REVIEW ARTICLE

Clinical Research

Obesity in COVID-19 era, implications for mechanisms, comorbidities, and prognosis: a review and meta-analysis

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Abstract

Background Recent studies have shown that obesity is associated with the severity of coronavirus disease (COVID-19). We reviewed clinical studies to clarify the obesity relationship with COVID-19 severity, comorbidities, and discussing possible mechanisms.

Materials and methods The electronic databases, including Web of Science, PubMed, Scopus, and Google Scholar, were searched and all studies conducted on COVID-19 and obesity were reviewed. All studies were independently screened by reviewers based on their titles and abstracts.

Results Forty relevant articles were selected, and their full texts were reviewed. Obesity affects the respiratory and immune systems through various mechanisms. Cytokine and adipokine secretion from adipose tissue leads to a pro-inflammatory state in obese patients, predisposing them to thrombosis, incoordination of innate and adaptive immune responses, inadequate antibody response, and cytokine storm. Obese patients had a longer virus shedding. Obesity is associated with other comorbidities such as hypertension, cardiovascular diseases, diabetes mellitus, and vitamin D deficiency. Hospitalization, intensive care unit admission, mechanical ventilation, and even mortality in obese patients were higher than normal-weight patients. Obesity could alter the direction of severe COVID-19 symptoms to younger individuals. Reduced physical activity, unhealthy eating habits and, more stress and fear experienced during the COVID-19 pandemic may result in more weight gain and obesity.

Conclusions Obesity should be considered as an independent risk factor for the severity of COVID-19. Paying more attention to preventing weight gain in obese patients with COVID-19 infection in early levels of disease is crucial during this pandemic.

Introduction

In December 2019, coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection has been emerged in Wuhan, China, and has spread rapidly and caused a global health crisis. By November 15, 2020, 53,766,728 confirmed

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cases of COVID-19, including 1,308,975 deaths, were reported to the World Health Organization [1] globally. COVID-19 manifestations include a spectrum of illnesses, ranging from asymptomatic infection [2] to severe pneumonia, adult/acute respiratory distress syndrome (ARDS), and even death [3]. This has caused medical researchers to identify risk factors related to the severity of COVID-19. Preexisting diseases such as hypertension (HTN), cardiovascular disease, diabetes, chronic respiratory disease, or cancer were identified as risk factors for developing severe COVID-19 [4–6]. However, recently, obesity was proposed as a significant independent risk factor for developing severe COVID-19 [7].

The obesity prevalence has recently increased in many developed and developing countries [8, 9], and has doubled in 73 countries since 1980 [10]. It is estimated that obesity prevalence is about 12% (603.7 million) among adults and 5% among children (107.7 million) worldwide [10]. This global increase in the prevalence of obesity shows the need for more assessment of this possible risk factor.

The effects of obesity on the respiratory system have been observed since long before. Avicenna [11], the famous Persian physician, recognized obesity as a medical disorder, and also in his book titled *Canon of Medicine*, referred to the respiratory problems of obese patients [12]. Also, the association between obesity and worse prognosis in the respiratory virus infections was observed in the "Spanish" influenza pandemic of 1918 [13]. Moreover, during the 2009 H1N1 pandemic, obesity was considered as an independent risk factor for severe disease or complications [14].

Surprisingly, level 1 evidence supports an obesity association with better prognosis in patients with ARDS [15]. However, previous studies have broken this paradox in COVID-19 patients [16–18]. These results and experiments with other viral respiratory infections reinforce the necessity of further research on this possible risk factor. Therefore, the aims of the present study were to: (1) review clinical studies in order to clarify the association between obesity and the severity of COVID-19, comorbidities and (2) discuss possible mechanisms.

Materials and methods

Search strategy and data collection

All studies conducted on COVID-19 and obesity were searched and reviewed. For this purpose, the electronic databases, including Web of Science, PubMed, Scopus, and Google Scholar, were searched. The search algorithm included all possible combinations of keywords from the following: "Severe acute respiratory syndrome coronavirus 2," "COVID-19," "2019-nCoV," "SARS-CoV-2," "coronavirus," "obesity," "weight," "obese," "body mass index,"

and "adipose tissue." Also, references of relevant review and editorial articles were reviewed to increase the coverage of included articles and ensure literature saturation.

All studies were independently screened by authors based on their titles and abstracts. The full texts of articles, potentially suitable for the review, were obtained to determine the relevance based on the study inclusion/exclusion criteria. The total of studies focusing on clinical characteristics and complications for SARS-CoV-2 was eligible for inclusion. The total of applicable studies (including case report, case series, and editorial, cross-sectional and cohort studies) was identified. We screened all reference lists of relevant studies in order to identify any missing publications. Studies that met the following criteria were included in the meta-analysis [1]: cohort studies; [2] body mass index (BMI) assessment $\geq 25 \, \text{kg/m}^2$ reported; [3] those indicating the odds ratio for the obesity risk [4]; age and gender were not kept as a bar for inclusion. The primary outcomes were the body weight, BMI, morbidities, and other outcomes. The data were extracted independently from the included studies by two authors based on a predefined data extraction sheet. The extracted data included (a) general information (author, type of study, and location), (b) participants (sample size, sex, and age), (c) outcomes (BMI, most common comorbidities, and mortality), and (d) main findings.

Any disagreements in the assessment of data were resolved by discussion between the two authors, and all potential discrepancies were resolved on consultation with a third reviewer. Forty relevant articles were selected, and their full texts were reviewed.

The meta-analysis was performed on outcomes with at least three studies conducted on their effects on obesity. All studies that evaluated the effect of the obesity on all outcomes, poor outcome, intensive care unit (ICU) admission, required IMV, and mortality were included in the meta-analysis. We used STATA Direct 3.1.22 to perform meta-analysis. A p value $\leq$ 0.05 was considered statistically significant. ORs were reported for the effect estimate, along with its 95% confidence intervals (CIs). Adjusted ORs (aORs) were pooled for meta-analysis of obesity and poor outcome, ICU admission, IMV, and mortality. Random-effects model was used for the data analysis, regardless of heterogeneity. The degree of heterogeneity was quantified using I^2 statistics. I^2 values of 25%, 50%, and 75% were considered to correspond to low, medium, and high levels of heterogeneity, respectively.

Results

Description of the included studies

After searching PubMed, Scopus, Web of Science, and Google Scholar databases, all relevant studies were

identified. Finally, 55 articles were included in the study, and the full texts of the articles were reviewed. The characteristics of the included clinical trials and reasons behind the exclusion are summarized in Table 1.

All cohort, cross-sectional, descriptive, and retrospective studies were included in the study. Most countries that have conducted the studies on COVID-19 and obesity are China, the United States, Italy, UK, and France.

Obesity and COVID-19 severity and outcomes

We learned from the H1N1 Influenza epidemic that obesity is associated with more hospitalization, comorbidities, mechanical ventilation, and death [19, 20]. An increasing body of evidence shows that obesity influences severity and outcomes of COVID-19 (Table 1). A recent report released by the Intensive Care National Audit & Research Centre has shown that 39.3% of 9949 critically ill COVID-19 patients were obese, higher than the prevalence of 31.8% in the British age- and sex-matched general population. Also, the hazard ratio in survival analysis increased slightly above 1, when BMI rose above 30 kg/m^2 [21].

Other studies also had similar results. A study conducted on 4103 COVID-19 patients in New York considered BMI > 40 kg/m^2 as the most significant predictor of hospitalization after age [16]. Moreover, a study performed on 383 patients in China showed that obese patients had a 2.42-fold increased risk of severe pneumonia compared to normal-weight patients, even after adjusting for potential confounders [22]. Furthermore, Hajifathalian et al. [23] in a study conducted on 770 COVID-19 patients in New York found that patients with obesity were more likely to present overt symptoms and have twofold increased risk of ICU admission or death compared to normal-weight patients. Also, one study from China established that 88.24% of COVID-19 non-survivors had a BMI > 25 kg/m^2 [24].

Mechanical ventilation, in addition to ICU admission, is considered as one of the most important indicators of severe disease. A small study in Seattle showed that 85% of obese patients need the mechanical ventilation [25]. Other studies confirmed the higher need for mechanical ventilation in obese patients. A study of 124 COVID-19 patients admitted in the ICU in a university hospital in Lille, France, reported a 7.36-fold need for intubation in patients with BMI > 35 (85.7% of them) compared to those with BMI < 25 kg/m^2, independent of other comorbidities. Obesity (BMI ≥ 30) and severe obesity (BMI ≥ 35) were found in 47.6% and 28.2% of cases [17]. However, the results of another study in Lyon, France, were different. This study reported a lower prevalence of obesity and mechanical ventilation as compared to the Lille study. These differences may occur due to lower obesity prevalence in the Lyon area and different treatment protocols. However, the mechanical ventilation requirement was higher in obese

patients (BMI ≥ 35 kg/m^2) compared to lean patients (81.8 vs. 41.9%) [26]. Also, another study on 92 patients with COVID-19-associated pneumonia in Italy demonstrated that obesity is linked to a higher requirement of assisted ventilation (mechanical or noninvasive ventilation) and ICU admission, as two important indicators of disease severity, after adjusting for other variables. This study reported intensive or semi-intensive respiratory unit admission and mortality in 41.3 and 47.4% of obese patients. However, in this study, obese patients did not show significantly higher mortality rates [27].

Obesity and COVID-19 severity in age groups

Obesity could lead to severe COVID-19 both in young and old patients, but obesity in elderly individuals may be accompanied by more comorbidities, for example, obesity is associated with type-2 diabetes mellitus (T2DM) that is seen frequently in those aged 65 years [28]. Relative fat mass increases and muscle mass decreases in older individuals, even in nonobese ones, especially in patients with respiratory and cardiac diseases [29]. It was furthermore shown that risk of ICU admission in obese patients is higher than that in lean individuals across all age groups [23].

However, a study in New York showed that younger people with COVID-19 admitted to the ICU were obese [30]. Similarly, another study in New York demonstrated that people with a BMI between 30 and 34 kg/m^2 and >35 kg/m^2 were 1.8 and 3.6 times more likely to be admitted to the ICU, respectively. [18]. Moreover, in an Italian study, obese patients were ~9 years younger than normal-weight patients and needed more assisted ventilation and intensive or semi-intensive care [27]. It is essential to note that obesity may increase the chance of severe COVID-19 disease in younger individuals, especially in populations with high obesity prevalence.

Virus shedding in obese patients

Adipose tissue, as a viral reservoir, could make the virus shedding longer in obese patients. This pattern was also seen in influenza infection. More specifically this disease in obese patients was more contagious due to more prolonged shedding of virus [31], a lower interferon level [32], and a positive relationship of obesity with the virus load in exhaled air [33]. Viral shedding is also prolonged in obese patients due to impaired immune response, particularly reduced macrophage activation and impaired B- and T-cell responses [34].

Challenges in diagnosis and managing of obese patients

Many countries face a heavy burden of the COVID-19 pandemic on the health care system. Obesity and the heavy

Table 1 Obesity and COVID-19 outcomes.

First author	Country	Type of study	Sample size (n)	Obesity prevalence		Sex	Age (years)	BMI (kg/m²)	Disease severity (total); n (%)		Comorbidities; n (%)	Note
				Obese patients	Control (nonobese)				ICU admission	Mortality		
McMichael et al. [90]	USA	Retrospective study	167 In-patients (n = 101) Health care personnel (n = 50) Visitors (n = 16)	37 (22.2%) BMI ≥ 30	70 (42.4%)	F: 112 (67.1) M: 55 (32.9)	Median: 72 Range: (21–100)	–	–	35 (21.0)	HTN: 74 (44.3) Cardiac diseases: 68 (40.7) Renal: 43 (25.7) DM: 38 (22.8) Pulmonary Diseases: 36 (21.6) Cancer: 15 (9.0) Liver: 6 (3.6)	Hospitalized (total): 66 (39.5)
Lighter et al. [18]	USA	Editorial	3615	Obesity: 775 (21%) Severe obesity: 595 (16%) <60 years, 30 < BMI < 34: OR, 2.0 (1.6–2.6) to acute care and OR, 1.8 (1.2–2.7, p = 0.006) to critical care compared to BMI < 30 BMI > 35: OR, 2.2 (1.7–2.9) and OR, 3.6 (2.5–5.3) to acute and critical care compared to BMI < 30	–	–	>18	–	431 (12%)	–	–	–
Liu et al. [91]	China	Retrospective study	30	Obesity: 27 ± 2.5	22 ± 1.3	F: 20	35 ± 8 (66.7) M: 10 (33.3)	–	–	–	–	Patients including 22 doctors and 8 nurses and 26 common type and 4 severe type.
Liu et al. [92]	China	Retrospective study	64	BMI ≥ 24 (12.0%) (HR 0.14; 95% CI 0.03–0.73)	–	F: 64.0% M: 36.0%	Median: 35 (IQR, 29–43)	21.4 (19.9–23.0)	–	–	HTN: 3 (5%) DM: 1 (2%) Depressive disorders: 1 (2%) Thyroid nodules: 1 (2%)	Patients including 67% nurses. No patients was transferred to ICU or died, and 34 (53%) had been discharged
Yang et al. [93]	China	Retrospective cohort study	149	23.7 ± 4.5/ overweight*	–	F: 68 (45.6%) M: 81 (54.4%)	45.11 ± 13	23.75 ± 4.54	–	–	CVD: 28 (18.79%) Digestive system diseases: 8 (5.37%) Endocrine diseases: 9 (6.04%) Malignant tumor: 2 (1.34%) Respiratory system diseases: 1 (0.67%)	No medical staff were patients in this cohort
Richardson et al. [94]	USA	Case series	5700	n = 1737 (41.7%) BMI ≥ 30	4170 (42.4)	Female: 2263 (39.7) Male: 3437 (60.3)	63 (IQR, 52–75)	–	373 (14.2%)	553 (21%)	HTN: 3026 (56.6) DM: 1808 (33.8) Cancer: 320 (6) CAD: 595 (11.1) HF: 371 (6.9) Asthma: 479 (9) COPD: 287 (5.4) Obstructive sleep apnea: 154 (2.9) HIV: 43 (0.8) Renal diseases: 454 (8.5) Liver disease: 30 (0.6)	Oxygen saturation < 90%: 1162 (20.4) and median (IQR): 95 (91–97) 2634 (discharged or died) Invasive mechanical ventilation (total): 320 (12.2%)
Peng et al. [95]	China	Retrospective study	112 (general group: 96 and ICU = 16)	Critical group: 25.5 (23.0, 27.5) General group: 22.0 (20.0, 24.0) Obesity in non-survivor group: 88.24% and in survivor group: 18.95%	–	F: 52.7% M: 47.3%	Median: 62.0 (IQR, 55.0–67.0)	Median: 22.0 IQR 20.0–25.0	16 (14.28%)	17 (15.17%)	DM: 23 (20.54%) HTN: 92 (82.14%) CAD: 62 (55.36% HF: 40 (35.71%)	General group: n = 96. The BMI of the critical group was significantly higher than that of the general group. Among the non-survivors, there were 88.24% (15/17) patients with BMI > 25

Table 1 (continued)

First author	Country	Type of study	Sample size (n)	Obesity prevalence		Sex	Age (years)	BMI (kg/m²)	Disease severity (total); n (%)		Comorbidities; n (%)	Note
				Obese patients	Control (nonobese)				ICU admission	Mortality		
Huang et al. [96]	China	Descriptive study	60 (severe cases)	Improvement (n = 52): 25.2±3.4, Deterioration (n = 8): 23.7±2.5	–	F: 25 (41.7%) M: 35 (58.3%)	Median: 57 (range 26–97) (proportion of patients >50 y: 63.3%)	25.0 ± 3.3	–	–	HTN: 14 (23.3) DM: 10 (16.7) Autoimmune disease: 4 (6.7) Stroke: 4 (6.7) CVD: 3 (5.0) Chronic obstructive pulmonary disease: 2 (3.3) Chronic kidney diseases: 1 (1.7)	Mortality rate of these severe cases: 0%
Cai et al. [97]	China	Retrospective study	298	Non-severe: 22.9 (20.6–25.2) Severe: 24.5 (22.0–27.8) BMI (OR 1.17, 95% CI 1.03–1.34)	–	F: 149 (50%) M: 149 (50%)	Median: 47 (IQR, 33–61)	Median: 23.2 (IQR, 21.1–25.6)	–	3 (1%)	HTN: 47 (15.8%) DM: 18 (6.04%) CVD: 25 (8.39%) Liver diseases: 28 (9.4%) Cancer: 41.3%)	Severe patients than non-severe patients (80.5 vs.19.5%)
Xu et al. [98]	China	Retrospective study	45	Intubation: 23.2 (21.4–25.3) Non-intubation: 25.2 (22.9–26.9)	–	F: 16 (35.6%) M: 29 (64.4%)	56.7 ± 15.4	24.2 (22.0–26.7)	–	1 (2.2%)	HTN: 21 (46.7%) DM: 13 (28.9%) CCD: 6 (13.3%) Chronic pulmonary disease: 4 (8.9%) Cancers: 3 (6.7%)	PaCO2, mm Hg: 38.3 (35.5–41.5) Median time from ICU admission: 10 (IQR, 8–13) days Discharged from ICU: 23 (51.1%) Recovered and discharged from hospital: 11 (24.4%)
Simonnet et al. [17]	France	Retrospective cohort study	124	BMI >30 kg/m²: 47.6% BMI >35 kg/m²: 28.2% Median: 29.6 (IQR, 26.4–36.5) OR 25–30 kg/m²:1.69 (0.52–5.48) OR 30–35 kg/m²: 3.45 (0.83–14.31) OR ≥35 kg/m²: 7.36 (1.63–33.14)	BMI >30 kg/m²: 25.2% BMI >35 kg/m²: 10.8% Median: 24.0 (IQR, 18.9–29.3)	F: 34 (27.0%) M: 90 (73.0%)	Median: 60 (IQR, 51–70)	Median: 29.6 (IQR, 26.4–36.4)	46 (37%)	18 (15%)	HTN: 60 (49%) DM: 28 (23%) Dyslipidemia: 34 (28%)	Discharged from ICU: 60 (48%)
McMichael et al. [99]	USA	–	129	Total obesity: 30 (23.3%)	–	F: 84 (65.1%) M: 45 (34.9%)	Median: 71 (IQR, 22–100)	–	–	23 (17.8%)	HTN: 58 (45.0%) Cardiac disease: 51 (39.5%) Renal disease: 36 (27.9%) Pulmonary disease: 30 (23.3) Cancers: 11 (8.5%) Liver disease: 5 (3.9%)	Hospitalized: 53 (41.1%)
Liao et al. [100]	China	Retrospective study	46 young adults (n = 32), adolescents (n = 14)	Underweight: 4 (8.7%) Normal BMI: 24 (52.2%) Overweight/obesity: 17 (37.0%)	–	F: 22 (47.3%) M: 24 (52.7%)	Range: 10–35	–	–	–	DM: 1 Chronic lung disease: 1 Hyperthyroidism: 1 Kidney stones: 1	Hospital admission: 10 (21.7%) Discharged: 36 (78.3%)
Goyal et al. [101]	USA	Retrospective study	393	BMI >30: 136 (35.8%)	168 (42.8%)	F: 155 (39.4%) M: 238 (60.6%)	Median: 62.2 (IQR, 48.6–73.7)	–	–	40 (10.2%)	HTN: 197 (50%) DM: 99 (25.2%) CAD: 54 (13.7%) Chronic obstructive pulmonary disease: 20 (5.1%)	Discharge: 260 (66.2%)
Cai et al. [22]	China	Retrospective study	383	Underweight: 16 (4.2%) Overweight: 123 (32%) Obese: 41 (10.7%)	17.8 Normal weight: 203 (53.1%)	F: 209 (52%) M: 184 (48%)	Median: 48 (IQR, 39–54)	–	–	–	HTN: 58 (15%) DM: 22 (5.7%) CVD: 35 (9.1%) Liver disease: 38 (9.9%) Cancers: 5 (1.3%)	n = 383, critically and not critically ill

Table 1 (continued)

First author	Country	Type of study	Sample size (n)	Obesity prevalence		Sex	Age (years)	BMI (kg/m²)	Disease severity (total); n (%)		Comorbidities; n (%)	Note
				Obese patients	Control (nonobese)				ICU admission	Mortality		
Bhatraju et al. [102]	USA	–	24	33.2 ± 7.2 kg/m²	–	F: 9 (37%) M: 15 (63%)	64 ± 18	–	–	12 (50%)	DM: 14 (58%) Kidney disease: 5 (21%) Asthma: 3 (14%) Hemorrhagic or ischemic stroke: 2 (8%)	Extubated: 6/ 18 (33%) Discharged: 5 (21%)
Wu et al. [103]	China	Retrospective study	280	Mild-moderate: 23.6 ± 3.2 Severe: 25.8 ± 1.8 BMI: 1.30 (1.09–1.54)	–	F:129 M: 151	43.12 ± 19.02	24.1 ± 3.0	–	0 (0.0%)	DM: 34 (12.14%) CVD: 57 (20.36%) Respiratory diseases: 6 (2.14%) Chronic liver disease: 7 (2.50%) Cancer: 5 (1.79%) Chronic kidney disease: 3 (1.07%)	PaO2: 84 (64–98) Remained in hospital: 59 (21.07%) Discharged: 221 (78.93%)
Khorrami et al. [104]	Iran	–	31,050	Death: IRR: 2.75 (1.49–5.10) Hospitalization: IRR: 1.58 (0.91, 2.77)	–		>18	–	–	–	HTN: IRR: 1.88 (1.03, 3.44)	–
Yu et al. [105]	China	Cross-sectional	95 (73 with pneumonia)	23.71 ± 3.41 with pneumonia 20.78 ± 3.15 without pneumonia	–	F: 42 (44.2%) M: 53 (55.8%)	42.66 ± 17.93 with pneumonia 23.86 ± 13.8 without pneumonia	–	–	–	–	BMI: OR: 1.327 (1.03–1.69) independent risk factor for pneumonia
Yu et al. [105]	China	Cross-sectional	95 (24 with ARDS)	24.26 ± 3.32 with ARDS 22.64 ± 3.55 without ARDS	–	F: 42 (44.2%) M: 53 (55.8%)	45.92 ± 18.44 with ARDS 35.73 ± 13.32 without ARDS	–	–	–	–	–
Bruno et al. [106]	Italy	Descriptive study	31	BMI ≥ 30: 11 (35.4%)	–	F: 12 (38.7%) M: 19 (61.3%)	≥65 median: 74	–	8 (25.8%)	6 (19.35%)	HTN: 27 (87.1%) CVD: 5 (16.1%) Kidney disease: 3 (9.6%) Respiratory disease: 5 (16.1%) Neurological disease: 6 (19.3%) DM: 4 (12.9%) Cancers: 2 (6.4%)	SpO2 (%): 92 (91–94) Duration of hospital stay: 23 (16–30)
Wei et al. [107]	China	Descriptive study	167	Total: 24.52 ± 3.41 Non-severe (n = 137): 24.22 ± 2.19 Severe: (n =30): 24.55 ± 3.19	–	F: 72 (43.1%) M: 95 (56.9%)	42.31 ± 15.29	24.52 ± 3.41	–	–	CVD: 24 (14.37%) DM: 11 (6.59%) Digestive diseases: 9 (5.39%) Respiratory diseases: 4 (2.4%)	Length of stay in hospital: median 15.00 (IQR, 12.00, 20.00)
Chao et al. [108]	USA	Retrospective study	46	14 (30.4%)	–	F: 15 (32.6%) M: 31 (67.4%)	Median: 13.1 (IQR, 0.4–19.3)	Median: 22.8 (IQR, 17.6–32.9)	13 (28.3%)	1 (7.14%)	Asthma: 11 (24.4%)	–
Chen et al. [109]	China	Retrospective study	145	BMI (severe patients): 24.78 (23.07–26.96) BMI (non-severely patients): 23.20 (21.66–25.71)	–	F: 66 (45.5%) M: 79 (54.5%)	47.5 ± 14.6	–	1 (0.69%)	–	HTN: 22 (15.2%) DM: 14 (9.7%) COPD: 6 (4.13%) Chronic liver disease: 6 (4.13%) Chronic kidney disease: 3 (2.06)	Severe cases: 43
Dreher et al. [110]	Germany	–	50	25 < BMI < 30: 14 (28%) BMI ≥ 30 kg/m²: 17 (34%) BMI ARDS patients: median 29 (IQR, 27–32) BMI Non-ARDS patients: median 27 (IQR, 24–30)	–	F: 17 (34%) M: 33 (66%)	Median: 65 (IQR, 58–76)	Median: 29 (IQR, 25–31)	–	7 (14%)	HTN: 13 (70%) DM: 29 (58%) Respiratory disease: 25 (50%) Chronic kidney disease: 10 (20%) Cancers: 7 (14%)	Hospitalization: median: 4 (IQR, 1–8) ICU: median 9 (IQR, 4–12) Discharged: 8 (16%) Continued hospitalization: 35 (70%) Oxygen saturation (%): 95 (90–97)

Table 1 (continued)

First author	Country	Type of study	Sample size (n)	Obesity prevalence — Obese patients	Obesity prevalence — Control (nonobese)	Sex	Age (years)	BMI (kg/m²)	Disease severity — ICU admission	Disease severity — Mortality	Comorbidities; n (%)	Note
Palaiodimos et al. [111]	USA	Retrospective study	200	Mortality: BMI ≥ 35, 3.78 (1.45–9.83) Oxygen requirements: BMI ≥ 35, 3.09 (1.43–6.69) Incubation: BMI ≥ 35, 3.87 (1.47–10.18)	Mortality: BMI <25, OR, 1.37 (0.52–3.64) Oxygen requirements: BMI <25: OR, 0.95 (0.43–2.11) Incubation: BMI <25: OR, 0.76 (0.26–2.22)	F: 102 (51%) M: 98 (49%)	Median: 64 (IQR, 50–73.5)	Median: 30 (IQR, 26–35)	–	48 (24%)	HTN: 152 (76%) DM: 79 (39.5%) Hyperlipidemia: 92 (46.2%) Chronic renal disease: 58 (29%) CAD: 33 (16.5%) COPD: 28 (14.0%)	BMI < 25 (n = 38): 12 (31.6) 25 < BMI < 34 (n = 116): 20 (17.2%) BMI ≥ 35 (n = 46): 14 (34.8%) ↑ O2 requirement: 90 (45%)
de Lusignan et al. [112]	UK	Cross-sectional	3802 (negative: 3215 (84.6%), positive: 587 (15.4%))	SARS-CoV-2 Positivity: overweight: 198/ 1095 (18.1%), OR: 1.26 (0.99–1.61) Obese: 142/680 (20.9%), OR 1.41 (1.04–1.91) Severely obese: 26/ 145 (17.9%), OR: 1.28 (0.78–2.10)	SARS-CoV-2 positivity: normal weight: 171/1296 (13.2%)	Total: F: 2190 (57.6%) M: 1612 (42.4%) SARS-CoV-2 positivity F: 291/2190 (13.3%) M: 296/1612 (18.4%)	Median: 58·0 (IQR, 34–73) for men and 51.5 (IQR, 33–70) for women	–	–	–	HTN: 1094 (28.8%) CAD: 600 (15.8%) DM: 503 (13.2%) Chronic respiratory disease: 258 (6.8%) Chronic kidney disease: 207 (5.4%)	–
Yu et al. [113]	China	Descriptive study	333	Overweight: 146 (46.3%) Non-pneumonia/ mild pneumonia: 131 (45.2%) Severe/critical pneumonia: 15 (60.0%)	Normal weight: 150 (47.6%) Non-pneumonia/ mild pneumonia: 141 (48.6%) Severe/critical pneumonia: 9 (36.0%)	F: 161 (48.3%) M: 172 (51.7%)	Median: 50 (IQR, 35–63)	–	–	2 (0.06%)	HTN: 64 (19.2%) DM: 28 (8.4%) Heart disease: 24 (7.2%) Respiratory disease: 5 (1.5%)	Incubation period: median, 7.8 (IQR, 5.0–8.2 days)
Kalligeros et al. [114]	USA	Retrospective cohort study	103	Hospitalized patients: 49 (47.5%) ICU admission: 25 (56.8%) Required IMV: 65.5% Severe obesity (BMI ≥ 35 kg/m²) and ICU admission: aOR 5.39 (1.13–25.64) Required IMV and obesity: aOR6.85 (1.05–44.82) Required IMV and severe obesity: aOR 9.99 (1.39–71.69)	–	F: 40 (38.83%) M: 63 (61.17%)	Median: 60 (IQR, 52–70)	–	41 (39.8%)	–	HTN: 66 (64%) DM: 38 (36.8%) Heart disease: 25 (24.2%) Lung disease: 20 (19.4%) Chronic renal: 11 (10.6%) Cancer: 9 (8.7%)	Required (IMV): 29 (70.7%)
Petrilli et al. [16]	USA	Cross-sectional	4103	BMI >30: 1100 (26.8%) BMI >40: OR, 6.2 (4.2–9.3), 25<BMI <35: 50% BMI>35: 25%	BMI <30: 3003 (73.2%)	F: 2031 (49.5 %) M: 2072 (50.5 %)	Median: 52 (IQR, 36–65)	–	–	292/1999 (14.6%)	CVD: 1235 (30.1%) HTN: 938 (24%) Hyperlipidemia: 738 (18%) DM: 614 (15%) Chronic kidney disease: 215 (5.2%) Cancers: 185 (4.5%)	Hospitalized: 1999 (48.7%) Discharged: 981/ 1999 (49.1%)
Kass et al. [30]	USA	Cross-sectional	265		BMI <25: 25%	F: 111 (42%) M: 154 (58%)	–	Median: 29·3 with	–	–	–	–
Zheng, K.I. [115]	China	Cross-sectional	66 (45 obese and 21 non-obese)	Obesity and COVID-19 severity: OR: 6.32 (1.16–34.54)	–	F: 17 (25.8%) M: 49 (74.2%)	47	26.5±3.9	–	–	Dyslipidemia: 45 (68.2%) HTN: 19 (28.8%) DM: 16 (24.2%)	Non-severe: 47 (71.2%) Severe: 19 (28.8%) Severe patients more obese: 89.5 vs. 59.6%

Table 1 (continued)

First author	Country	Type of study	Sample size (n)	Obesity prevalence		Sex	Age (years)	BMI (kg/m²)	Disease severity (total); n (%)		Comorbidities; n (%)	Note
				Obese patients	Control (nonobese)				ICU admission	Mortality		
Palmieri et al. [116]	Italy	Retrospective study	3032 death (368 aged < 65 years and 2664 aged ≥ 65 years)	BMI > 30: 335 (11.0%) (<65: 108 (29.3%), ≥65: 227 (8.5%))	–	F: 1013 (33.4%) M: 2019 (66.6%)	–	–	–	–	HTN: 2071 (68.3%) DM2: 914 (30.1%) HF: 490 (16.2%) IHD: 856 (28.2%) COPD: 498 (15.8%) Stroke: 310 (10.2%) Cancer: 480 (15.4%)	Prevalence of obesity was more in younger adults (<65 years)
Argenziano et al. [117]	USA	Cohort study	1000	BMI > 30: 352/841 (48.3%)	–	F: 404 (40.4%) M: 596 (59.6%)	Median: 63 (IQR, 50–75)	Median: 28.6 (IQR, 25.2–31.1)	236 (23.6%)	211 (21.1%)	HTN: 601 (60.1%) DM: 372 (37.2%) CAD: 131 (13.1%) Pulmonary disease: 223 (22.3%) Renal disease: 137 (13.7%) Cancer: 67 (6.7%)	–
Caussy et al. [118]	France	Cross-sectional study	340	BMI > 30: 85 (25%) OR: 1.35 (CI: 1.08–1.66) in patients with severe COVID-19 and OR: 1.89 (CI: 1.33–2.53) in ICU than in the general French population	–	–	–	–	–	–	–	–
Zachariah et al. [119]	USA	Retrospective study	50	BMI > 30: 11 (22%)	–	F: 23 (46%) M: 27 (54%)	Median in non-severe: 9 Median in severe: 14	–	–	1 (2%)	Asthma: 6 (12%) Cardiac disease: 4 (8%) DM: 3 (6%)	–
Bello-Chavolla et al. [120]	Mexico	Retrospective study	Positive: 51,633 Negative: 98,567	Positive: 10708 (20.7%) HR: 1.25 (CI: 1.17–1.34)	Negative: 14,011 (14.2%)	F: 21,830 (42.3%) M: 29,803 (57.7%)	Positive: 46.65 ± 15.83 Negative: 40.25 ± 17.33	–	1893 (3.7%)	5332 (10.3%)	Pneumonia: 14,919 (28.9%) HTN: 11,151 (21.6%) DM: 9460 (18.3%) COPD: 1131 (2.2%)	Hospitalization: 19,831 (38.4%)
Yates et al. [121]	UK	Retrospective study	882	Overweight: 1.31 (CI: 1.05–1.62) Obesity: 1.55 (CI: 1.19–2.02) Severe obesity: 1.57 (CI: 1.14–2.17)	–	–	Median: 71 (IQR, 61–76)	Median: 27.6 (IQR, 24.7–31.1)	–	–	–	–
Hajifathalian et al. [23]	USA	Retrospective study	770	Obesity (BMI > 30) in ICU admission: 92 (33%), intubation: 91 (33%), death: 22 (8%) RR: 1.58 (CI: 1.18–2.13) ICU admission: 1.76 (CI: 1.24–2.48) Intubation: 1.72 (CI: 1.22–2.44)	–	F: 302 (39.2%) M: 468 (60.8%)	Mean: 64 ± 16.7	Mean: 29 ± 7.9	–	–	HTN: 432 (56.1%) DM: 238 (30.9%) CVD: 162 (21.0%) COPD: 98 (12.7%)	–
Busetto et al. [27]	Italy	Cross-sectional	92	Overweight: 31 (33.7%) Obesity: 29 (31.5%) BMI ≥ 25 kg/m²: ICU admission, OR: 12.46 (CI: 3.48–44.54)	Normal weight: 32 (34.8%)	F: 35 (38.1%) M: 57 (61.9%)	Mean: 70.5 ± 13.3	Mean: 27.2 ± 4.6	16 (17.4%)	12 (13.0%)	HTN: 59 (64.1%) CVD: 29 (31.5%) DM: 28 (30.4%) Respiratory chronic disease: 12 (13.0%) Cancer: 12 (13.0%)	–
Buckner et al. [122]	USA	Retrospective study	105	Obesity (BMI > 30): 44/93% (47) Severe: 23/43% (53)	–	–	–	–	–	35 (33%)	Hypertension (59%) Cardiovascular disease (38%) Diabetes (33%)	–

Table 1 (continued)

First author	Country	Type of study	Sample size (n)	Obesity prevalence — Obese patients	Obesity prevalence — Control (nonobese)	Sex	Age (years)	BMI (kg/m²)	Disease severity (total); n (%) — ICU admission	Disease severity (total); n (%) — Mortality	Comorbidities; n (%)	Note
Caussy et al. [26]	France	Retrospective study	291	Overweight (25–30): 121 Obese (>30): 96	Normal (<25): 74	–	–	–	–	–	–	All of cases were in ICU. The requirement for IMV (58.4%; n = 170) A higher requirement for IMV in severe obesity (BMI ≥ 35) compared with lean patients (81.8% vs. 41.9%)
Docherty et al. [123]	UK	Prospective observational cohort study	20,133	Obesity HR: 1.33 CI: (1.19–1.49)	–	M: 60%, n = 12,068; F: 40%, n = 8065	Median: 73 (IQR, 58–82, range, 0–104)	–	17% (3001/18,183)	26% (5165/20,133)	Chronic cardiac disease (31%, 5469/17,702), uncomplicated diabetes (21%, 3650/17,599), non-asthmatic chronic pulmonary disease (18%, 3128/17,634), chronic kidney disease (16%, 2830/17,506)	–
Giacomelli et al. [124]	Italy	Prospective cohort study	233	Obesity: 38 (16.3%) aHR 3.04 (95 % CI 1.42 – 6.49)	–	M: 161 (69.1%) F: 72 (30.9%)	Median: 61 years (IQR 50–72)	–	–	48 (20.6 %)	–	–
Hu et al. [125]	China	Retrospective study	323	BMI <25: 229/ 323 (70.9) BMI 25–30: 52/ 323 (16.1) BMI ≥ 30: 13/ 323 (4)	–	M: 166/ 323 (51.4 F: 157/ 323 (48.6)	Median: (range) 61 (23–91)	–	–	–	Hypertension: 105/323 (32.5%) Diabetes: 47/323 (14.6%) Cerebrovascular disease: 7/ 323 (2.2)	Patients with diabetes and body mass index (BMI) of ≥30 were more likely to have unfavorable outcomes
Hur et al. [126]	USA	Retrospective observational study	486	BMI <30: 227 (46.7%) BMI 30–39.9: 187 (38.5%) BMI ≥40: 72 (14.8%)	–	M: 271 (55.8%) F: 215 (44.2%)	Median: 59 (IQR 47–69)	Median: 30.6 (IQR, 26.5–35.6)	–	21 (15.2%)	HTN: 267 (54.9%) DM: 160 (32.9%) CVD: 111 (22.8%) Pulmonary disease: 78 (16.0%) Cancer: 60 (12.3%) Obstructive sleep apnea: 46 (9.6%) Immunosuppressed state: 45 (9.5%) Chronic kidney disease: 42 (8.6%) Organ transplant: 13 (2.7%)	Intubated patients had a significantly higher median age (65 vs. 57 years, P <.001) and rate of diabetes (56 [40.6%] vs. 104 [29.9%], P =.031)
Intensive Care National Audit & Research Centre [127]	UK	Retrospective study	2249	[n = 1926] BMI 25 to <30 688 (35.7%) BMI 30 to <40 592 (30.7) BMI <40,134 (7.0)	BMI <18.5 14 (0.7) BMI 18.5 to <25 498 (25.9)	F: 607 (27.0) M: 1641 (73.0)	Mean (SD) 60.1 (13.1) Median (IQR) 61 (52, 70)	–	–	346/690 (50.1%)	[n = 2124] cardiovascular 6 (0.3%) Respiratory 23 (1.1%) Renal 35 (1.6%) Liver 5 (0.2%) Metastatic disease 9 (0.4%) Hematological malignancy 24 (1.1%) Immunocompromised 49 (2.3%)	2249 of cases admitted in critical care unit
Itelman et al. [128]	Israel	Retrospective study	162	19% were obese (BMI >30 kg/m²)	–	F:57 (35.2%) M: 105 (64.8%)	Mean (SD) 52 (20)	MedianBMI: 27 IQR: 24–31	–	–	Ischemic heart disease 7% Hypertension 30% Diabetes 19%	–

Table 1 (continued)

First author	Country	Type of study	Sample size (n)	Obesity prevalence		Sex	Age (years)	BMI (kg/m²)	Disease severity (total); n (%)		Comorbidities; n (%)	Note
				Obese patients	Control (nonobese)				ICU admission	Mortality		
Klang et alo. [129]	USA	Retrospective study	Age ≤ 50: 572	Survivors BMI <30 272 (53.1) BMI 30–40 171 (33.4) BMI ≥ 40 69 (13.5) Non-survivors BMI <30 25 (41.7) BMI 30–40 16 (26.7) BMI ≥ 40 19 (31.7)	Survivors Non-survivors	Survivors 352 (68.8) Non-survivors 45 (75.0)	Survivors Median (IQR), 40.0 (34.0–46.0) Non-survivors Median (IQR), 46.5 (42.8–49.0)	Survivors 29.4 (25.4–36.4) Non-survivors 31.5 (26.8–43.0)	–	60; 10.5%	Survivors CAD 26 (5.1) CHF 25 (4.9) HTN 151 (29.5) DM 129 (25.2) Hyperlipidemia 63 (12.3) CKD 53 (10.4) Cancer 30 (5.9) Non-survivors CAD 6 (10.0) CHF 10 (16.7) HTN 24 (40.0) DM 24 (40.0) Hyperlipidemia 11 (18.3) CKD 17 (28.3) Cancer 9 (15.0)	Younger patients with BMI ≥ 40 are at a fivefold higher risk for mortality from COVID-19
Klang et al. [129]	USA	Retrospective study	Age > 50: 2834	Survivors BMI <30 1151 (65.5) BMI 30–40 496 (28.2) BMI ≥ 40 111 (6.3) Non-survivors BMI <30 727 (67.6) BMI 30–40 274 (25.5) BMI ≥ 40 75 (7.0)	Survivors Non-survivors	Survivors 949 (54.0) Non-survivors 615 (57.2)	Survivors 68.0 (60.0–77.0) Non-survivors 76.0 (67.0–84.0)	Survivors 27.5 (24.0–31.9) Non-survivors 27.3 (23.4–31.6)	–	1076; 38.0%	Survivors CAD 358 (20.4) CHF 254 (14.4) HTN 1260 (71.7) DM 839 (47.7) Hyperlipidemia 704 (40.0) CKD 298 (17.0) Cancer 290 (16.5) Non-survivors CAD 354 (32.9) CHF 224 (20.8) HTN 864 (80.3) DM 607 (56.4) Hyperlipidemia 502 (46.7) CKD 299 (27.8) Cancer 201 (18.7)	–
ldh.la.gov [130]	USA	Retrospective study	5416	Mortality BMI >25 239 BMI <25 5177	–	–	–	–	–	–	–	–
Lodigiani et al. [131]	Italy	Retrospective cohort study	388	BMI ≤ 25 130/361 (36.0%) BMI 25–30 144/361 (39.9%) BMI ≥ 30 87/361 (24.1%)	–	F:124 (32%) M: 264 (68%)	Median 66 (Q1–Q3, 55–85)	–	61 (16%)	92 (26%)	Arterial hypertension 183/388 (47.2%) Diabetes mellitus 88/388 (22.7%) Chronic renal dysfunction 61/388 (15.7%) Dyslipidemia 76/388 (19.6%)	–
Palmieri et al. [116]	Italy	Retrospective study	18,641	Obesity: 182 (11.4%)	–	M: 12,302 (66.0%) F: 6339 (34.0%)	Median: 80, range: 5–100, IQR: 73–86	–	–	–	Ischemic heart disease: 446 (27.9%) Atrial fibrillation: 357 (22.4%) Heart failure:249 (15.6%) Stroke: 174 (10.9%) HTN: 1126 70.6%) T2DM: 520 (32.6%) Dementia: 236 (14.8%) COPD: 286 (17.9%) Cancer: 261 (16.4%) Chronic liver disease: 60 (3.8%) Chronic renal failure: 365 (22.9%)	18,641 SARS-CoV-2 patients dying in Italy

Table 1 (continued)

First author	Country	Type of study	Sample size (n)	Obesity prevalence		Sex	Age (years)	BMI (kg/m²)	Disease severity (total); n (%)		Comorbidities; n (%)	Note
				Obese patients	Control (nonobese)				ICU admission	Mortality		
Ong et al. [132]	Singapore	Retrospective study	182	BMI 25–30: 29 (31.9%) BMI 30–35: 7 (7.7%) BMI >35 4 (4.4%)	BMI <25: 51 (56.0%)	BMI <25 M: 24 (47.1%) BMI ≥25 M: 27 (67.5%)	BMI <25 58 (43–68) BMI ≥25 51 (35–61)	BMI <25 22.3 (21.4–23.5) BMI ≥25 27.8 (25.9–30.3)	BMI <25 15 (29.4) BMI ≥25 12 (30.0)	BMI <25 3 (6.1) BMI ≥25 1 (2.6)	BMI <25 DM 11 (21.6%) HTN 15 (29.4%) CVD 4 (7.8%) BMI ≥25 DM 7 (17.5%) HTN 15 (37.5%) CVD 5 (12.5%)	–
Wang et al. [133]	China	Retrospective study	141	Mortality BMI >25 45 (32%)	–	–	–	–	–	–	–	–

BMI body mass index, *OR* odd ratio, *RR* relative risk, *HR* hazard ratio, *CI* confidence inter.

burden associated with COVID-19 have a two-sided relationship. Obese patients require more ICU beds [23], and due to the pandemic, many ICU beds are occupied. On the contrary, a high prevalence of obesity among a population could lead to the lack of ICU beds. Also, shortage of bariatric beds and the difficulty of positioning and transportation make more burden on nurses and other health care workers [7, 35].

Furthermore, appropriate requirements for obese patients are frequently scarce in many hospitals, e.g., computed tomography (CT) machines that are not able to accommodate obese patients' weights. Besides these weight limits on CT machines, diagnosis based on pulmonary ultrasound is more difficult in obese patients, and these challenges make an early diagnosis more difficult in obese patients [36]. Also, difficult intubation due to additional adipose tissue on the larynx and difficult insertion of catheters are other factors that make managing obese patients so challenging [35, 36].

How obesity affects COVID-19?

Effects of obesity on the respiratory system

There are many hypotheses about the mechanism of how obesity affects COVID-19 (Fig. 1). It is not surprising that obese patients have many respiratory complications if infected with SARS-CoV-2. Obesity could affect the respiratory system in various ways. Previous studies have confirmed that obesity is a risk factor for many respiratory system diseases like asthma, obstructive sleep apnea syndrome, acute lung injury, and ARDS [37]. Frequently, there are alterations in the respiratory system and chest wall physiology of obese individuals due to fat deposits in the mediastinum and abdomen. Reduced chest wall elasticity, limited truncal expansion, low respiratory muscle strength, and limited diaphragm excursion predispose these individuals to lower respiratory system compliance with a decrease in expiratory reserve volume [10, 28, 38]. Obesity is associated with increased airway resistance, impaired gas exchange, positional gas trapping, and surfactant dysfunction [38, 39]. These functional and physiological changes predispose them to hypoventilation-associated pneumonia, pulmonary HTN, and cardiac stress [25].

Moreover, the impaired ventilation of the base of the lungs in obese patients could result in reduced oxygen saturation of the blood [40]. Lower lung zones have higher perfusion due to gravity; however, these zones are not well-ventilated because obese individuals' functional residual capacity is near their residual volume [41–43]. This ventilation–perfusion mismatch could lead to lower partial pressure of oxygen (PO2) [40]. Furthermore, obese patients require more oxygen consumption to reach this
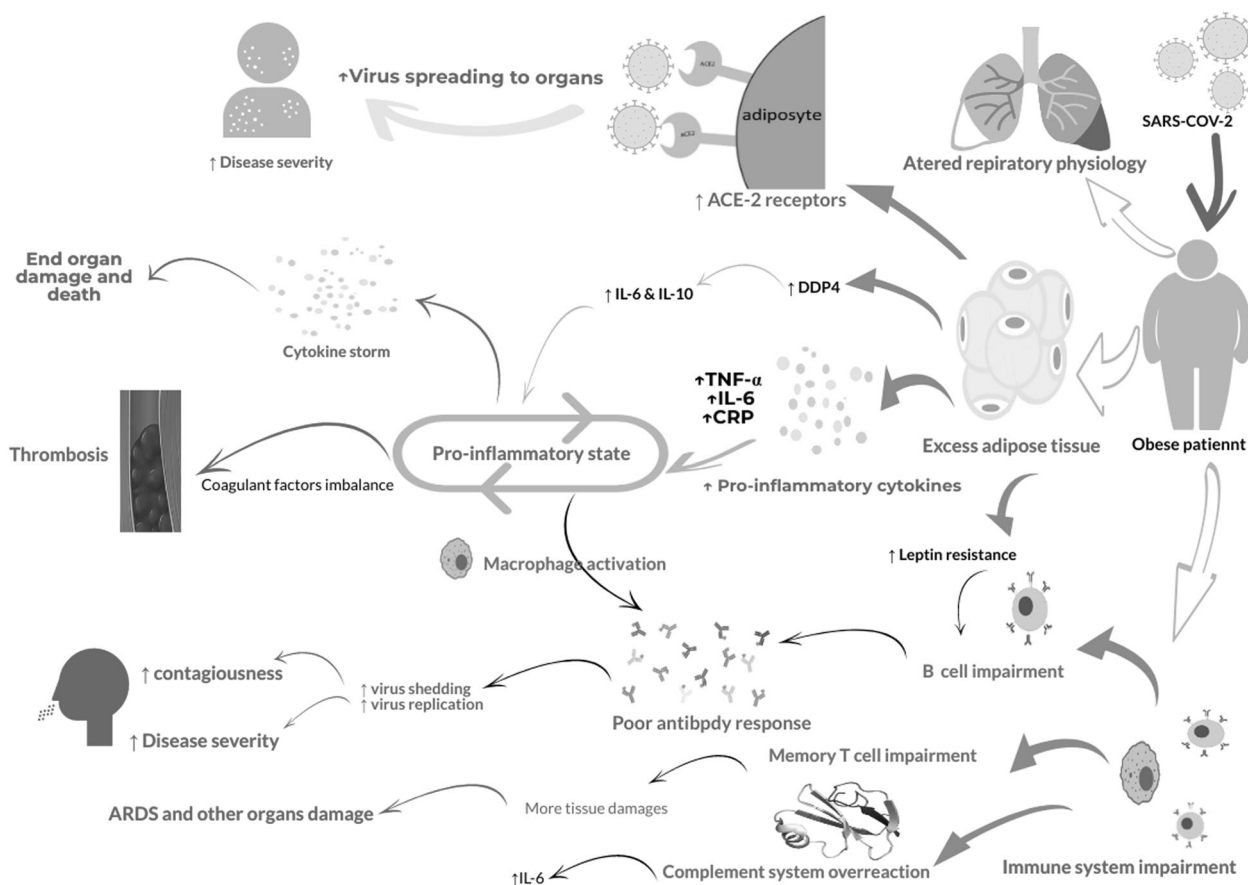
Fig. 1 Mechanism of disease severity during SARS-CoV-2 infection in obese patients. ACE-2 angiotensin-converting enzyme 2, DDP4 dipeptidyl peptidase-4, IL-6 interleukin-6, IL-10 interleukin-10, TNF-α tumor necrosis factor, CRP C-reactive protein, ARDS adult respiratory distress syndrome.

lower PO2 [44]; thus, more oxygen requirement and hypoxia in obese patients could lead to the exacerbation of problems in oxygenation.

Effects of obesity on the immune system

Obesity could impair the immune system in various ways. From past experiences, we know that antibody response to influenza vaccine was reduced in obese individuals, and their infection risk was double than that of lean individuals [32, 45]. Moreover, in animal studies, the severity and duration of viral infection were increased in obese animals [32]. Also, obesity is an independent risk factor for an immune-mediated disease like psoriasis [46].

A balance between cytokines is necessary for an appropriate immune response. However, a pro-inflammatory state in obese patients disrupts this essential balance. This state may be due to the inappropriate secretion of adipokines and cytokines like tumor necrosis factor, interleukin-6 (IL-6), and C-reactive protein by adipocytes in hypoxic conditions [47, 48]. A previous study has shown that IL-6 is an independent risk factor for developing severe COVID-19 [49], and adipose tissue is one of the primary sources of IL-6 secretion [50]. The creation of an auto-regenerating inflammation loop in this pro-inflammatory state by recruitment of immune cells (macrophages, T cells, and B cells) impairs the immune system [48]. In this status, a viral infection could simply start an impaired immune response, leading to a cytokine storm by over-production of pro-inflammatory cytokines. The cytokine storm could lead to vascular hyperpermeability and multiorgan failure seen in severe cases of COVID-19 [51]. In the human model, studies have shown that IL-6 is responsible for the activation of multiple cytokine pathways in this pro-inflammatory state [52].

Obesity could lead to the incoordination of innate and adaptive immune responses by disruption of lymphoid tissue integrity and alterations in leukocyte development and activity [36]. In particular, the impairment of CD8+ memory T cells was seen in obese patients vaccinated for influenza and considered as the leading cause of their weak antibody response to the vaccine [53]. A decrease in macrophage activation due to pro-inflammatory status was regarded as another cause of this inadequate response [34, 53]. Also,

memory T-cell impairment could lead to more tissue damage during viral infection challenge [54]. Furthermore, a study in Wuhan showed that patients with severe COVID-19 had less memory, and regulatory T cells [22].

Leptin Leptin is an adipose tissue-derived cytokine that signals the body to stop caloric consumption [35]. Also, leptin plays an essential role in the maturation, development, and function of B lymphocytes [55]. Leptin function in obese individuals is impaired. Surprisingly, leptin serum levels were very high in obese patients due to leptin resistance, like insulin resistance in T2DM [35], and this leptin resistance was associated with disease severity in H1N1 influenza [55].

Complement system The complement system is inappropriately activated in obese patients [56]. This overreaction is one of the possible mechanisms of the impaired immune reaction to SARS-CoV-2. In a study conducted on SARS-CoV, C3 deficient mice had better respiratory function and a lower level of IL-6 [57].

Dipeptidyl peptidase-4 (DDP4) Furthermore, a high level of DDP4 in obese patients is another possible mechanism of immune system impairment. DDP4 is a transmembrane enzyme in human adipose tissue and has an association with obesity-related T2DM [58]. DDP4 inhibition led to GLP-1 increasing and improved insulin sensitivity in adipose tissue [59]. Even in nonobese patients, DDP4 inhibition could suppress pro-inflammatory cytokines like IL-6 and IL-10 [60].

SARS-CoV-2 receptors in obese patients

Visceral adipose tissues like epicardial fat tissue and ectopic fat tissue in the alveolar space may play a significant role in severe disease by expressing a high level of angiotensin-converting enzyme 2 (ACE-2) receptors. SARS-CoV-2 has a high affinity to bind the ACE-2 receptors [61]. This receptor is expressed in many organs and tissue, particularly lung tissue [62]. However, adipose tissue has a higher level of ACE-2 expression than lung tissue [63]. Obese patients have more adipose tissue than lean individuals, resulting in more ACE-2 receptors.

Obesity and other comorbidities

Obesity could accompany other COVID-19 severity risk factors like T2DM, cardiovascular disease, and kidney diseases [25] (Fig. 2). In diabetic and obese patients, insulin resistance due to excess fat could lead to inadequate metabolic response to immunologic challenge and more insulin requirement during COVID-19 severe infection [29].

Even in the absence of other comorbidities, HTN, dyslipidemia, and insulin resistance could increase the risk of

cardiovascular events in obese patients infected with SARS-CoV-2 [25]. Left ventricular (LV) hypertrophy due to HTN is the most common cardiac morphology change [64, 65]. In addition, the hyperactivity of the renin–angiotensin–aldosterone system in obese patients could affect myocardium by increasing levels of angiotensin II [66]. Furthermore, obesity could lead to right ventricular dysfunction as an issue in COVID-19 patients due to higher circulating plasma volume [51]. Also, LV diastolic dysfunction and heart failure are common in obese patients [64, 65, 67]. Moreover, the pro-inflammatory state in obese patients may increase the risk of thrombosis by creating an imbalance of procoagulant and anticoagulant factors, increasing thrombin generation, and enhancing platelet activation [68, 69]. Recently, in some patients with severe COVID-19 infection, a generalized thrombotic microvascular injury was observed in pulmonary and cutaneous biopsy and autopsy samples [70].
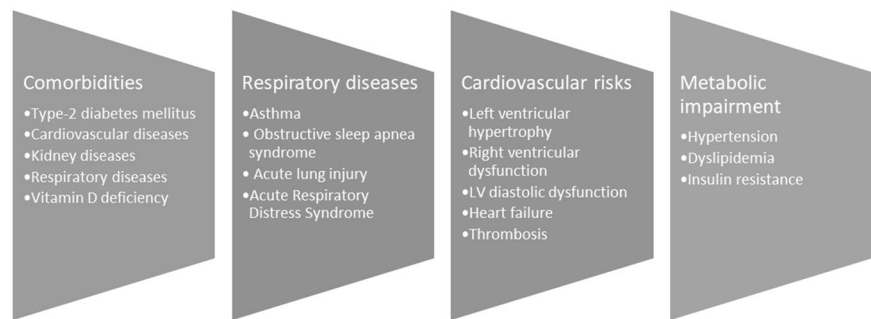
Vitamin D deficiency is another possible risk factor for developing severe COVID-19 [71]. Vitamin D as an immunomodulator plays an essential role in decreasing the production of pro-inflammatory cytokines [72]. About 40–80% of the obese population is vitamin D deficient [72] due to volumetric dilution, sequestration of vitamin D in adipose tissue, and negative feedback from 1,25-dihydroxy vitamin D [73]. Also, in the ICU, obese patients with malnutrition have worse outcomes than those without malnutrition [74]. Moreover, increasing the need for calorie consumption due to a severe acute inflammatory state in SARS-CoV-2 infection could provoke malnutrition [28].

Role of visceral and abdominal adipose tissue

Adipose tissues in each part of the body could play a role in the severity of COVID-19. For example, abdominal obesity is linked to the impaired ventilation, particularly in the supine state, by reducing diaphragmatic excursion [75]. There are two layers of adipose tissue in the abdomen: visceral and subcutaneous. Abdominal visceral fat is associated with T2DM, HTN, and cardiovascular disease [76]; however, a similar prevalence of T2DM to the USA in China may relate to more visceral and ectopic adipose tissue instead of abdominal fat in patients of Asian descent [7].

Visceral adipose tissue, either abdominal or non-abdominal, is responsible for a pro-inflammatory state by abnormal adipokine and cytokine secretion [54, 77]. This state makes visceral adipose tissue capable of driving inflammation in organs (such as heart, liver, kidney, and lungs) and also leads to immune response impairment [54]. Moreover, adipose tissue expresses a high level of ACE-2 receptors, and this may ease the local spreading of the virus in visceral intrathoracic (lungs), epicardial (heart), and perirenal (kidney) adipose tissue [54]. H5N1 viral tropism has been shown for adipose tissue [78]. Also, adipose tissue is

Fig. 2 **Obesity and other comorbidities.** Obesity is the risk factor for severe COVID-19 in accompanied with other comorbidities.

Comorbidities
- Type-2 diabetes mellitus
- Cardiovascular diseases
- Kidney diseases
- Respiratory diseases
- Vitamin D deficiency

Respiratory diseases
- Asthma
- Obstructive sleep apnea syndrome
- Acute lung injury
- Acute Respiratory Distress Syndrome

Cardiovascular risks
- Left ventricular hypertrophy
- Right ventricular dysfunction
- LV diastolic dysfunction
- Heart failure
- Thrombosis

Metabolic impairment
- Hypertension
- Dyslipidemia
- Insulin resistance

capable of more influenza virus shedding [31]. Moreover, visceral adipose tissue is one of the main sources of IL-6 secretion, and higher levels of IL-6 are associated with more mortality in SARS-CoV-2 [4].

Epicardial adipose tissue is another visceral fat tissue associated with increased BMI. This fat tissue could decrease myocardial function, in addition to adipokines secretion. Also, a high level of ACE-2 receptors in epicardial fat tissue could increase the risk of myocarditis in obese COVID-19 patients [79].

How COVID-19 lead to more obesity?

Social distancing during COVID-19 pandemic in many countries leads to significant changes in the individuals' lifestyle. Decreasing activity, changing eating habits, sleep disorders, stress, and experiencing fear are some significant changes in people's lives that may result in weight gain and obesity. Reduced level of daily physical activity may be due to the lockdown and keeping schools, gym, and parks closed, teleworking, depression, and fear.

On the other hand, stress and anxiety in people experiencing bad news may result in weight gain [80]. Stress could result in weight gain by cortisol release (activation of the hypothalamo-adrenal-pituitary axis) [81] and more fat and sweet food consumption (activation of reward centers in the brain) [82]. Also, stress is associated with sleep disruption and lower physical activity, resulting in weight gain [83].

Changing the diet to canned food due to food insecurity and fresh food unavailability, eating high-caloric snacks or junk foods during other activities and eating food late at night are unhealthy eating habits during the COVID-19 lockdown [81, 83]. These eating habits have more carbohydrate, fat, and sodium, and also processed food could lead to more food consumption by addictive-like behaviors. Furthermore, inadequate sleep may alter the circadian rhythm of hormones and immune system efficacy [83].

Moreover, self-isolation and depression are frequent in obese individuals due to weight stigma [84]. During the lockdown, there were lots of fat-shaming memes on social media [85], and this content could lead to more isolation.

Depression or stigmatizing may lead to delay in referring to health care centers in obese patients [86].

Meta-analysis

Obesity and poor outcome

In 17 studies, meta-analysis demonstrated that obesity (BMI ≥ 30) was associated with poor outcome (OR: 1.297 [1.178–1.416], $p < 0.001$; I^2: 0.0%, heterogeneity = 13.69) (Fig. 3A).

Obesity and ICU admission

In six studies, meta-analysis demonstrated that obesity (BMI ≥ 30) was not associated with ICU admission and obesity did not significantly increase the ICU admission (OR: 1.189 [0.955–1.424], I^2: 0.0%, heterogeneity = 1.92) (Fig. 3B).
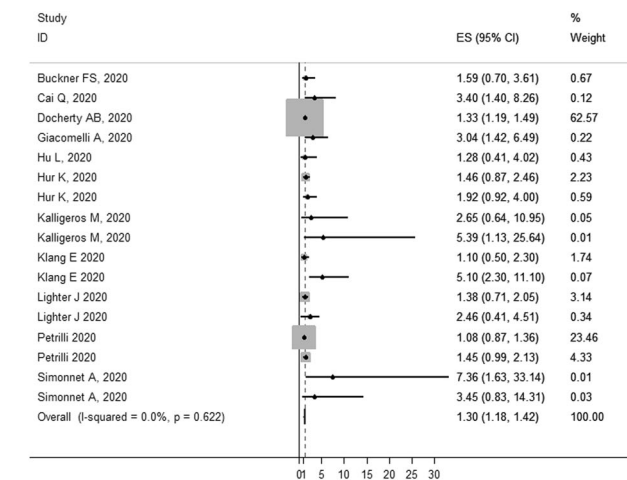
Obesity and IMV

In eight studies, meta-analysis suggested that in patients hospitalized with COVID-19, obesity (BMI ≥ 30) was associated with invasive mechanical ventilation (OR: 2.049 [1.420–2.678], I^2: 75.3%, heterogeneity = 28.34) (Fig. 3C).
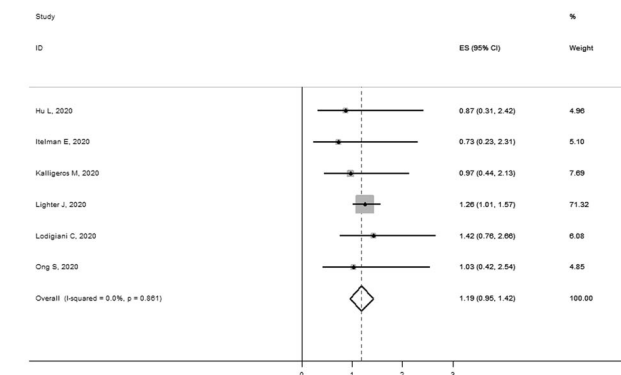
Obesity and mortality

Ten retrospective cohort studies reported the effect of obesity on the mortality. Meta-analysis demonstrated that obesity (BMI ≥ 30) was associated with mortality and obesity increased mortality (OR: 1.35 [1.241–1.459], I^2: 76.6%, heterogeneity = 38.44) (Fig. 3D).

### Recommendations on weight control in COVID-19 era

Because of obesity effects on COVID-19, weight gain prevention is highly recommended during the pandemic. Changing lifestyle has been found to play an important role in the prevention of weight gain. Increased physical activity and exercise at home or outdoors with social distancing are
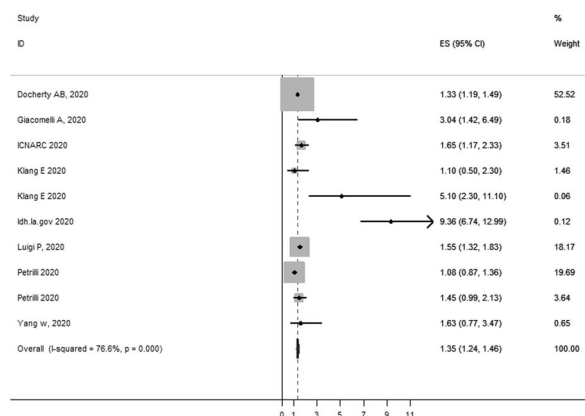
(A). Obesity and poor outcome

(B). Obesity and ICU admission
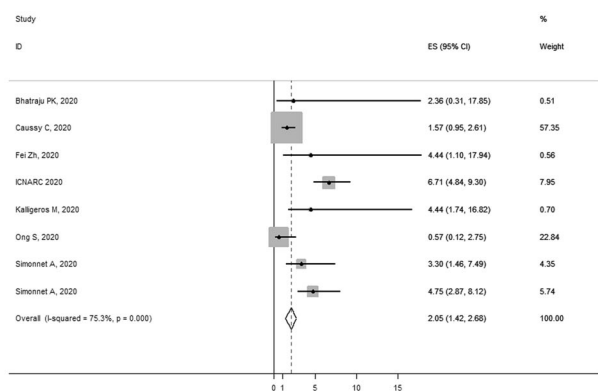
(C). Obesity and IMV

(D). Obesity and Mortality

Fig. 3 Forest-plot of obesity and poor outcome, ICU admission, IMV, and mortality in COVID-19. Forest-plot showing the association between obesity and poor outcome (**A**), ICU admission (**B**), IMV (**C**), and mortality (**D**). 95% CI 95% confidence interval.

critical ways to prevent weight gain in normal-weight people and also lose weight in overweight or obese individuals. Exercise also could improve the metabolic and immunologic functions of the body [87]. Creative methods to do exercise more at home and high activity games with children may lead to more activity despite limitations. Reduced high-caloric food consumption is another feasible way to prevent weight gain. Increased fresh food and decreased canned and junk food consumption are notable points that should be considered during the pandemic. Moreover, psychological support and treatment or medical interventions to control stress and avoid emotional eating, and also, sleep regulation could also be useful to reach this goal.

In addition to these recommendations, obese patients should consider a steady low-caloric diet and proven weight loss drugs (synthetic or herbal drugs under physician observation) to lose weight due to their increased risk of disease [88, 89]. Furthermore, obese patients who have diabetes should tightly control their glycemic status and

adjust their medication and calorie consumption with these new circumstances. As a result, telemedicine could play a crucial role in the close monitoring of obese patients during COVID-19 pandemic.

Recommendations and conclusion

Obesity affects the respiratory and immune systems through various mechanisms. Cytokine and adipokine secretion from adipose tissue leads to a pro-inflammatory state in obese patients, and this predisposes them to thrombosis, incoordination of innate and adaptive immune responses, inadequate antibody responses, and cytokine storm. Also, viral shedding is more in obese patients. Obesity is associated with other comorbidities such as HTN, cardiovascular disease, diabetes mellitus, and vitamin D deficiency.

Hospitalization, ICU admission, mechanical ventilation, and even mortality in obese patients are higher than normal-weight people. It seems obesity could shift severe COVID-

19 symptoms to younger individuals. Also, early diagnosis and management of obese patients are harder than those of lean individuals. Decreasing activity, changing eating habits and, more stress and fear experienced during the COVID-19 pandemic may result in more weight gain and obesity. More attention to weight gain prevention is necessary during this pandemic.

Obesity should be considered as an independent risk factor for developing severe COVID-19. We recommend that clinicians consider more serious treatments in the early stages of disease for obese patients.

Reviewing all relevant studies conducted on "Obesity and COVID-19" and various possible mechanisms were the strength of this study. However, we have some limitations such as full-text unavailability for some non-English studies and lack of cohort studies. Most of the studies were cross-sectional and retrospective and also some had small sample sizes; we recommend that prospective cohort studies be conducted on larger sample sizes.

Author contributions SMMA, MP, and ME participated in the study design, drafting of the paper, and had significant role in development of the selection criteria and data extraction criteria. SMMA, BA, ZS, MPS, MQ, and BL contributed to the development of the selection criteria, data extraction criteria, and drafting of the paper. SMMA provided final approval of the version to publish. ZS, MPS, and MQ developed the search strategy. BL participated in critical review. MQ participated in the study design and interpretation. MP and ME supervised the project from scientific view of point and advised on experimental design. All authors read, provided feedback, and approved the final paper.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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