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Obesity Paradox and Critical Covid -19 Disease: Debunking a Myth

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Abstract

Introduction: Short-and long-term morbidity and mortality associated with Covid-19 disease remains high. Obesity is a recognized risk factor for symptomatic Covid-19, disease, hospitalization, critical Covid-19 disease, and fatal organ dysfunctions. Whether obesity is causally linked with mortality of critically ill Covid-19 patients is an unresolved question.

Methodology: This narrative review describes the prevalence of obesity in critical Covid-19 disease, highlights the pathophysiologic mechanisms and clinical interplay linking the two pandemics and critically appraises the epidemiologic data proving for or against the existence of a survival benefit of obese ICU Covid-19 patients (obesity paradox).

Results: Most observational studies reported that obesity confers a survival advantage among patients with critical Covid-19 disease (muti-organ failure), or organ failure associated with Covid-19 infection (acute respiratory distress syndrome or acute kidney injury). However, few dose-response meta-analyses or analyses of nation-wide population studies found a linear (J-shaped curve) or nearly linear (U-shaped curve) association between obesity/overweight (measured by BMI) and risk of all-cause mortality of critically ill Covid-19 patients. Moreover, other cohort analyses found no association between BMI and all-cause Covid-19 mortality. The spurious association of BMI and mortality risk cannot be explained by proposed biologic mechanisms but is likely a consequence of clinical and methodological limitations of observational studies.

Conclusions: There is no prove of an obesity paradox. Obesity should be considered a negative prognostic factor for critically ill Covid-19 patients. More aggressive prevention (hygienic measures, vaccination), timely recognition of progressive Covid-19 disease, and early start of critical care dominant treatment patterns for organ dysfunctions should be employed.

Keywords: Covid-19; Mortality; Obesity; Survival paradox.

Introduction

The ongoing Covid-19 pandemic created an unprecedented health crisis worldwide. The WHO reported 760.360.956 confirmed cases of Covid-19 resulting in 6.873.477 deaths as of 14 March 2023. Compared to the first wave of the pandemic, Covid-19 related morbidity and mortality improved during subsequent waves [1-3]. Numerous factors have contributed to the declining incidence of critical Covid-19 disease including the introduction and widespread use of vaccines, high prevalence of infection-induced immunity, increased availability of effective outpatient and specific in-hospital treatments and changes in the case mix of the patients and in the load and shedding

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of variants of Covid-19. Nevertheless, Covid-19 was the third leading cause of death in the USA during the height of the pandemic, surpassed only by cardiovascular diseases and cancer.

Covid-19 disease is a heterogeneous disorder regarding individual susceptibility, risk factors, clinical manifestations, and patients´ short and long-term prognosis. During the initial course of the pandemic the Center for Disease Control and Prevention listed obesity (BMI values above 30 kg/m²) among 12 conditions with epidemiologic evidence of an increased risk for Covid-19 disease. Nearly two thirds (63.5%) of more than 900,000 US hospitalizations due to Covid-19 were attributed to cardiometabolic disease [4]. Top risk factors were obesity and obesity related conditions (chronic arterial hypertension, type 2 diabetes mellitus, hyperlipidemia, chronic kidney disease).

Impact of obesity on the course of Covid-19 disease

The onset and progression of Covid-19 infection to a more severe and critical stage depends on a broad spectrum of factors. Amongst them are individual susceptibility factors (older age, male gender, genetic disposition, ethnicity), comorbidities, medical treatments (immunosuppressants), characteristics of the virus strain and vaccination status [5].

Numerous meta-analyses and large-scale nationwide data analyses underline the increased risk for obese patients. They were more susceptible to Covid-19 infection, more likely to be hospitalized and more likely to progress to higher categories of disease severity. In the subgroup of obese patients more potentially fatal respiratory and extrapulmonary organ dysfunctions were observed [6]. In the retrospective analyses by Lighter et al. patients aged less than 60 years with obesity class 1 (BMI 30-34,9 kg /m²) or class 2-4 (BMI≥35 kg/m²) were 1.8 or 3 times more likely to be admitted to intensive critical care [7]. A systematic review of 75 studies revealed that obese individuals, compared to people with normal weight, were 113% more likely to be hospitalized, 74% more likely to be admitted to the intensive care unit, and 46% more likely to die [8].

Up to one third of hospitalized high-risk patients contracted critical Covid-19 disease. These patients very often presented with multiple organ failure which portends a poor prognosis [9]. The most common form of organ failure was the Acute Respiratory Distress Syndrome (ARDS) in up to three quarters of ICU Covid 19 patients. The need for mechanical ventilation is a known mayor risk factor. During the pandemic, non-invasive respiratory support modalities were used with increasing frequency. Two thirds of the critically ill patients with Covid-19 required vasopressors for cardiogenic or septic shock and about 20-30% needed renal replacement therapy [10-14].

A recent meta-analysis estimated the case fatality rate for mechanically ventilated Covid-19 patients to be approximately 45% [15]. Covid-19 acute kidney injury severe enough to necessitate renal replacement therapy was associated with hospital mortality over 60% [10]. Obese ICU patients needed more and longer organ support therapies, and higher BMI categories were associated with higher in -hospital mortality [16].

Obesity prevalence and Covid-19 death rates

Epidemiological studies found an association between pooled obesity prevalence rates and progressively increasing Covid-19 disease severity. This association was stronger in ICU patients compared to pooled obesity prevalence rates in the background general population [17-19].

The Covid-19 death rates were more than 10-times higher in countries such as USA, United Kingdom or Mexico with an overweight/obesity prevalence rate of more than 50% of adults compared to countries such as Vietnam, Japan or Bangladesh where fewer than 10% of the general population are overweight/obese [8].

The Covid-19 pandemic disproportionally affected racial groups and ethnic minorities with higher rates of death in African American, Native American, and Latino communities. These disparities of Covid-19 outcomes may arise both from high prevalence of chronic cardio-metabolic conditions and from lower access to healthcare [20].

Potential mechanisms linking obesity and critical Covid-19 disease

Currently, the mechanisms responsible for the greater risk of obese patients for potentially fatal critical Covid-19 disease are largely unknown. However, experience from other viral infections like influenza point to potential mechanisms in Covid-19 disease. The higher expression of angiotensin-converting enzyme 2, a functional receptor for Covid-19 invasion in adipose tissue, may lead to prolonged viral shedding and exposure in patients with obesity. It may be a critical factor increasing the susceptibility to and the risk of progression of Covid-19 to critical illness. Obesity driven low grade systemic inflammation, aberrant cytokine activation, decreased adiponectin and increased leptin secretion, may result in dysfunction of innate and adaptive immunity, and metabolic and cardiac dysfunction. Aggravation of endothelial dysfunction in obese Covid-19 patients may impair organ perfusion and cause a procoagulant state resulting in both macro- and microvascular thrombotic events. Obese people are more likely to have chronic diseases that may be an additional risk factor for Covid-19 severity such as diabetes, heart disease, or kidney disease. Obesity-induced changes of the mechanical properties of the lungs and chest wall predispose obese patients to respiratory failure in the case of pulmonary infections. Other proposed mechanisms are vitamin D deficiency induced immune dysregulation and the bidirectional effects of organ dysfunction on the function of other organs (organ cross-talk) [21-23].

Obesity paradox and critical Covid-19 disease

In the general population the association between obesity and premature mortality is well-known. Among certain ICU cohorts of patients with a variety of chronic diseases, observational studies suggest that obesity confers a survival advantage, termed obesity paradox. However, it is important to note that in all studies reporting a survival benefit of obesity in critical illness, the obesity paradox has been discovered using statistical analyses of non-randomized cohorts. Observational studies reveal potential associations, but they do not prove causality. The debatable evidence for the existence of an obesity paradox in critically ill patients conjured the notion that overweight or even obesity was protective by some unknown biological mechanisms. Even though the concept seems reasonable, the daily practice of intensivists caring for critically ill patients challenges the idea. Moreover, the conflicting results of observational analyses did not result in a revision of intensive care support recommendations for obese patients [24,25].

Critical illness syndromes, like critical Covid-19 disease, aren´t characterized by histologic features, genetic mutations, microbiological cultures, or serologic tests, but rather, by collections

of signs and symptoms of organ dysfunction that together paint the picture of a clinically recognizable entity. Critical Covid-19 disease is not only heterogeneous *per se* but also in its temporal progression through different discernible phases. Moreover, there is tremendous heterogeneity in the host response to Covid-19 from one individual to the next. This situation is aggravated by wide variations across observational studies regarding the diagnosis of Covid-19 illness severity and criteria to identify patients requiring intensive care. These heterogeneities clearly resonate the day-to-day experience of physicians caring for critically ill patients with Covid 19 who exhibit substantial variation in their clinical courses and outcomes.

Studies analyzing the association of BMI and mortality of obese critically ill Covid-19 patients reported remarkable inconsistencies.

Dose response meta-analyses found a strong positive dose -dependent nonlinear (J-shaped or U shaped) relationship between BMI categories (ranging from underweight to obesity Class III) and in-hospital mortality of patients with critical Covid-19 disease [26,27,19,28-31]. These dose-response curves indicated that both underweight and overweight or obesity was associated with a higher mortality rate than normal weight (J-shaped curve). This observation was also found in those with BMI values near the junction from normal weight to overweight (26 /27 kg/m²). These dose-response analyses clearly reject the concept of an obesity paradox for ICU Covid-19 patients. There is a grey zone regarding patients who are just above the threshold between normal weight and overweight. Slight overweight does not necessarily indicate an increased health risk in the general population. Two systematic reviews concluded that the existence of an obesity paradox cannot be confirmed for this subgroup of individuals [18,32].

Nationwide observational cohort studies, register analysis single center cohort analyses or meta-analyses reported that obesity did not affect hospital mortality of critically ill Covid-19 patients [33-36].

Other studies found that Covid-19 patients admitted to the ICU with moderate obesity (BMI 30-39 kg/m²) had a lower risk of death than normal weight individuals [37], particularly among those critically ill patients with Covid-19 disease who were less than 45 years old [36].

The exact mechanisms for the puzzling paradox remain unclear. Controversial explanations for the existence of an obesity paradox in critical Covid-19 disease ranged from true survival benefit by increased stamina in obese critically ill patients to fake statistics.

Hypothesis 1: The obesity paradox is a real survival benefit: biological mechanisms

Numerous potential biological mechanisms that may contribute to a better prognosis of ICU patients with Covid-19 disease include the following [38-41]:

a) High energy stores and a better nutritional status of obese Covid-19 patients could counteract catabolic stress and energy consuming situations (ARDS, sepsis, AKI) and withstand the drop in calorie intake that usually occurs when critically ill patients are admitted to the ICU. Protein and calorie malnutrition as well as involuntary weight loss may result in immunodeficiencies associated with the higher risk of severe bacterial infections.

b) Hypertension secondary to activation of the renin-angiotensin-aldosterone system and sympathetic nervous system is common in obese patients. This may have protective hemodynamic effects and reduce the need for fluid and vasopressor support during circulatory failure.

c) The chronic inflammatory pre-conditioning and the anti-inflammatory immune profile of obese patients may provide resistance to critical illness. Obese patients are at high risk for thromboembolisms and receive more aggressive heparin prophylaxis which inhibits both systemic inflammation and lethal thrombotic events.

d) Higher levels of circulating lipids in obese Covid-19 patients may result in more effective binding of endotoxins, thereby removing an important inflammatory trigger and providing an additional explanation for the survival benefit of obese patients with critical Covid-19 disease.

e) High serum adiponectin has been associated with weight loss, low skeletal muscle mass, low muscle density, and poor physical functioning. By contrast obesity is associated with low circulating adiponectin levels.

None of the proposed biological mechanisms could convincingly explain the large inconsistency of data obtained by observational studies. Measurements of circulating levels of various inflammatory cytokines, including the anti-inflammatory mediators interleukin 18 and interleukin 1-receptor antagonist in critically ill Covid-19 patients, found no differences between obese and nonobese ICU patients. The presence of circulating endotoxin has been reported in critically ill Covid-19 patients, but the clinical relevance of this phenomenon remained unclear [40]. Moreover, a prospective observational study from the Netherlands explored adipocytokine plasma concentrations and clinical outcomes of Covid-19 patients. The authors concluded that it is unlikely that BMI-related adipocytokines or differences in inflammatory response were associated with clinical outcomes [42]. There is a need for more prospective studies assessing the association of potential biologic factors and outcome of obese critically ill patients.

Hypothesis 1: The obesity paradox is a real survival benefit. Clinical factors

It is generally believed that obese patients infected with Covid-19 are more ill or in need for closer monitoring than non-obese patients with comparable Covid-19 illness severity. This concept favors more timely hospitalization, earlier ICU admission and start of organ support in these patients. However, this hypothesis is not supported by data from a recent large-scale study. In this study disease activity scores were similar between ICU Covid-19 patients with different BMI categories [40].

The influence of age and comorbidities was analyzed by Tartof and coworkers [43]. The risk of death from Covid 19 critical disease was most striking among obese patients aged 60 or younger compared to older obese patients with a higher burden of comorbid diseases. This observation suggests that obesity is a more profound risk factor for worse outcomes than age.

Finally, limited epidemiological data suggested that metabolically unhealthy versus metabolically healthy obese individuals had a higher risk of worse outcomes of critical Covid-19 disease. However, this cohort study with Asian patients lacks generalizability. The metabolically healthy state may transition to the metabolically unhealthy state in a crisis such as Covid-19 dis-

ease [44,45]. Currently, there are no available data on the numbers of metabolically healthy and unhealthy obese COVID-19 patients.

Hypothesis 2: Obesity paradox and critical Covid-19 disease is a statistical aberrancy.

There are no prospective randomized trials assessing the causality of the relationship between obesity and worse short-term prognosis of critically ill Covid 19 patients. The assumed positive correlation between BMI and survival of ICU Covid-19 patients is subject to numerous methodological limitations and the clinical heterogeneity in epidemiological studies.

Epidemiological studies are prone to confounding and several sources of bias. Factors contributing to the divergent results in the literature are the significant heterogeneity in study design and patients` characteristics, in sample size and lack of stratified statistical analyses, and in the time and method of BMI assessment. Most studies did not control for confounders or adjust for variability (age, sex, and race/ethnicity) and direction of the association of BMI and mortality risk of critically ill Covid-19 patients. These methodological limitations of observational research are aggravated when a heterogeneous clinical syndrome such as critical Covid-19 disease is analyzed.

The failure to control properly for known and unknown confounders is probably the most recognized limitation of observational studies assessing the association of body mass index and mortality of patients with critical Covid-19 disease. Small retrospective cohort analyses often failed to account for potential confounders such as comorbidities, socioeconomic status, and physical activity. Many large-scale studies failed to collect or extract all data from medical records or administrative data bases. Classic examples of confounding in the obesity Covid-19 mortality association are smoking and pre-existing conditions that cause unintended weight loss including chronic infections, cancer, advanced chronic kidney disease, heart failure, neurological or mood disorders. Smokers tend to have a lower BMI, but a higher risk for critical Covid-19 disease [46,47]. Smoking remains a strong confounder, even after typical adjustments for smoking status (smokers, ex-smokers, or non-smokers) and duration of exposure to cigarettes (pack years).

A second potential bias producing an underestimation of the mortality risk of obesity has been referred to as “reverse causation.” Patient populations included in studies assessing the survival benefit of obesity in critically ill Covid-19 patients are a mix of individuals with normal weight and those who lost weight either by loss of appetite or increased metabolic demands. A disproportionate number of weight loss individuals in the reference group may attenuate the obesity associated mortality from critical Covid-19 disease.

The problem of collider bias has major implications for many studies of Covid-19 disease risk and severity. A collider is most simply defined as a variable affected both by exposure and by outcome. This selection induces a false association or even reversed association between exposure (BMI) and outcome (mortality). The impact of collider bias may increase the confounding bias of smoking. The collider stratification bias has been used to explain the non-existence of the obesity paradox in critical illness including critical Covid-19 disease [48,49,25].

The obesity paradox has also been termed BMI paradox [50]. Undoubtedly, BMI is the most generally used measure of body fatness in epidemiologic studies. However, BMI is only a surrogate measure for excess fat because it measures excess weight rather than excess fat. It does not provide any indication of the fat distribution (abdominal) among individuals. Moreover, the use of BMI to identify obesity has a high specificity, but low sensitivity suggesting the under-detection of excess adipose tissue. This may attenuate the obesity -mortality association. The validity of BMI is low in older adults (on average more body fat than younger adults for an equivalent BMI), women (on average greater amounts of total body fat than men with the same BMI) or muscular individuals (high BMI due to increased muscle mass). Thus, the BMI in these patients’ subpopulations may be misleading.

Cohort studies assessing the mortality of critical Covid-19 disease included only patients with recorded height and weight information. The results of their analyses may not be representative of the entire patient population with critical Covid-19 disease. A nation-wide US population analysis found that 28% of hospitalized Covid-19 patients were missing BMI data [19]. Missing data on BMI can bias and distort the exposure- outcome relation of interest. Missing data are also problematic if they decrease the statistical power by effectively decreasing the sample size of small cohort analyses.

The time of BMI measurements varied widely across studies with critical Covid-19 patients (pre diagnosis of Covid-19-, perihospitalization, at admission to the ICU). Of clinical relevance, patients with critical Covid-19 disease are likely to experience significant fluctuations in body weight during the disease. This includes true loss of body weight, as well as alterations in body fluid volume state after resuscitation of patients with hypotension /shock or during oligo-anuric AKI. One-time measurements of BMI may not reflect the correct BMI category. Estimations of body height or weight of ICU patients by anthropometric formulas, morphometric measures or by visual judgement without use of bed scales are incorrect [51]. Repeated measurements of BMI are infrequently performed, and the BMI is rarely documented in ICU patients [52].

Reports including non-BMI measures of body weight are scarce, but their data corroborate the association of obesity and mortality risk of patients with critical Covid-19 disease. Anthropometric measures such as waist circumference, waist-to-hip-ratio, and waist-to-height-ratio were each associated with a greater risk of death from critical Covid-19 disease [53,54].

Using electronic health records from approximately 1.5 million individuals, a population-based cohort study [55] reported differences in age and sex adjusted ethnicity -specific BMI cutoffs for obesity-associated type 2 diabetes in Whites, South Asians, Blacks and Arabs. The authors recommended a revision of current ethnic specific BMI cutoffs to prevent obesity-associated complications in non-white populations.

Meta-analyses summarizing existing evidence for the existence of an obesity paradox of critical Covid-19 disease reported mixed results. The results and quality of meta-analyses may be limited by incomplete sets of published studies, inclusion of studies with small sizes, or lack of control for confounding. These factors may contribute to erroneous interferences.

Finally, most observational studies exploring the existence of a survival benefit were performed during the first wave of the Covid-19 pandemic. Large database analyses showed that over time (wave 1 to 3) the severity of critical Covid-19 disease decreased, as defined by less mechanical ventilation, lower need

for vasopressor agents and renal replacement therapies. Even so, the risk for in-hospital mortality remained high (24%) [3].

Conclusion

The epidemiologic phenomenon "obesity paradox" in critical Covid-19 disease is explained by the heterogeneity of clinical studies and their numerous limitations. The high mortality of obese Covid-19 patients underscores the need for optimal vaccination, timely intensive care management as obesity class increases.

Declarations

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Ethics committee: This narrative review is based on previously based studies and does not contain any study with participants performed by any of the authors.

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