg/m^2

Table 3: Significant association between patient BMI and severity of COVID-19

Study	Hazard ratio	Odds Ratio	Confidence Interval (95%)	p-value	Sample Size
Frank and colleagues	2.1	-	1.2-3.9	0.02	305
Simonnet and colleagues	-	7.36	1.63-33.14	0.01	124
Caussy and colleagues	-	1.69	1.10-2.56	0.017	1210
Lighter and colleagues	-	2	1.6-2.6	0.001	3615
Pettit and colleagues	-	1.7	1.1-2.8	0.016	238

Unfortunately, not all studies included in this paper provided p-values. Of the studies that did include p-values, 5 had significant results (Table 3). These studies found a significant association between patient BMI and severity of COVID-19.

4. Discussion

4.1 Primary outcome

In this meta-analysis consisting of 9 studies with a total of 340,811 patients, we determined that increasing BMI levels is associated with COVID-19 severity in which patients are either admitted to an ICU or placed on a ventilator. The severity pooled odds ratios after adjusting for heterogeneity for each BMI category includes BMI of 25-29.9 kg/m^2 1.24 (random; 95% CI: 1.03-1.48; p = 0.374; I^2 =0.000), BMI of 30-34.9 kg/m^2 2.01 (random; 95% CI: 1.41-2.88; p = 0.041; I^2 = 59.942), and BMI of ≥ 35 kg/m^2 2.16 (random; 95% CI: 1.61-2.89; p = 0.172; I^2 = 43.242); all of which are significantly high. The primary focus of this meta-analysis was to study the association of obesity with the severity of COVID-19 disease. We determined that as a patient's BMI increases, they are more likely to develop COVID-19 severity. Patients with BMI ≥25 kg/m^2 and COVID-19 are more likely to require ICU admission or a mechanical ventilator. Our current investigations corroborate with the findings of Sales-Peres and de Azevedo-Silva and colleagues [11]. Another study by Luzi and Radaelli [16], justified the relationship between BMI and COVID-19 severity. It has been suggested that three factors make obese individuals infected with COVID-19 more contagious than normal weight individuals: (a) obese individuals with influenza shed the virus for a longer period of time, possibly raising the ability to transmit the virus to others [17]; (b) due to the decreased and delayed capacity of obese individuals to produce interferons, the obese microenvironment favors the emergence of novel strains. The delay in the development of interferon to oppose viral replication in turn enables further replication of viral RNA, raising the likelihood of new, more virulent viral strains emerging [18]; and (c) the body mass index (BMI) correlates positively with severity in COVID-19 patients [19]. Table 2 and Figure 3 presents the intercorrelation between severity of COVID-19

cases and BMI. Recently, a retrospective study from Lille, France by Simmonet and colleagues demonstrated a spike in prevalence of severe COVID-19 cases with 47.10% (<25 kg/m^2), 60.40% (25-29.9 kg/m^2), 75% (30-34.9 kg/m^2), and 85.70% (≥35 kg/m^2)[12]. In all the studies on Table 2, a BMI ≥ 35 kg/m^2 has the greatest risk factor in disease severity. There is a 1.7-fold to 3.1-fold increase from normal-weight to BMI ≥ 35 kg/m^2 patients requiring ICU admission or invasive mechanical ventilation. The most drastic fold increases are seen in the studies from Kalligeros and colleagues and Nakeshbandi and colleagues being 2.8 and 3.1 respectively[7,10]. Similarly, Simmonet and colleagues study also has the greatest odds ratio and largest 95% confidence interval (see Table 3) with the odds ratio for severity in patients with BMI >35 kg/m^2 versus patients with BMI < 25 kg/m^2, being 7.36 (1.63-33.14; P = 0.02)[12]. A New York study by Lighter and colleagues also showed results that, patients with BMI between 30-34.9 kg/m^2 were two times more likely to be severe cases when compared to patients with BMI < 30 kg/m^2 (Figure 4C)[13]. Frank and colleagues retrospective cohort study in Massachusetts, USA assessed whether obesity is a strong independent risk factor of severity[14]. They compared COVID-19 patients of different BMIs and found obesity in the absence of other comorbidities, there is an increased risk of invasive mechanical ventilation, ICU admission or death. Obese patients were at higher risk of immune dysfunction and pneumonia. They found that excess body weight and poor pulmonary reserve seen in obesity causes impaired respiratory mechanics and restrictive lung physiology that may contribute to worsening of COVID-19.

4.2 Pathogenesis

The pathogenesis of increased COVID-19 severity in patients with obesity is still unknown. Obesity causes impairment of the adaptive immune response against influenza and other viruses. The influenza A H1N1 epidemic in 2009 had also resulted in increased severity and death in patients with obesity[12]. Excess free fatty acids seen in obesity induces lipo-toxicity which causes damage to many organs. Damage to the liver and pancreas leads to impairment of insulin receptors causing insulin resistance, hypertriglyceridemia, and progression to metabolic syndrome[7]. Obesity also induces a pro-inflammatory state by increasing the expression of cytokines (tumor necrosis factor alpha, monocyte chemoattractant protein-1, interleukin-6), C-reactive protein, and amyloid antigen. These cytokines cause hypertension by renin-angiotensin-aldosterone system activation, damage to vascular endothelium, atherosclerosis, and thrombosis[7]. There is also a decrease in anti-inflammatory adipokine (adiponectin) concentrations which causes dysregulation in immune response[9]. Pulmonary dysfunction is also seen in obesity such as a hypoxemia, ventilation/perfusion defects, and a decrease in functional residual capacity and expiratory reserve volume[10]. Adipose tissue expresses a high level of angiotensin-converting enzyme 2 (ACE2) which is a receptor that COVID-19 has a high affinity for[10].

4.3 Strengths

This is one of the few large meta-analysis exploring the specific influence obesity has on the severity of COVID-19. A major strength of this meta-analysis is that we included large racially and ethnically diverse studies from around the world. Multiple databases were searched and studies from the US, UK, France, and China were gathered. The study setting and author list of each article were carefully reviewed. We limited our search to English studies only and ensured to avoid any duplications. Each study has more than 100 patients

which strengthens the data on the obesity–COVID-19 association. While processing the results, we have adjusted for heterogeneity and other potential biases with the appropriate statistical tools.

4.4 Implications

The results of our meta-analysis have major clinical implications and contributions during the current COVID-19 pandemic. Our findings further establish that patients with obesity are at greater risk for severe disease in COVID-19. Given the high prevalence of obesity in the general population and that over two-thirds of Westernized society are overweight or obese, these findings can have a significant impact on the evaluation of patients and implications for policy[8]. Prevention of COVID-19 in obese patients is imperative as they are at risk for increased disease severity. Medical professionals should recognize that obesity is a risk factor in COVID-19 severity and adjust their prioritization for higher level care or drug resources accordingly. Obese patients should be advised to take prevention precautions such as hand hygiene and social distancing to protect themselves from COVID-19 contamination[12,15]. Out-patient clinics and hospitals should be hypervigilant of obesity for COVID-19 and lower the threshold for testing, extra monitoring and ICU admission for obese patients. Future COVID-19 reporting studies should include obesity as a comorbidity and further explore the mechanisms that cause increase disease severity. Streamlining prevention and treatment strategies is warranted for these patients.

4.5 Limitations

Our meta-analysis has a few limitations. Although we have established that obesity is associated with COVID-19 severity; we were unable to assess the effect that BMI has on mortality the rate of COVID-19 patients because of insufficient data. Further more, systemic literature searching should recognize studies that showed a relationship of increasing BMI with more likelihood of severe cases of COVID-19, but would also include studies that investigated the opposite effect (increasing BMI not affecting the likelihood of severe COVID-19 cases). Unfortunately, there is lack of research in this area. Once this gap in research is filled, a stronger, more balanced meta-analysis may be conducted. Additionally, some of the studies' 95% confidence intervals were relatively wide (Simonnet and colleagues Kalligeros and colleagues Cai and colleagues), which may be due to the small sample size. Also, in some of the studies the predominant population is minorities[7,9,20]. This may not be a true representation of the general population as obesity rates are higher in minorities such as African Americans. In order to determine if obese population are more susceptible to COVID-19 infection compared to the general population, further studying of true prevalence would be necessary.

5. Conclusion

In this study, we carry out a meta-analysis and systematic appraisal of nine articles with the aim of evaluating the validity of obesity as one of the main causes of increased severity of COVID-19. We found that higher BMI is a risk factor for progression to severe COVID-19.

6. Recommendation

The most obvious finding to emerge from this study established obesity as a factor in COVID-19 disease severity. Therefore, we recommend the following steps to mitigate an underlining condition such as Obesity that can increase a person's chances of having a severe illness from COVID-19 infection:

1. Ensuring easy access for obesity screening and awareness among early care and education settings
2. Feeding on a healthy diet (Good nutrition) can help support optimal immune functions.
3. Being active with regular physical activity for calorie reduction in weight loss

However, further study could assess the relationship between mortality rate and obesity among COVID-19 patient, another possible area of future research would be to investigate the relationship between severity of COVID-19 and obesity for critically ill patients requiring intensive care unit (ICU) care while a large number of randomized controlled trials could provide more definitive evidence.

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