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## Review

## COVID-19 infection and body weight: A deleterious liaison in a J-curve relationship

Antonis S. Manolis<sup>a,\*</sup>, Antonis A. Manolis<sup>b</sup>, Theodora A. Manolis<sup>c</sup>, Naomi E. Apostolaki<sup>d</sup>, Helen Melita<sup>e</sup>

<sup>a</sup> Athens University School of Medicine, Athens, Greece

<sup>b</sup> Patras University School of Medicine, Patras, Greece

<sup>c</sup> Aghia Sofia University Hospital, Athens, Greece

<sup>d</sup> University of Bristol, Bristol, UK

<sup>e</sup> Onassis Cardiac Surgery Center, Athens, Greece



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## ABSTRACT

During the course of the COVID-19 pandemic, obesity has been shown to be an independent risk factor for high morbidity and mortality. Obesity confers poor outcomes in younger (<60 years) patients, an age-group considered low-risk for complications, a privilege that is negated by obesity. Findings are consistent, the higher the body mass index (BMI) the worse the outcomes. Ectopic (visceral) obesity also promotes proinflammatory, prothrombotic, and vasoconstrictive states, thus enhancing the deleterious effects of COVID-19 disease. Less, albeit robust, evidence also exists for a higher risk of COVID-19 infection incurred with underweight. Thus, the relationship of COVID-19 and BMI has a J-curve pattern, where patients with both overweight/obesity and underweight are more susceptible to the ailments of COVID-19. The pathophysiology underlying this link is multifactorial, mostly relating to the inflammatory state characterizing obesity, the impaired immune response to infectious agents coupled with increased viral load, the overexpression in adipose tissue of the receptors and proteases for viral entry, an increased sympathetic activity, limited cardiorespiratory reserve, a prothrombotic milieu, and the associated comorbidities. All these issues are herein reviewed, the results of large studies and meta-analyses are tabulated and the pathogenetic mechanisms and the BMI relationship with COVID-19 are pictorially illustrated.

## Introduction

One of the most feared complications of coronavirus-disease-2019 (COVID-19) is acute lung injury, which leads to acute respiratory-distress syndrome (ARDS) in ~30–40% of patients presenting with pneumonia, and 60–80% of those requiring intensive care [1–3]. Before this pandemic, there was no difference noted in hospital mortality across body-mass index (BMI) strata (overweight, obesity and severe obesity) in patients with moderate/severe ARDS [4]. Even lower mortality was suggested by a meta-analysis of 5 studies for patients with obesity and ARDS, supporting a possible “obesity paradox” (inverse association between BMI and mortality) [5]. Indeed, another meta-analysis of 24

studies also provided evidence of an “obesity paradox” in a very large cohort of patients with ARDS (N = 9,187,248); although obesity was associated with increased risk of ARDS, it conferred a lower risk of mortality in ARDS patients (pooled odds ratio-OR 0.63, P = 0.04, I<sup>2</sup> = 96%) [6].

However, during the course of the COVID-19 pandemic, obesity has been shown to be an independent risk-factor for high mortality in a prospective UK study, in which the clinical features of >20,000 hospitalized patients with COVID-19 were analyzed [7]. Over the last several months, many other studies have demonstrated that COVID-19 patients with overweight and obesity have more severe disease, are at increased risk for intubation and have higher mortality compared to those with

**Abbreviations:** ARDS, acute respiratory distress syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19, corona virus 2019; CVD, cardiovascular disease; DPP4, dipeptidyl peptidase 4; GDP, gross domestic product; ICU, intensive care unit; IL, interleukin; IMV, invasive mechanical ventilation; SNS, sympathetic nervous system; TNF, tissue necrosis factor; VAT, visceral adipose tissue.

\* Corresponding author at: First Department of Cardiology, Ippokratieo Hospital, Vas. Sofias 114, Athens 115 27, Greece.

E-mail address: [asm@otenet.gr](mailto:asm@otenet.gr) (A.S. Manolis).

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normal BMI. On the other hand, high frequency of obesity has been reported among COVID-19 patients admitted in intensive care units (ICUs); apparently, disease severity increases with BMI [8]. Interestingly, a recent analysis of differences in factors influencing COVID-19-related mortality among various countries showed that in addition to low socio-economic status as reflected by the gross domestic product (GDP), obesity was the second-best predictor of death with a correlation coefficient (*R*) value of 0.43 vs an *R*-value of 0.65 for GDP [9]. Finally, a large multicenter observational cohort study (*N* = 35,506) indicated that the “obesity paradox” is not present in critically ill (ICU) patients with COVID-19-related respiratory failure [10].

### Individual studies

The main large individual studies reporting on the association between obesity and COVID-19 outcomes in >1000 participants are displayed in Table 1. A population study in England (*N* = 334,329; age 56.4 ± 8.1 years; 54.5% women), where ~0.2% (*n* = 640) were hospitalized for COVID-19, indicated that there was a linear trend in the likelihood of COVID-19 hospitalization with increasing BMI, that was evident in the overweight (odds ratio-OR 1.39) and obese stage I (OR 1.70) and stage II (OR 3.38) compared to normal weight [11]. Another multicenter retrospective cohort study enrolling 1461 patients (median age 64 years; 73% males; median BMI 28.1 kg/m<sup>2</sup>) showed a significant linear relation between BMI and invasive mechanical ventilation (OR 1.27 per 5 kg/m<sup>2</sup>) and a significant association between BMI and mortality, which was only increased in obesity class III (≥40 kg/m<sup>2</sup>) (HR 1.68) [12].

In a study of 6916 patients with COVID-19, there was a J-shaped association between BMI and risk for death, even after adjustment for obesity-related comorbidities [13]. Patients with BMI of 40–44 kg/m<sup>2</sup> had a relative risk (RR) of 2.68, and those with BMI > 45 kg/m<sup>2</sup> had an RR of 4.18 compared with patients with BMI of 18.5–24 kg/m<sup>2</sup>. This risk was most striking among those aged ≤60 years and men. A study aiming to identify risk factors for severe COVID-19 disease in 158 African-Americans, indicated that patients admitted to ICU were older (62 vs. 55 years, *P* = 0.003) and had higher BMI (36.5 kg/m<sup>2</sup> vs. 31.9 kg/m<sup>2</sup>, *P* = 0.002) [14]. In multivariate analysis, the factors most associated with ICU-admission were age (adjusted odds ratio-aOR: 1.073), BMI (aOR: 1.115), and lung disease (aOR: 3.097).

A retrospective study of 3530 hospitalized patients with COVID-19 disease (median age 65 years; women ~45%; median BMI 28.8 kg/m<sup>2</sup>) showed a J-shaped association between BMI and in-hospital mortality [15]. In men, BMI 35–39.9 kg/m<sup>2</sup> and BMI ≥ 40 kg/m<sup>2</sup> had a significant association with higher in-hospital mortality, while only BMI ≥ 40 kg/m<sup>2</sup> was found significant in women. Obesity classes II and III in men and obesity class III in women were independently associated with higher in-hospital mortality in patients with COVID-19.

Another retrospective study of 3406 hospitalized COVID-19 patients indicated that in the younger (<50) age group (*n* = 572, 17%), 60 (10.5%) patients died, while in the older age group, 1076 (38%) patients died [16]. For the younger population, BMI ≥ 40 was independently associated with mortality (aOR 5.1) and to a lesser extent for the older group (aOR 1.6).

An observational study followed 10,861 patients with COVID-19 infection, comprising 243 (2.2%) patients who were underweight, 2507 (23.1%) with normal weight, 4021 (37.0%) having overweight, 2345 (21.6%) with obesity class I, 990 (9.1%) with obesity class II, and 755 (7.0%) with obesity class III [17]. Patients who had overweight (OR 1.27), obesity class I (OR 1.48), obesity class II (OR 1.89), and obesity class III (OR 2.31) had an increased risk of requiring invasive mechanical ventilation (IMV). Underweight (OR 1.44) and obesity classes II (OR 1.25) and III (OR 1.61) conferred increased risk of death. Among patients who were on IMV, BMI was not associated with inpatient deaths. The authors concluded that COVID-19 patients who are underweight or who have obesity are at risk for mechanical ventilation and death.

A retrospective cohort study of 1019 SARS-CoV-2 positive patients

(median age 64 years, 58.7% men, prevalence of overweight and obesity 75.2%; median BMI 28.5 kg/m<sup>2</sup>) showed by multivariable logistic regression that BMI was associated with complications including intubation (OR 1.03), septic shock (OR 1.04), renal replacement therapy (OR 1.07), and mortality (OR 1.04) [18]. The odds of death were highest among those with BMI ≥ 40 kg/m<sup>2</sup> (OR 2.05). The authors concluded that severe complications of COVID-19 and death are more likely in patients with obesity, independent of age and comorbidities.

A study examining the link between BMI and risk of a positive test for COVID-19 infection and risk of COVID-19-related death among 4855 UK Biobank participants, of whom 839 were positive and of these 189 died from COVID-19, showed that BMI was associated strongly with positive test, and risk of death related to COVID-19 [19]. The BMI-related risk was higher in those under 70.

A large prospective, community-based cohort study comprising 6,910,695 individuals (mean BMI 26.78 kg/m<sup>2</sup>), of whom 13,503 (0.20%) were admitted to hospital, 1601 (0.02%) to an ICU, and 5479 (0.08%) died after a positive test for SARS-CoV-2, found a J-shaped association between BMI and admission to hospital due to COVID-19 (adjusted hazard ratio - aHR per kg/m<sup>2</sup> from the nadir at BMI of 23 kg/m<sup>2</sup> of 1.05) and death (aHR 1.04), and a linear association across the whole BMI range with ICU admission (aHR 1.10) [20]. There was also significant interaction between BMI and age and ethnicity, with higher HR per kg/m<sup>2</sup> above BMI 23 kg/m<sup>2</sup> for younger people (aHR per kg/m<sup>2</sup> above BMI 23 kg/m<sup>2</sup> for hospital admission 1.09 in 20–39 years age group vs 1.01 in 80–100 years age group) and Black people than White people (aHR 1.07 vs 1.04).

Similar findings were reported by smaller studies. A retrospective study of 504 COVID-19 patients indicated that after controlling for other factors, there was an increased risk of mortality in the overweight (RR 1.4) and obese groups (RR 1.3) [21]. Another study (*N* = 482) showed that a BMI 30–34.9 kg/m<sup>2</sup> increased the risk of respiratory failure (OR 2.32, *P* = 0.004) and admission to the ICU (OR 4.96, *P* < 0.001) [22].

According to a study of 297 COVID-19 patients, the occurrence of bilateral pneumonia was higher (92.50% vs. 73.57%, *P* = 0.033) in patients with obesity than lean patients, as was the proportion of severe illness in patients with overweight (12.82% vs. 2.86%, *P* = 0.006) and obesity (25% vs. 2.86%, *P* < 0.001) [23]. More patients with obesity developed respiratory failure (20% vs. 2.86%, *P* < 0.001) and ARDS (5% vs. 0%, *P* = 0.024). Overweight (OR 4.222, *P* = 0.015) and obesity (OR 9.216, *P* = 0.001) were independent risk factors of severe illness; obesity (HR 6.607, *P* = 0.002) was an independent risk factor of respiratory failure.

Similarly, among 210 COVID-19 patients <45 years, each of the primary outcomes (hospital admission, mechanical ventilation, mortality) was associated with a BMI > 30 (OR 2.61, *P* = 0.0008; mechanical ventilation OR = 6.01, *P* = 0.0001; mortality OR = 6.29, *P* = 0.0046) [24]. These results were confirmed in a larger study of 2466 COVID-19 patients [25]. Patients, particularly those <65 years, with BMIs >30 kg/m<sup>2</sup> were more likely to be intubated or die. These findings were further corroborated by an analysis of BMI stratified by age in 3615 COVID-19-patients [26]. Patients aged <60 years with a BMI of 30–34 were 1.8–2.0 times more likely and those with BMI ≥ 35, 2.2–3.6 times more likely to be admitted to ICU, compared to individuals with a BMI < 30.

Thus, in the younger age-group of <60 years who are generally considered a lower-risk group of COVID-19 severity, obesity seems to negate this age-advantage and becomes a risk factor for hospital admission and need for ICU monitoring [24–26]. This has practical implications for countries with high prevalence of obesity, like the US where ~40% or the UK where ~30% of adults are obese (BMI ≥ 30) [27, 28]. Importantly, even in the young, particularly in adolescents, obesity has been shown to be an independent risk factor for critical illness [29].

In summary, obesity is a risk factor for COVID-19 hospital admission and an independent risk factor of severe illness, including respiratory failure and need for intubation and ICU care. Importantly, obesity is an

**Table 1**

Main individual studies comparing outcomes between obese and non-obese patients with COVID-19 infection.

Author/year	Type of study	No. of patients	Outcome	Comments
Docherty et al./2020 [7]	Prospective observational cohort	20,133 UK patients	<ul style="list-style-type: none"> <li>● Obesity was an independent predictor of hospital mortality (HR 1.33; <math>P &lt; 0.001</math>)</li> <li>● Factors associated with in-hospital mortality were increasing age, male sex, obesity, and major comorbidities</li> </ul>	Prevalence of obesity in this study (11%) was much lower than the overall UK prevalence (29%)
Anderson et al./2020 [25]	Retrospective cohort	2466	<ul style="list-style-type: none"> <li>● Compared with overweight pts, obese pts had higher risk for intubation or death, with the highest risk among those with class 3 obesity (HR 1.6)</li> <li>● This association was primarily observed among pts &lt;65 years</li> </ul>	<ul style="list-style-type: none"> <li>● Over a median hospital stay of 7 days, 533 pts (22%) were intubated, 627 (25%) died, and 59 (2%) remained hospitalized</li> <li>● BMI was not associated with levels of biomarkers of inflammation, cardiac injury, or fibrinolysis</li> </ul>
Lighter et al./2020 [26]	Retrospective	3615 (775 [21%] with a BMI of 30–34 kg/m <sup>2</sup> , and 595 [16%] with a BMI $\geq 35$ kg/m <sup>2</sup> )	<ul style="list-style-type: none"> <li>● mmmPts aged &lt;60 years with a BMI 30–34 were 2.0 (<math>P &lt; 0.0001</math>) and 1.8 (<math>P = 0.006</math>) times more likely to be admitted to acute and critical care, respectively, compared to individuals with a BMI &lt; 30</li> <li>● Pts with a BMI <math>\geq 35</math> and aged &lt;60 years were 2.2 (<math>P &lt; 0.0001</math>) and 3.6 (<math>P &lt; 0.0001</math>) times more likely to be admitted to acute and critical care than patients in the same age category who had BMI &lt; 30</li> </ul>	Significant differences in admission and ICU care were found only in pts <60 years of age with varying BMIs
Hamer et al./2020 [11]	General population	334,329 (~0.2%, $n = 640$ , of the sample were hospitalized for COVID-19)	There was an upward linear trend in the likelihood of COVID-19 hospitalization with increasing BMI, that was evident in the overweight (OR, 1.39; crude incidence 19.1 per 10,000) and obese stage I (OR 1.70; 23.3 per 10,000) and stage II (OR 3.38; 42.7 per 10,000) compared to normal weight (12.5 per 10,000)	<ul style="list-style-type: none"> <li>● The observed gradient was little affected after adjustment for several covariates;</li> <li>● however, controlling for biomarkers, e.g., high-density lipoprotein cholesterol and glycated hemoglobin, led to greater attenuation</li> </ul>
Chetboun et al./2021 [12]	Retrospective cohort	1461	<ul style="list-style-type: none"> <li>● Significant linear relation between BMI and invasive mechanical ventilation (OR 1.27 per 5 kg/m<sup>2</sup>)</li> <li>● Significant association between BMI and mortality, which was only increased in obesity class III (<math>\geq 40</math> kg/m<sup>2</sup>) (HR 1.68)</li> </ul>	The association between BMI and the need for mechanical ventilation was independent of other metabolic risk factors
Tartof et al./2020 [13]	Retrospective cohort	6916	<ul style="list-style-type: none"> <li>● Compared with pts with a BMI of 18.5–24 kg/m<sup>2</sup>,</li> <li>● RR was 2.68 for BMIs of 40–44 kg/m<sup>2</sup> and</li> <li>● 4.18 for BMI &gt; 45 kg/m<sup>2</sup></li> <li>● This risk was most striking among those aged <math>\leq 60</math> years and men</li> </ul>	There was a J-shaped association between BMI and risk for death, even after adjustment for obesity-related comorbidities
Klang et al./2020 [16]	Retrospective	3406 (572/17% younger than 50)	BMI $\geq 40$ was independently associated with mortality (adjusted OR 5.1 for the younger group and 1.6 for the older group)	<p>Mortality:</p> <ul style="list-style-type: none"> <li>● 60 pts (10.5%) in the younger (&lt;50) age group</li> <li>● 1076 pts (38%) in the older age group</li> </ul>
Czernichow et al./2020 [66]	Prospective cohort	5795	<p>Mortality was significantly higher in pts with obesity (reference class: 18.5–25 kg/m<sup>2</sup>):</p> <ul style="list-style-type: none"> <li>● OR 1.89 in BMI 30–35 kg/m<sup>2</sup></li> <li>● OR 2.79 in BMI 35–40 kg/m<sup>2</sup></li> <li>● OR 2.55 in BMI &gt; 40 kg/m<sup>2</sup></li> <li>● This increase holds for all age groups</li> </ul>	891 deaths occurred at 30 days
Kim et al./2021 [17]	Observational	10,861 (4090–38% obese, 4,021–37% overweight, 2507–23% normal weight, 243–2.2% underweight)	<ul style="list-style-type: none"> <li>–Increased risk of requiring IMV in pts who had: <ul style="list-style-type: none"> <li>● Overweight (OR 1.27)</li> <li>● Obesity class I (OR 1.48), class II (OR 1.89), and class III (OR 2.31)</li> </ul> </li> <li>–Increased risk of death in pts with: <ul style="list-style-type: none"> <li>● Underweight (OR 1.44)</li> <li>● Obesity class II (OR = 1.25) and class III (OR 1.61)</li> </ul> </li> </ul>	Among pts who were on IMV, BMI was not associated with inpatient deaths, suggesting that although pts with obesity are more likely to experience a severe COVID-19 course (reflected by increased odds of IMV), once mechanically ventilated, all pts, regardless of BMI, have similar odds of death
Guerson-Gil et al./2021 [15]	Retrospective	3530	<ul style="list-style-type: none"> <li>● A J-shaped association between BMI and in-hospital mortality</li> <li>● In men, BMI 35–39.9 kg/m<sup>2</sup> and BMI <math>\geq 40</math> kg/m<sup>2</sup> had a significant association with higher in-hospital mortality, while only BMI <math>\geq 40</math> kg/m<sup>2</sup> was found significant in women</li> </ul>	<ul style="list-style-type: none"> <li>● No association between BMI and IL-6</li> <li>● Obesity classes II and III in men and obesity class III in women were independently associated with higher in-hospital mortality</li> </ul>
Page-Wilson et al./2021 [18]	Retrospective cohort	1019	<p>BMI was associated with complications including:</p> <ul style="list-style-type: none"> <li>● Intubation (OR 1.03)</li> <li>● Septic shock (OR 1.04)</li> <li>● Renal replacement therapy (OR 1.07)</li> <li>● Mortality (OR 1.04)</li> </ul>	The odds of death were highest among those with BMI $\geq 40$ kg/m <sup>2</sup> (OR 2.05)

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Table 1 (continued)

Author/year	Type of study	No. of patients	Outcome	Comments
Gao et al./2021 [20]	Prospective, community-based, cohort	6,910,695	<ul style="list-style-type: none"> <li>● J-shaped associations between BMI and admission to hospital due to COVID-19 (aHR per kg/m<sup>2</sup> from the nadir at BMI of 23 kg/m<sup>2</sup> of 1.05) and death (aHR 1.04)</li> <li>● Linear association across the whole BMI range with ICU admission (aHR 1.10).</li> <li>● Significant interaction between BMI and age and ethnicity, with higher HR per kg/m<sup>2</sup> &gt;BMI 23 kg/m<sup>2</sup> for younger people (aHR for hospital admission 1.09 in 20–39 years age group vs 80–100 years group 1.01) and Black people than White people (aHR 1.07 vs 1.04)</li> </ul>	The risk of admission to hospital and ICU due to COVID-19 associated with unit increase in BMI was slightly lower in people with type 2 diabetes, hypertension, and CVD than in those without these morbidities
Foulkes et al./2021 [88]	Observational	3828 (cohort 1, n = 1202; cohort 2, n = 2626)	<ul style="list-style-type: none"> <li>● Cohort 1 (n = 1202): obesity was associated with increased likelihood of mechanical ventilation or death (OR 1.73, P &lt; 0.001) and higher peak of CRP compared with nonobese pts</li> <li>● Cohort 2 (n = 2626): findings were replicated</li> </ul>	The estimated proportion of the link between obesity and ventilation or death mediated by CRP was 0.49 (P < 0.001), more pronounced in pts <65 years (P < 0.001)

ACI = acute cardiac injury; aHR = adjusted hazard ratio; AKI = acute kidney injury; aOR = adjusted odds ratio; ARDS = acute respiratory distress syndrome; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CVD = cardiovascular disease; ESR = erythrocyte sedimentation rate; HR = hazard ratio; ICU = intensive care unit; IL-6 = interleukin-6; IMV = invasive mechanical ventilation; pts = patients; OR = odds ratio; qSOFA = quick sepsis-related organ failure assessment (score); RR = relative risk.

independent risk factor for poor outcomes including intubation and death in younger (<65–45 years), mostly male, patients, an age-group generally considered a lower-risk group of COVID-19 disease severity, a privilege that is cancelled-out by obesity. Furthermore, more severe obesity, central obesity, or genetic predisposition for obesity confer higher risk of severe-COVID-19 [30,31]. Higher BMI levels are associated with higher risk of contracting COVID-19 [32]. Interestingly, COVID-19 patients who are underweight are also at risk for mechanical ventilation and death (see discussion below).

### Meta-analyses

Meta-analyses of studies comparing obese vs non-obese patients with COVID-19 are included in Table 2. A meta-analysis of 9 studies comprising 6577 patients indicated that for patients with severe complications, the overall pooled-event rates were highest at 56.2% (P = 0.015; I<sup>2</sup> = 71.5) for obesity [33]. Similar findings were obtained from another meta-analysis of 34 studies reporting on comorbidities in COVID-19 patients [34]. In patients with severe/fatal COVID-19, the most prevalent chronic comorbidity was obesity (42%). The pooled OR for prediction of severe or fatal outcomes was strongest for chronic respiratory disease (OR 3.56), and still quite strong for obesity (OR 1.72).

Another meta-analysis of 12 studies (N = 34,390) demonstrated that obesity was associated with poor composite outcome (mortality and severity) (OR 1.73, P < 0.001; I<sup>2</sup>:55.6%), mortality (OR 1.55, P = 0.003; I<sup>2</sup>:74.4%), and clinical severity (OR 1.90, P < 0.001; I<sup>2</sup>:5.2%) in patients with COVID-19 [35]. A pooled analysis of highest vs reference BMI indicated that a higher BMI was associated with composite poor outcome (aOR 3.02), mortality (aOR 2.85), and severity (aOR 3.08).

A meta-analysis of 20 studies (N = 7671) indicated higher rates of complications among people with obesity [36]. A meta-analysis of 14 studies (N = 26,507) indicated higher mortality (21.7%) among patients with BMI > 25 kg/m<sup>2</sup> vs patients (7.1%) with BMI < 25 kg/m<sup>2</sup> (P = 0.005, OR 3.68) [37].

According to a meta-analysis of 24 studies, obesity was a risk factor for ICU admission (OR = 1.21; I<sup>2</sup> = 0%) and invasive mechanical ventilation (OR = 2.05; I<sup>2</sup> = 34.9%) in COVID-19 [38]. A higher BMI carries a higher risk [38,39]. Other meta-analyses also showed an association between obesity and COVID-19 severity and poor outcomes [40–43]; also, excessive visceral adiposity is associated with poor COVID-19 outcomes [41].

A large meta-analysis of 75 studies (N = 399 461; ~55% male)

showed that individuals with obesity were more at risk for COVID-19 positive, >46% higher (OR 1.46; P < 0.0001); for hospitalization, 113% higher (OR 2.13; P < 0.0001); for ICU admission, 74% higher (OR 1.74); and for mortality, 48% increase in deaths (OR 1.48; P < 0.001) [44]. A major concern was expressed by the authors that vaccines may be less effective for the individuals with obesity.

A recent meta-analysis of 22 studies indicated that obesity is associated with an increased likelihood of presenting with more severe COVID-19 symptoms (OR 3.03, P = 0.003; 4 studies, n = 974), developing ARDS (OR 2.89, P = 0.025; 2 studies, n = 96), requiring hospitalization (OR 1.68, P < 0.001; 4 studies, n = 6611), being admitted to an ICU (OR 1.35, P = 0.001; 9 studies, n = 5298), and undergoing invasive mechanical ventilation (OR 1.76, P < 0.001; 7 studies, n = 1558) compared to non-obese patients [45]. However, obese patients had similar mortality rates from COVID-19 as non-obese patients (OR 0.96, P = 0.750; 9 studies, n = 20,597). A more recent meta-analysis of 38 studies with 902,352 COVID-19 patients showed that obesity was significantly associated with an increased risk for ICU admission among COVID-19 patients (pooled effect size = 1.84) [46]. Similar findings were reported by another recent meta-analysis (217 observational studies, N = 624,986) examining the predictive value of chronic diseases for COVID-19 severity and mortality; patients with obesity were at a higher risk of experiencing severe symptoms of COVID-19 (OR 2.63) rather than mortality [47]. Also, a meta-analysis of 12 studies, comprising 405,359 patients, showed that the pooled risk of COVID-19 severity was 1.31 times higher based on both fixed and random effect model among those overweight patients (I<sup>2</sup> 0%) and 2.09 and 2.41 times higher based on fixed and random effect respectively among obese patients (I<sup>2</sup> 42%) compared to healthy individuals [48].

A meta-analysis of 4752 hospitalized adult overweight/obese patients with COVID-19 from 18 sites in 11 countries showed that overweight patients were more likely to require oxygen/noninvasive ventilatory support (random effects adjusted odds ratio - aOR, 1.44) and invasive mechanical ventilatory support (aOR, 1.22) [49]. There was no association between overweight and in-hospital mortality (aOR, 0.88). Similar effects were noted in patients with obesity.

A meta-analysis of 28 studies comprising 112,682 COVID-19 patients showed that those with a high BMI had an elevated risk of mortality (pooled RR 1.33; P < 0.001), with moderate heterogeneity (I<sup>2</sup> = 54.2%) [50]. A positive dose-response association between BMI and mortality was found based on the linear model. However, a significant nonlinear relationship between BMI and mortality was observed. A J-shaped curve was noted, indicating that both underweight and obese patients had a



**Table 2**  
Meta-analyses of studies comparing obese vs non-obese patients with COVID-19 infection.

Author/year	No of studies	Patients (obese vs non-obese)	Outcome	Comments
Sales-Peres et al./2020 [33]	9 (1 prospective, 5 retrospective cohort, 2 cross-sectional, 1 case series)	6577 (2833/3744)	Severe complications: overall pooled event rate 56.2% (random; $P = 0.015$ ; $I^2 = 71.46$ ) for obesity	Pooled event rate was highest for obesity compared to rates for hypertension (46%), diabetes (23.6%), smoking (20%), lung diseases (21.6%), and CVD (20.6%)
Zhou et al./2020 [34]	34 (23 retrospective cohort, 7 case series, 4 surveillance)	16,110 (42% obese)	Pooled OR 1.72 for obesity in pts with severe or fatal COVID-19 when compared to pts with non-severe/fatal COVID-19	Obesity was the most prevalent comorbidity (42%)
Pranata et al./2020 [35]	12 (3 prospective cohort, 9 retrospective cohort)	34,390 (31% obese)	<ul style="list-style-type: none"> <li>● OR 1.73 for composite poor outcome (mortality/severity) of obesity (<math>P &lt; 0.001</math>; <math>I^2: 55.6\%</math>), OR 1.55 for mortality (<math>P = 0.003</math>; <math>I^2: 74.4\%</math>), and 1.45 for severity (<math>P &lt; 0.001</math>; <math>I^2: 5.2\%</math>)</li> <li>● Highest vs reference BMI: adjusted OR 3.02 for composite poor outcome (<math>P &lt; 0.001</math>; <math>I^2: 59.8\%</math>), 2.85 for mortality (<math>P = 0.002</math>; <math>I^2: 79.7\%</math>), and 1.78 for severity (<math>P &lt; 0.001</math>; <math>I^2: 11.7\%</math>)</li> </ul>	Dose-response meta-analysis showed an increased risk of composite poor outcome by aOR of 1.052 for every 5 kg/m <sup>2</sup> increase in BMI. The curve became steeper with increasing BMI
de Siqueira et al./2020 [36]	20 (5 cohort, 1 case control, 2 case series, 1 case report, 6 review, 5 other)	7671 (45% obese)	<ul style="list-style-type: none"> <li>● In 19 of the 20 studies: more severe forms of COVID-19 disease were observed</li> <li>● In 14 of them, there were higher rates of complications among obese vs nonobese pts</li> </ul>	Higher mortality was observed among pts with obesity in 4 publications
Hussain et al./2020 [37]	14 (NR)	403,535 (NR)	<ul style="list-style-type: none"> <li>● MR: 2.7% vs 7.1% (OR 3.68; <math>P = 0.005</math>)</li> <li>● Advanced respiratory support (ARS): 75% with BMI &gt; 25 vs 29% with BMI &lt; 25 (OR 6.98, <math>P = 0.00001</math>)</li> <li>● Critical illness: 39% with BMI &gt; 30 vs 18.1% with BMI &lt; 30 (OR 2.03, <math>P &lt; 0.00001</math>)</li> <li>● ↑ICU admission (OR = 1.21; <math>I^2 = 0.0\%</math>)</li> </ul>	<ul style="list-style-type: none"> <li>● MR reported for 26,507 pts (2451 obese vs 24,056 nonobese) (6 studies)</li> <li>● ARS: 1497 pts (630 vs 867) (5 studies)</li> <li>● Critical illness: 4611 pts (1186 vs 3425) (3 studies)</li> </ul>
Foldi et al./2020 [38]	24 (retrospective cohort; 9 included in meta-analysis)	3279 (1429/1850)	<ul style="list-style-type: none"> <li>● ↑invasive mechanical ventilation (IMV) (OR = 2.05; <math>I^2 = 34.86\%</math>)</li> <li>● COVID-19 pts with composite poor outcome had higher BMI with mean difference 1.12 (<math>P &lt; 0.001</math>)</li> </ul>	6 studies (N = 2770) reported on ICU admission/5 studies (N = 509) reported on IMV requirement
Soeroto et al./2020 [40]	16 (observational: 9 retrospective, 7 prospective)	6690	<ul style="list-style-type: none"> <li>● Obesity was associated with composite poor outcome with OR = 1.78 (<math>P &lt; 0.001</math>)</li> <li>● ORs of severe COVID-19 associated with higher BMI: <ul style="list-style-type: none"> <li>● 2.09 overall OR for severe COVID-19 (<math>P &lt; 0.001</math>)</li> <li>● 2.36 (<math>P = 0.002</math>) for hospitalization</li> <li>● 2.32 (<math>P = 0.001</math>) for requiring ICU admission</li> <li>● 2.63 (<math>P = 0.006</math>) for IMV support, and</li> <li>● 1.49 (<math>P &lt; 0.001</math>) for mortality</li> </ul> </li> </ul>	The association between BMI and obesity on composite poor outcome was affected by age, gender, diabetes, and hypertension
Huang et al./2020 [41]	33 (29 retrospective)	45,650	<ul style="list-style-type: none"> <li>● Severe vs non-severe COVID-19 pts showed higher VAT accumulation with a mean difference of 0.49 for hospitalization (<math>P = 0.011</math>), 0.57 (<math>P &lt; 0.001</math>) for ICU admission and 0.37 (<math>P = 0.035</math>) for IMV support</li> </ul>	
Malik et al./2020 [42]	10 (observational)	10,233	<ul style="list-style-type: none"> <li>● COVID-19 pts with obesity had higher odds of poor outcomes with a pooled OR of 1.88 (<math>P = 0.002</math>; 86% heterogeneity)</li> </ul>	Overall prevalence of obesity: 33.9%
Seidu et al./2020 [31]	9 (8 retrospective, 1 prospective cohort)	4920	<ul style="list-style-type: none"> <li>● Comparing BMI <math>\geq 25</math> vs &lt;25 kg/m<sup>2</sup>, the RRs of severe illness and mortality were 2.35 and 3.52, respectively</li> <li>● In a pooled analysis of 3 studies, the RR of severe illness comparing BMI &gt; 35 vs &lt;25 kg/m<sup>2</sup> was 7.04</li> </ul>	High levels of heterogeneity were partly explained by age (BMI $\geq 25$ kg/m <sup>2</sup> conferred increased risk of severe illness in pts $\geq 60$ years, whereas the association was weaker in pts <60 years)
Chang et al./2020 [43]	16 (observational)	11,390	<ul style="list-style-type: none"> <li>● BMI was higher in pts with severe disease than in those with mild/moderate disease in China (<math>P = 0.0002</math>; <math>I^2 = 75\%</math>)</li> <li>● Elevated BMI was associated with IMV use in Western countries (<math>P &lt; 0.0001</math>; <math>I^2 = 0\%</math>)</li> <li>● There were increased odds of IMV use (OR 2.0; <math>P &lt; 0.0001</math>) and hospitalization (OR 1.4; <math>P &lt; 0.00001</math>; <math>I^2 = 0\%</math>) in pts with obesity</li> </ul>	
Popkin et al./2020 [44]	75 (5 case-control, 33 retrospective or prospective, 37 observational cross-sectional)	399,461	<ul style="list-style-type: none"> <li>● Individuals with obesity had: <ul style="list-style-type: none"> <li>● &gt;46% higher risk for COVID-19 infection (OR = 1.46; <math>P &lt; 0.0001</math>);</li> <li>● 113% higher risk for hospitalization (OR = 2.13; <math>P &lt; 0.0001</math>);</li> <li>● 74% higher risk for ICU admission (OR = 1.74);</li> <li>● and 48% increased mortality (OR = 1.48; <math>P &lt; 0.001</math>)</li> </ul> </li> </ul>	Concern was raised that vaccines may not be as effective in individuals with overweight/obesity
Zhang et al./2021 [45]	22 (cohort)	30,141	<ul style="list-style-type: none"> <li>● Compared to non-obese patients, obesity conferred: <ul style="list-style-type: none"> <li>● more severe COVID-19 symptoms (OR 3.03, <math>P = 0.003</math>; 4 studies, n = 974)</li> <li>● more ARDS (OR 2.89, <math>P = 0.025</math>; 2 studies, n = 96)</li> </ul> </li> </ul>	● Obese patients had similar mortality rates from COVID-19 as non-obese patients (OR 0.96, $P = 0.750$ ; 9 studies, n = 20,597)

(continued on next page)

Table 2 (continued)

Author/year	No of studies	Patients (obese vs non-obese)	Outcome	Comments
Wang et al./2021 [46]	38 (32 retrospective, 5 prospective, 1 NA)	902,352	<ul style="list-style-type: none"> <li>● more hospitalizations (OR 1.68, <math>P &lt; 0.001</math>; 4 studies, <math>n = 6611</math>)</li> <li>● more ICU admissions (OR 1.35, <math>P = 0.001</math>; 9 studies, <math>n = 5298</math>)</li> <li>● increased need for IMV (OR 1.76, <math>P &lt; 0.001</math>; 7 studies, <math>n = 1558</math>)</li> </ul>	Sensitivity analysis showed that the results were robust and stable, with no publication bias detected
Geng et al./2021 [47]	217 (observational)	624,986	<ul style="list-style-type: none"> <li>● Pts with obesity were at a higher risk of experiencing severe symptoms of COVID-19 (OR 2.63)</li> <li>● No significant correlation between obesity (OR 1.19) and death</li> </ul>	<ul style="list-style-type: none"> <li>● Obesity (OR 1.86) was a significant predictive factor for admission to ICU</li> </ul>
Chowdhury et al./2021 [48]	12 (7 cohort, 4 case-control, 1 cross-sectional)	405,359	Pooled risk of COVID-19 severity, compared to healthy individuals:	<ul style="list-style-type: none"> <li>● Significant association between obesity (OR 2.25) and occurrence of ARDS</li> </ul>
Longmore et al./2021 [49]	Data from 18 sites in 11 countries	4752	<ul style="list-style-type: none"> <li>● 1.31 times higher based on both fixed and random effect model among overweight pts (<math>I^2</math> 0%)</li> <li>● 2.09 and 2.41 times higher based on fixed and random effect respectively among obese pts (<math>I^2</math> 42%)</li> </ul>	<ul style="list-style-type: none"> <li>● There was no association between overweight and in-hospital mortality (aOR, 0.88)</li> </ul>
Huang et al./2021 [50]	28 (retrospective cohort)	112,682	<ul style="list-style-type: none"> <li>● Pts with high BMI had an increased risk of mortality (pooled RR 1.33; <math>P &lt; 0.001</math>; <math>I^2</math> 54.2%)</li> <li>● With BMI of 15 kg/m<sup>2</sup> as reference, the RRs for mortality decreased with BMI initially, and this trend continued until a BMI of ~27 kg/m<sup>2</sup> (RR 0.836). The relationship between BMI and mortality was then reversed, and an upward trend was observed with BMI &gt; 27 kg/m<sup>2</sup> (<math>I^2 = 62.3%</math>)</li> </ul>	<ul style="list-style-type: none"> <li>● Similar effects were noted in pts with obesity</li> </ul>
Poly et al./2021 [51]	17 (16 retrospective cohort, 1 prospective)	543,399	<ul style="list-style-type: none"> <li>● Obesity conferred an increased risk of mortality among pts with COVID-19 (RR<sub>adjust</sub>: 1.42; <math>P &lt; 0.001</math>)</li> <li>● The pooled RR for class I, II, and III obesity were 1.27 (<math>P = 0.01</math>), 1.56 (<math>P &lt; 0.01</math>), and 1.92 (<math>P &lt; 0.001</math>), respectively</li> <li>● In subgroup analysis, pts with obesity who were &gt;65 years had a higher risk of mortality (RR: 2.54; <math>P &lt; 0.001</math>)</li> </ul>	This study showed that obesity was associated with an increased risk of death from COVID-19, particularly in pts >65 years
Ho et al./2020 [52]	61 (38 cohort, 2 case-control, 8 cross-sectional and 13 case series)	270,241	Obesity was significantly associated with: <ul style="list-style-type: none"> <li>● more severe disease (OR 3.13, <math>P = 0.005</math>, <math>I^2 = 82.6</math>),</li> <li>● mortality (OR 1.36, <math>P = 0.006</math>, <math>I^2 = 88.5</math>) and</li> <li>● a positive COVID-19 test (OR 1.50, <math>P &lt; 0.001</math>)</li> </ul>	The pooled prevalence of obesity was 27.6% in hospitalized pts

aOR = adjusted odds ratio; ARDS = acute respiratory distress syndrome; ARS = advanced respiratory support; BMI = body mass index; CVD = cardiovascular disease; IMV = invasive mechanical ventilation; MR = mortality rate; NA = not available; NR = not reported; OR = odds ratio; pts = patients; RR = risk ratio; VAT = visceral adipose tissue.

higher mortality than those with normal weight. A BMI of ~27 kg/m<sup>2</sup> appeared to confer the lowest mortality risk. In the sensitivity analysis of studies with data on underweight patients ( $n = 13$ ), the J-shaped relationship between BMI and mortality remained unchanged.

Similar findings were shown by additional meta-analyses (Table 2) [51,52]. In general, meta-analyses indicate that individuals with obesity seem to be at higher risk for serious illness when infected with COVID-19 and obesity seems to play a role in the progression and prognosis of COVID-19, with linear dose-response association between BMI and both COVID-19 severity and mortality; a higher degree of obesity may predict a higher risk [39,53–56]. Obesity as a risk factor may be greater in younger patients [57]. Furthermore, genetic evidence supports higher BMI as a causal risk factor for COVID-19 susceptibility and severity [58].

Importantly, a non-linear association between BMI and the severity of COVID-19 has been demonstrated [59], with obese and underweight persons being at increased risk (see discussion below).

In *summary*, in keeping with the results of individual studies, meta-analyses indicate a strong relationship between obesity, ICU admission, severe COVID-19, disease progression and mortality in patients with COVID-19; the higher the BMI the worse the clinical outcomes.

### Severity of COVID-19 illness

Overweight and obesity are independent risk factors of severe illness and respiratory failure in COVID-19 patients.<sup>23</sup> In a retrospective analysis of 140 COVID-19 patients with ARDS admitted to ICU who were

compared with 247 ‘other ARDS’ patients, BMI was higher in COVID-ARDS patients (median 28 vs 25 kg m<sup>-2</sup>,  $P < 0.0001$ ) [60]. More patients with overweight (BMI 25–29.9 kg/m<sup>2</sup>) and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) in COVID-ARDS group were admitted to ICU (49% vs 33% and 29% vs 16%, respectively;  $P < 0.0001$ ). Strong associations were found between COVID-ARDS and male sex and with patients with overweight/obesity. As mentioned, a dose-response meta-analysis showed that increased BMI was associated with poorer outcome in COVID-19 patients; the curve became steeper with increasing BMI [35].

Among 383 hospitalized COVID-19 patients, compared with normal-weight patients, patients with overweight had 1.84-fold odds of developing severe COVID-19 ( $P = 0.05$ ), while patients with obesity were at 3.40-fold odds of developing severe disease ( $P = 0.007$ ), after adjusting for age, sex, other comorbidities, and drug treatment [61]. Also, men with obesity were at increased odds of developing severe COVID-19 (OR 5.66,  $P = 0.003$ ). In another study, obesity was associated with ~6-fold increased risk and need for invasive mechanical ventilation [62]. A study of 100 patients with COVID-19 pneumonia indicated that patients with obesity ( $n = 29$ ) required longer hospitalization, more intensive and longer oxygen treatment, and had longer virus-shedding [63]. A study of 770 patients reported that obesity was associated with an increased risk of critical illness with higher rate of ICU admission or death compared to normal-weight patients (RR = 1.58,  $p = 0.002$ ) even after adjusting for age, race and troponin level [64].

## Complications

In patients dying with COVID-19 in Italy, particularly in those aged <60 years, obesity was shown to be associated with more non-respiratory complications, particularly shock (aOR 1.54; aOR 2.00 in young adults) and acute renal failure (aOR 1.33; aOR 2.37 in young adults) [65]. As mentioned, a meta-analysis of 9 studies ( $N = 6577$ ) indicated that COVID-19 patients with obesity had the highest overall pooled-event rates for severe complications (56.2%,  $p = 0.015$ ) [33].

However, results are not consistent across studies regarding particular complications. As mentioned, a study of 504 patients, stratified according to BMI, indicated that COVID patients with overweight (RR 2.0) and obesity (RR 2.4) had an increased relative risk for intubation, but obesity did not affect rates of acute kidney injury, acute cardiac injury, or ARDS [21]. Nevertheless, increased mortality was observed in patients with overweight (RR 1.4) and obesity (RR 1.3) compared with those with normal BMI.

## Mortality

As mentioned, most of the studies and meta-analyses have reported a significantly higher mortality-risk in COVID-19 patients with overweight and obesity compared with patients with normal BMI [7,13,21,24,25,35–37]. In a French prospective study including 5795 patients aged 18–79 years, obesity doubled mortality in patients hospitalized with COVID-19; OR 1.89 for BMI 30–35, 2.79 for BMI 35–40 and 2.55 for BMI > 40 kg/m<sup>2</sup> (18.5–25 kg/m<sup>2</sup> was the reference-class); this increase held true for all age-groups [66]. As mentioned, recent analysis of COVID-mortality related factors in various countries indicated that obesity was the second-best predictor of death rate after the GDP [9].

## Pathogenetic mechanisms

Some investigators suggest that adipose tissue is playing crucial role and therefore it is necessary to evaluate fat-mass and not simple BMI. A prospective study of 22 patients, affected by COVID-19 pneumonia and admitted to the ICU, discerned two groups, lean ( $n = 10$ ) and obese ( $n = 12$ ), according to percentage of fat mass (FM%) [67]. They noted that patients with obesity had a reduced survival.

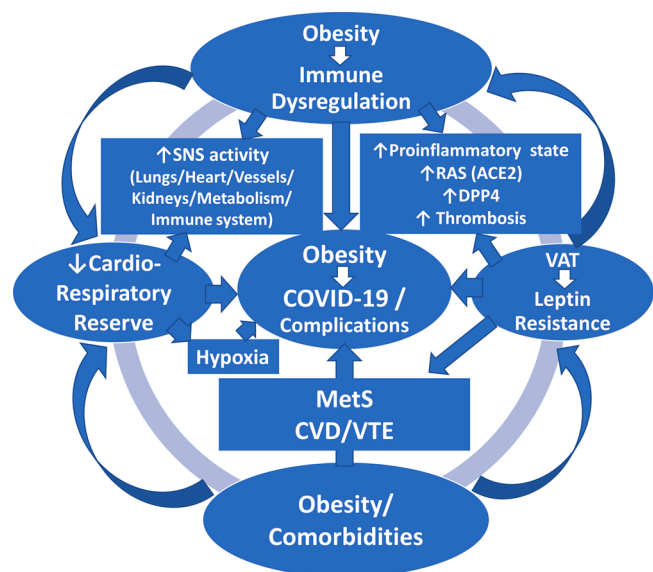
Other investigators have suggested that *visceral adipose tissue* (VAT) fat is more specifically the marker of worse clinical outcomes in patients

with COVID-19 [68,69]. In a retrospective study of 150 COVID-19 patients undergoing a chest computed tomography (CT) scan, VAT was higher in patients requiring intensive care ( $P = 0.032$ ) [70]. Multivariate analysis showed that Lung Severity Score and VAT were independently associated with the need of intensive care (OR: 1.262;  $P = 0.005$  and OR: 2.474;  $P = 0.046$ , respectively). A meta-analysis of 5 studies comprising 539 patients showed that visceral, but not subcutaneous, adiposity was associated with increased COVID-19 severity (OR 1.9,  $P = 0.002$ ;  $I^2$  49.3%) [69]. Other investigators have attributed worse prognosis in ARDS patients to higher visceral/subcutaneous adipose tissue ratio, rather than just higher VAT [71,72]. Furthermore, the cardiometabolic risk can also be predicted by other unhealthy fat distribution indicated by impaired ability to expand subcutaneous fat in the lower part of the body, in the gluteofemoral region and in the legs [73]. Such pattern of lower-body fat mass distribution is equally important to a high amount of visceral fat mass as a determinant of cardiometabolic diseases. In a similar context, data from the UK Biobank have indicated that anthropometric indices that are more sensitive to adipose volume and its distribution than BMI, as well as concomitant cardiometabolic disorders, are associated with higher odds of COVID-19-related mortality [74].

Regarding the pathophysiology underlying the suggested link between obesity and severity of COVID-19, investigators consider it multifactorial (Fig. 1). One aspect is attributed to the association of obesity with complement-system hyperactivation, chronic inflammation, and presence of comorbidities proposed in turn to be risk-factors for COVID-19 poor prognosis [75]. A more specific link may relate to the fact that VAT is capable of secreting pro-inflammatory cytokines which might augment the deleterious effects of COVID-19 [76]; VAT produces interleukin (IL)-6 at 2 to 3-fold higher levels than subcutaneous fat [77,78]; IL-6 levels have been found to be increased in COVID-19 non-survivors [79]. Furthermore, as COVID-19 has been shown to infect cells through an angiotensin-converting enzyme 2 (ACE2)-dependent mechanism, this receptor is also expressed by fat, including ectopic reservoirs, e.g., epicardial adipose tissue [80], indicating an additional direct proinflammatory role of COVID-19 in the adipose tissue that may thus possibly contribute to such detrimental effects of the virus. Some investigators have ascribed the elevated risk for hospital admission in COVID-19 patients with obesity to mechanisms involving impaired glucose and lipid metabolism [11]. In this context, a study of 640 COVID-19 patients, indicated an upward linear trend in the likelihood of COVID-19 hospitalization with increasing BMI, which was little affected after adjustment for several covariates [11]. Interestingly, metabolic dysfunction-associated fatty liver disease has been suggested as a surrogate for COVID-19 severity due to the accumulation of associated metabolic changes, representing a higher risk than obesity per se for COVID-19 severity [81].

There is evidence of smoldering *chronic inflammation* during obesity in the absence of an apparent infection or a specific autoimmune disease process [82–84]. In this context, there are data that the Nod-like receptor (NLR) family of innate immune-cell sensors, such as the pyrin domain-containing-3 (Nlrp3, also known as cryopyrin) inflammasome, senses obesity-associated danger-signals and contributes to obesity-induced inflammation and insulin-resistance [85]. Furthermore, COVID-19 leads to activation of both innate and adaptive immunity after recognition of viral antigens and produces a large amount of pro-inflammatory cytokines even in moderate cases; in some patients, this activation becomes exuberant and leads to a ‘cytokine storm’, with ensuing severe lung injury, multiple-organ failure and, ultimately, death [86,87]. In this framework, the co-existence of the two conditions, obesity and COVID, may lead to hyperinflammation which can exacerbate these deleterious processes with dire consequences [84,87]. The findings of a recent study support the involvement of systemic inflammatory pathways in obesity-associated severe COVID-19 infection, especially in younger (<65 years) patients, as reflected by increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [88].





**Fig. 1.** The schema illustrates the pathogenetic mechanisms involved in the interplay between obesity and COVID-19 infection (see text for discussion). ACE = angiotensin converting enzyme; CVD = cardiovascular disease; MetS = metabolic syndrome; DPP4 = dipeptidyl peptidase 4; RAS = renin-angiotensin system; SNS = sympathetic nerve system; VAT = visceral adipose tissue; VTE = venous thromboembolism.

Specifically, in one cohort of this study ( $n = 1202$ ), obesity was associated with increased likelihood of mechanical ventilation or death (odds ratio-OR 1.73,  $P < 0.001$ ) and higher peak of CRP compared with nonobese patients. The estimated proportion of the link between obesity and ventilation or death mediated by CRP was 0.49 ( $P < 0.001$ ), more pronounced in patients younger than 65 years ( $P < 0.001$ ). Similar results, albeit more moderate but consistent, were reported for peak ESR. Findings were replicated by a larger second cohort ( $n = 2626$ ).

Another parameter that has been suggested as an important factor in weakening immune response and thus predisposing patients with obesity to the COVID-19 ailments is the leptin-resistant state. *Leptin* is a cytokine produced in adipose tissue in amounts commensurate with adipose tissue mass. Leptin, among other functions, regulates metabolic homeostasis but also supports immune function by modulating both innate and adaptive immune responses [89]. However, obesity is characterized by leptin-resistance which leads to increased leptin levels, albeit with failure to promote its inherent actions that modulate a host of physiologic processes. Thus, leptin-resistance confers dysregulation of cytokine production and increased susceptibility toward inflammatory responses and infectious and viral diseases [90]. Furthermore, diminished leptin-signaling may enhance immunosuppression by T-regulatory cells and render the host immunity incompetent to manage pathogens' attack and invasion, resulting in accelerated infection and attenuated vaccine-specific antibody response [91]. Interestingly, there is evidence that leptin is not only expressed in adipose tissue but also in several organs, including the lungs [92]. An important role of leptin-signaling in the lungs has been proposed under physiological conditions and in disease, where leptin is a protective cytokine for lung infections. However, elevated levels, as in patients with obesity, may compromise this protection and allow for lung disease to develop.

The European Association for the Study of Obesity (EASO) recently discussed the immunological perturbations and alterations in the renin-angiotensin-aldosterone system (RAAS) in patients with obesity and COVID-19, and how these impairments may underlie the increased susceptibility and more dismal outcomes of COVID-19 in obese patients [93]. Among these factors, important role is played by an impaired immune response to infectious agents, increased viral load and life-cycle noted in individuals with obesity, obesity-associated increased

activation of the systemic and local adipose tissue RAAS with its component of ACE2 serving as the facilitator of viral entry into the host cells [94], all leading to an interplay between obesity and COVID-19 that promotes susceptibility, progression and unfavorable outcome in individuals with obesity. In the context of increased viral load, individuals with obesity may exhibit greater viral shedding, indicating potentially great viral exposure in families or groups with overweight/obese members [76].

In addition to adipose tissue overexpressing the receptors (ACE2) and proteases for viral entry, obesity may also compromise motile cilia on airway epithelial cells and impair functioning of the mucociliary escalators (the apparatus of mucus and cilia responsible for expelling of mucus from the respiratory tract), thus reducing the clearance of severe COVID-19 [95].

Other investigators have stressed the potential role of an increased sympathetic nervous system (SNS) activity that characterizes several comorbidities, including obesity, which may exert significant deleterious effects on COVID-19 patients, through actions on the lungs, heart, blood vessels, kidneys, metabolism, and/or immune system [96–98]. Furthermore, COVID-19 can certainly increase SNS discharge, through changes in blood gases (hypoxia, hyperpnea), ACE1/ACE2 imbalance, immune/inflammatory factors, or emotional distress. Thus, an interplay between obesity- and COVID-19-induced SNS overactivity, leading to a vicious circle between COVID-19 and obesity and/or other comorbidities, could offer an explanation for a potential link between obesity and COVID-19.

Obesity also affects cardiorespiratory reserve by reducing forced expiratory volume and forced vital capacity [76]. Thus, obesity leads to compromised lung function and furthermore to poor response to mechanical ventilation, with consequential high risk of severe illness and mortality from COVID-19 [99].

Furthermore, it has been documented that obesity enhances venous and pulmonary thromboembolism [100], while COVID-19 also predisposes patients to arterial and venous thrombosis [101]. Importantly, in COVID patients, pulmonary embolism may occur even in the absence of a recognizable deep venous thrombosis and may be due to *pulmonary arterial thrombosis* rather than embolism [102]. Thus, the thrombotic risk may be greatly exacerbated in patients with obesity and COVID-19 and may raise mortality, particularly in critically-ill patients.

In addition, it should be noted that obesity, and more so, extreme obesity (e.g.,  $BMI > 40 \text{ kg/m}^2$ ), may compromise care for patients with obesity managed in the ICU, as these patients are more difficult to image, ventilate, nurse, and rehabilitate [76]. Prone positioning, known to ameliorate patient aeration and oxygenation, presents more challenges and possible complications in patients with obesity [103,104].

Importantly, one needs to also take into account that individuals with obesity have many associated *comorbidities* in the form of metabolic syndrome and beyond [105], which greatly increase their health risk and invite a variety of metabolic, CV, respiratory and other complications when these patients are afflicted by COVID-19 [106,107].

Finally, the two diseases (obesity and COVID-19) appear to be interconnected, as the COVID-19 pandemic has been shown to exacerbate the obesity epidemic among adult and pediatric populations due to physical inactivity, stress and unhealthy diet [108–110]; on the other hand, obesity and impaired metabolic health are enhancers of severe COVID-19 infection [109]. Also, obesity might adversely affect the efficacy of COVID-19 vaccines due to reduced memory immune responses in these individuals leading to diminished long-term protection against re-infections [111]; hence, investigators propose strategies for the prevention and treatment of obesity and impaired metabolic health in the community during the COVID-19 pandemic [109].

On another note, *long COVID* emerges as an important post-acute sequela of COVID-19 infection, comprising a broad array of incident pulmonary and extrapulmonary clinical manifestations [112], and in this context, an excess burden of several metabolic disorders becomes evident, including lipid metabolism (HR 12.32), diabetes mellitus (HR

8.23) and obesity (HR 9.53) [113]. On the other hand, high BMI and previous pulmonary disease have been indicated as risk factors for the development of long COVID [114]. In addition, obesity has been associated with a greater number of long-term post-COVID symptoms and poor sleep quality in hospitalized COVID-19 patients [115].

### Normal-weight obesity

There are individuals who have excessive body fat, particularly VAT, despite a normal BMI [116]. These individuals may have a metabolic syndrome-like profile (higher levels of insulin and/or insulin-resistance, diabetes, hypertension, hypertriglyceridemia) and higher risk of atherosclerotic CVD, while their adipose tissue, usually VAT, may express higher levels of pro-inflammatory cytokines [28,76]. As mentioned, evaluating percentage of fat mass, rather than BMI, in COVID-19 patients, a number of patients with normal BMI could actually have an excess of adipose tissue and therefore have an unfavorable outcome similar to the obese patients [67].

Importantly, ectopic obesity, localized beyond the subcutaneous adipose tissue where there is increased local fat distributed in visceral, perivascular, and epicardial adipose tissue, seems to also promote chronic proinflammatory, prothrombotic, and vasoconstrictive states, which can manifest as insulin-resistance, diabetes, hypertension, CVD and immunocompromised state [13,76,117,118]. As mentioned, VAT also promotes increased mortality among critically-ill patients with ARDS [71]. In this context, ectopic fat and COVID-19 seem to share a common link converging in the upregulation of proinflammatory, prothrombotic, and vasoconstrictive states, thus enhancing the cumulative deleterious effects of both diseases (obesity and COVID).

In the context of metabolically unhealthy normal weight individuals, it is important to discern other phenotypes that characterize this population. One such phenotype is the *lipodystrophy*-like phenotype noted in lean persons with increased glucose, dyslipidemia, and hypertension, parameters commonly used to identify the metabolic risk, that may be more strongly associated with a relatively low gluteofemoral- and leg-fat mass than with high subcutaneous abdominal fat mass, visceral obesity, or fatty liver; also this phenotype is strongly characterized by reduced insulin secretion and insulin resistance, low cardiorespiratory fitness, and increased carotid intima media thickness (cIMT), a surrogate of atherosclerosis [119]. Genetic analyses indicate that metabolic risk appears to be determined by different pathways in normal weight and obese individuals, with all such findings having several implications for clinical and drug interventions. Thus, compared with individuals who are of normal weight and metabolically healthy, those who are of normal weight but metabolically unhealthy (~20% of the normal weight adult population) have a >3-fold elevated risk of all-cause mortality and/or CV events [119]. Importantly there is evidence that lipodystrophy might result in nonalcoholic fatty liver disease (NAFLD) [120,121]. NAFLD is not only associated with liver-related complications, but also with adverse cardiometabolic outcomes [122]. Within this pathogenesis [122,123], NAFLD may increase the risk of complications in COVID-19. In this context, a recent large study showed that NAFLD was associated with a higher risk of COVID-19 infectivity and severity among 74,244 individuals who underwent SARS-CoV-2 testing [124].

### Underweight

In addition to obesity, underweight also confers a health risk [125]. According to a large cohort study, a U-shaped association between BMI and all-cause mortality was observed in men and women. Compared with the normal-BMI group, an increased risk was found both in the highest BMI ( $\geq 35$  kg/m<sup>2</sup>, HR 2.13 in men and 1.60 in women), driven by CVD and cancer, and in the lowest BMI ( $< 18.5$  kg/m<sup>2</sup>, HR of 2.57 in men and 1.40 in women) [125], driven by respiratory diseases independently from smoking status.

As mentioned, a retrospective study of 6916 patients with COVID-19 also pointed to a J-shaped association between BMI and risk for death, even after adjustment for obesity-related comorbidities [13]. In particular, the risk ratio (RR) for death was 1.81 for BMI  $< 18.5$  kg/m<sup>2</sup>, 0.91 for BMI 25–29 kg/m<sup>2</sup>, 1.26 for BMI 30–34, 1.16 for BMI 35–39, 2.68 for BMI 40–44 and 4.18 for BMI  $\geq 45$  kg/m<sup>2</sup>, compared to reference BMI of 18.5–24 kg/m<sup>2</sup>. This J-curve relationship was similar when patients were stratified by age and gender, albeit with lack of data for underweight younger ( $< 60$ ) patients. A J-shaped association between BMI and death or intubation was also revealed by another study (N = 2466), with an inflection point of predicted risk at a BMI of 30 kg/m<sup>2</sup>; patients who were underweight and those with BMIs above the overweight range were more likely to be intubated or die than those who were simply overweight [25]. However, most studies do not provide data for the underweight, while a smaller study refutes these findings [61].

Regarding the mechanism of underweight-conferred health risk, the associated lipodystrophy, when present, may provide one plausible explanation. Lipodystrophies are hypoleptinemic disorders characterized by fat loss, severe insulin resistance, hypertriglyceridemia, and ectopic fat accumulation [126]. Non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH) are features of lipodystrophy [120, 126] and within this pathogenesis [122,123], lipodystrophy may increase the risk of complications in COVID-19 [127,128].

In summary, BMI is a strong predictor of clinical outcomes in the era of the COVID-19 pandemic. In this context, one could stress the deleterious liaison formed between obesity and COVID-19, especially in the younger population ( $< 60$  years), but could not also ignore the harmful effect of the underweight state in this relationship and therefore this risk could be depicted as a J-curve, where the strongest evidence, at least for cardiorespiratory problems, lies with the overweight/obese/severely obese, but reliable evidence also points to the risk incurred in the underweight individuals (Fig. 2).

### Conclusion/perspective

Obesity or excessive localized fat, like VAT, may pose a significant risk in patients with COVID-19. This risk factor apparently reduces protective cardiorespiratory reserve and enhances immune dysregulation that paves the way to disease progression to critical illness and organ failure. It also appears that obesity is an independent risk-factor for susceptibility to COVID-19, disease severity, complications and mortality. The risk is higher for younger ( $< 60$  years) individuals, where the age-related lower risk observed in normoweight individuals seems to

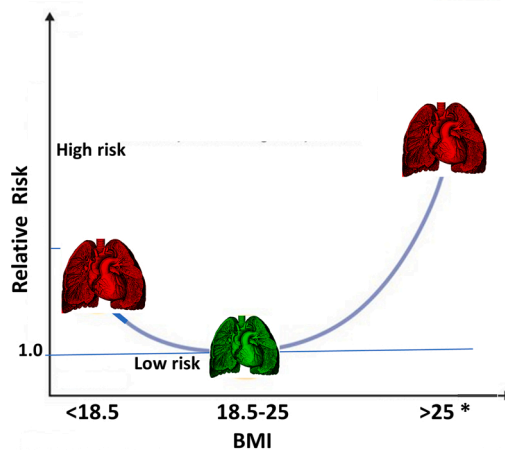


Fig. 2. The graph depicts the J-curve pattern of the relationship between body mass index (BMI) and risk of COVID-19 infection, severity and cardiorespiratory complications. \* kg/m<sup>2</sup>.

be cancelled-out in patients with obesity. Less, albeit solid, evidence also exists for a higher risk of COVID-19 incurred in individuals who are underweight. Thus, the relationship of COVID-19 and BMI seems to follow a J-curve pattern. However, ectopic obesity in individuals who are either normoweight or overweight/obese needs also to be taken into consideration, as the accumulation of fat in visceral, perivascular, and epicardial adipose tissue, seems to also promote chronic proinflammatory, prothrombotic, and vasoconstrictive states with their attendant adverse clinical outcomes in COVID-19 patients.

Expression of enzymes by adipose tissue, like ACE2, that facilitate viral entry, as well as multiple other adipose tissue-related mechanisms may contribute to development and progression of COVID-19, via complex interactions between the immune system and adipose tissue [129]. The overexpression of inflammatory adipokines from VAT can affect the immune response, impair chemotaxis, and alter macrophage differentiation. It is therefore logical that investigators have proposed therapeutic strategies targeting the adipose tissue as a countermeasure. However, some options, like ACE2 blockade, may prove to be a double-edged sword [130].

Human dipeptidyl peptidase 4 (DPP4), a transmembrane protein, was identified as a functional receptor for the spike protein of the Middle East respiratory syndrome (MERS)-coronavirus [131], and may have a similar function in COVID-19 [129]. DPP4 has been identified in human adipose tissue and is associated with obesity-related diabetes; its inhibition increases glucagon-like peptide-1 secretion, and improves insulin sensitivity and glucose metabolism within fat cells. DPP4 inhibition could therefore play a role in the immune response to COVID-19 by reducing inflammation via suppression of T-cell proliferation and the secretion of proinflammatory cytokines, such as IL-6 [129,132]. Thus, the use of DPP4-inhibitor drugs (gliptins) in patients with COVID-19 with or without diabetes, including patients with obesity, might reduce the virus entry and replication into the respiratory system and prevent or mitigate cytokine-storm and lung inflammation in these patients [133].

Individuals with obesity have been found to have higher levels of tumor-necrosis factor-alpha (TNF- $\alpha$ ), IL-6 and other cytokines, all of which are produced by macrophages emanating from the adipose tissue. Hence, the suggestion that TNF- $\alpha$  and/or IL-6-inhibitors might be of value in these patients to counteract these proinflammatory effects [134]. As mentioned, leptin-resistance characterizes the overweight/obese state, and is implicated in dysregulation of cytokine production and increased susceptibility toward inflammatory responses and infectious diseases [90]. Whether the antiobesogenic effect of agents, like melatonin, could restore leptin-resistance in individuals with obesity remains to be seen [135].

With regards to therapeutic strategies addressing the ectopic fat, epicardial fat has been shown to respond to thiazolidinediones, glucagon-like peptide-1 receptor agonists, DPP4-inhibitors and statins [136]. Abdominal VAT may respond to statins, metformin, sibutramine, orlistat, growth-hormone-releasing hormone analogue (tesamorelin), melatonin, etc.; however, there remain several important issues with these agents that relate to side-effects, inefficacy, rebound effect, etc [137]. However, these are not agents that could be used in the setting of an acute infection, like COVID-19, except perhaps for DPP4-inhibitors and statins [133,138]. They may be considered in the big picture of obesity management to normalize regulatory and cardiometabolic abnormalities associated with obesity and to complement dietary and exercise strategies. According to a recent systematic review on the role of nutrition in COVID-19 susceptibility and severity of disease, there is strong evidence that prevention of obesity and type 2 diabetes will reduce the risk of serious COVID-19 outcomes [139].

#### Author contributions

All authors contributed to the preparation of this manuscript and approved the final version. ASM conceived and designed the project,

curated/analyzed the data, wrote the initial draft, and edited the final product; AAM conducted literature search, constructed the Tables and edited/revised the manuscript; TAM conducted literature search, designed the Figures and edited/revised the manuscript; NEA conducted literature search, edited/revised the manuscript; HM supervised the project, analyzed the data, reviewed, revised, edited and approved the manuscript.

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#### Conflict of interest

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