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Hospital Santa Cruz

REVIEW ARTICLE

# COVID-19 in patients with obesity: clinicopathological features and immunological mechanisms associated with adverse clinical outcomes

## *Associação entre variáveis respiratórias e capacidade de exercício em portadores de DPOC*

## *Asociación entre variables respiratorias y capacidad de ejercicio en portadores de EPOC*

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## ABSTRACT

**Background and objectives**: The infection with the new coronavirus (SARS-CoV-2), which causes COVID-19, has been demonstrating to be more severe in patients with risk factors, increasing susceptibility of this patients to mechanical ventilation and mortality, with obesity standing out. The present study reviews the epidemiology of obesity and the possible immunological mechanisms that associate obesity one of the worst clinical scenarios in COVID-19. **Methods:** This study consists of an exploratory narrativereview. In data collection, were considered among the scientific publications of the studied topic, articles published in English, Spanish and Portuguese languages between June 2015 and June 2020, in the electronic databases, PubMed and Virtual Health Library (BVS). The indexing terms used were: "SARS-CoV-2", "Obesity", "COVID-19", "Risk Factors". **Content:** Obesity is a pandemic and its chronic inflammatory condition is a risk factor for several pathologies, including worse outcome in viral respiratory infections. The immunological analysis of this risk factor and its respective role in the immunopathology of SARS-CoV-2, reveals a deregulated pro-inflammatory response, with a marked increase in several cytokines, such as TNF-α, IL-6 and IL-1β. Such mechanisms result in a cytokine storm, with a consequent deterioration of the immune response for the new coronavirus infection that have been linked to the severe form of disease **Conclusion:** Obesity is a global relevant risk factor for SARS-CoV-2 infection because it disrupts the pro-inflammatory immune response, resulting in a worse clinical outcome, which deserves a special attention from the policies against the pandemia.

***Keywords:*** *SARS-CoV-2. Obesity. COVID-19. Risk factors.*

## RESUMO

**Justificativa e Objetivos:** A infecção pelo novo coronavírus (SARS-CoV-2), causador da COVID-19, apresenta-se de forma mais grave em pacientes portadores de fatores de risco para ventilação mecânica e mortalidade, destacando-se a obesidade. Neste contexto, o presente trabalho revisa a epidemiologia da obesidade e os possíveis mecanismos



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imunológicos que associam a obesidade como um dos piores cenários clínicos na COVID-19. **Métodos:** Este estudo consiste de uma revisão bibliográfica narrativa de caráter exploratório. Na coleta de dados, consideraram-se, entre as publicações científicas do tema estudado, artigos publicados nos idiomas inglês, espanhol e português no período de junho de 2015 a junho de 2020, nas bases eletrônicas PubMed e Biblioteca Virtual em Saúde (BVS). Os descritores adotados foram: "SARS-CoV-2", "Obesity", "COVID-19", "Risk Factors". **Conteúdo**: A obesidade é uma pandemia e sua condição inflamatória crônica é fator de risco para diversas patologias, incluindo pior desfecho em infecções respiratórias virais. A análise imunológica desse estado e seu respectivo papel na imunopatologia do SARS-CoV-2 revela uma resposta pró-inflamatória desregulada, com acentuado aumento de diversas citocinas, como TNF-α, IL-6 e IL-1β. Tais mecanismos têm por resultado uma tempestade de citocinas, com consequente piora da resposta imune frente à infecção pelo novo coronavírus que tem sido associada à forma grave da doença. **Conclusão**: A obesidade configura um fator de risco global relevante para a infecção do SARS-CoV-2 por proporcionar a desregulação da resposta imune pró-inflamatória, resultando em pior desfecho clínico, e que merece atenção especial por parte das políticas de combate à pandemia.

***Descritores**: SARS-CoV-2. Obesidade.COVID-19. Fatores de risco.*

## RESUMEN

**Justificación y Objetivos:** La infección por el SARS-CoV-2, causante de la COVID-19, se presenta de forma más grave en pacientes portadores de factores de riesgo que los predispone a la ventilación mecánica y mortalida, destacando la obesidade. En este contexto, el presente trabajo revisa la epidemiologia de la obesidad y los posibles mecanismos imunológicos que asocian la obesidade como uno de los peores escenarios clínicos en la COVID-19. **Métodos**: Este estudio consiste en una revisión bibliográfica narrativa de carácter exploratorio. En la colecta de datos, se consideraron, entre las publicaciones científicas del tema estudiado, artículos publicados en los idiomas ingles, español y portugués en el periodo de junio de 2015 a junio de 2020, en las bases eletrónicas PubMed e la Bilioteca Virtual de Salud (BVS). Los descriptores adoptados fueron: "SARS-CoV-2", "Obesity","COVID-19", "Risk Factors". **Contenido:** La obesidad es una pandemia y su condición inflamatoria crónica es factor de riesgo para diversas patologias, incluyendo un peor desenlace en infecciones respiratorias virales. El análisis imunológico de ese estado y su respectivo papel en la imunopatología del SARS-CoV-2 revela una respuesta pro-inflamatoria desregulada, con acentuado aumento de diversas citocinas, como TNF-α, IL-6 y IL-1β. Tal mecanismo tiene como resultado una tormenta de citocinas, el consecuente empeoramiento de la respuesta inmune frente a la infeción por el nuevo coronavírus que se ha relacionado con la forma grave de la enfermedad. **Conclusión**: La obesidad configura un factor de riesgo relevante global para la infección del SARS-CoV-2 por proporcionar la desregulación de la respuesta inmune pro-inflamatoria, resultando en un peor desenlace clínico, y merece una atención especial por parte de las políticas para combatir la pandemia.

***Descriptores:** SARS-CoV-2. Obesidad. COVID-19. Factores de riesgo.*

## INTRODUCTION

The coronavirus of severe acute respiratory syndrome (SARS-CoV), member of the genus Betacoronavirus of the family Coronaviridae, is an enveloped virus with a single-stranded positive sense RNA genome. The genetic sequence of SARS-CoV-2 has shown that more than 80% of identity is shared with SARS-CoV and 50% with MERS-CoV, the Middle East Respiratory Syndrome.[1]

It is known that one third of the SARS-CoV-2 genome encodes four main structural proteins: spike (S), envelope (E), nucleocapsid (N) and membrane (M). Like SARS-CoV, SARS-CoV-2 requires the angiotensin-converting enzyme 2 (ACE 2) as a receptor to enter the cell. The Protein S binds to the ACE2 receptor to cause fusion between the virus and the host's plasma membrane. Then, the viral RNA genome is released into the cytoplasm and translated into 2 polyproteins and structural proteins. Subsequently, viral replication begins, in which envelope glycoproteins and nucleocapsids are formed. Finally, the vesicles that contain these viral proteins merge with the plasma membrane to form the viral copies.[2]

The clinical manifestations of coronavirus infection range from asymptomatic to severe acute respiratory syndrome (SARS) and pneumonia.[1] In a study of 140 patients from China, the most common symptoms were fever (91.7%), followed by cough (75%), fatigue (75%), chest tightness or dyspnea (36.7%), and 39,6% complained of gastrointestinal symptoms including nausea, diarrhea, poor appetite, abdominal pain, belching and emesis.[3]

Another retrospective study carried out in Wuhan, showed that half of the patients had some comorbidity, the most common being hypertension, followed by diabetes and coronary disease.[4] However, in the USA, obesity is pointed out as a possible risk factor. For example, in New York, the most common comorbidities are hypertension (56.6%), obesity (41.7%) and diabetes (33.8%).[5]

According to the American CDC, until June, 2020, the main comorbidities related to hospitalizations for



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COVID-19 in adults were hypertension (56.2%), obesity (49.7%), metabolic syndrome (41.9%) and cardiovascular disease (33.2%).[6] This risk is particularly relevant in the USA because the prevalence of obesity is 40%, in contrast to other countries such as China whose obesity rate is 6.2%, Italy (20%) and Spain (24%).[7] In Brazil the prevalence of obesity is 22.1%, making it also a very important comorbidity that must be evaluated.[8]

In this sense, evidences have suggested that since obesity is a chronic inflammatory condition with high prevalence in several countries, it may be one of the risk factors that worse SARS-CoV-2 infection, especially in those who require mechanical ventilation, resulting in a challenge to hospital structures. The mechanisms that explain this association are recent, and point to a deregulation of mediators of the pro-inflammatory immune response.[9-11]

Considering the current clinical relevance of SARS-CoV-2 infection and its possible relationship with specific risk factors that are predominant in global population, the present study addresses the review of immunological mechanisms and clinicopathological data concerning obesity and COVID-19 that determine these condition as a poor SARS-CoV-2 clinical outcome.

## METHODS

This study consists of an exploratory literature review; which design is detailed in figure 1. To carry out the data collection, the following filters were considered, among the scientific publications of the studied topic: articles published in English, Spanish and Portuguese; articles published in 2020 referred to COVID-19 infection and articles related to obesity epidemiology and H1N1 pandemic published from 2009 to 2020. The objective was to perform a systematic analysis of original publications that reported evidences concerning SARS-CoV-2 infection and obesity. The search for data was conducted by two independent evaluators in the electronic databases PubMed and Virtual Health Library (BVS). The search terms were defined to attend the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). The following Health Science Descriptors (DeCS) were used: "SARS-CoV-2", "Obesity","COVID-19" and "Risk Factors". Eligibility criteria included original articles conducted in humans that addressed the mesh terms in the searching period. Articles that did not attend the eligibility criteria were excluded. The pre-selection of articles in the databases was carried out using the specific keywords. The abstracts were read from the inclusion criteria for the selection of full text articles. Results of the selected studies concerning obesity and COVID-19 are shown in table 1 and further detailed in the discussion.

## RESULTS AND DISCUSSION

Obesity can be defined by a body mass Index (BMI) over 30 kg/m$^2$. This is a complex and multifactorial disease, with serious social and psychological dimensions, which affects practically all age and socioeconomic groups globally. Obesity largely preventable, and if considered together with overweight, is currently affecting more than a third of the world population.[12] Epidemiological studies have pointed out BMI as a relevant risk factor for a wide range of chronic diseases, including cardiovascular pathologies, diabetes mellitus, chronic kidney disease and cancers.[13]

According to the WHO, the global prevalence of adults with obesity in 2016 was 13.1%, and the main cases are concentrated in Americas (28.6%); Europe (23.3%) and Eastern Mediterranean (20.8%).[8] In this trend, it is expected that by 2030 about 38% of the world's adult population will be overweight and another 20% will reach obesity.[12] Specifically, in the United States, obesity among adults is estimated as 39.8%. In general, the prevalence in the age group of 40 to 59 years (42.8%) is higher than that those with 20-39 years, with no significant difference

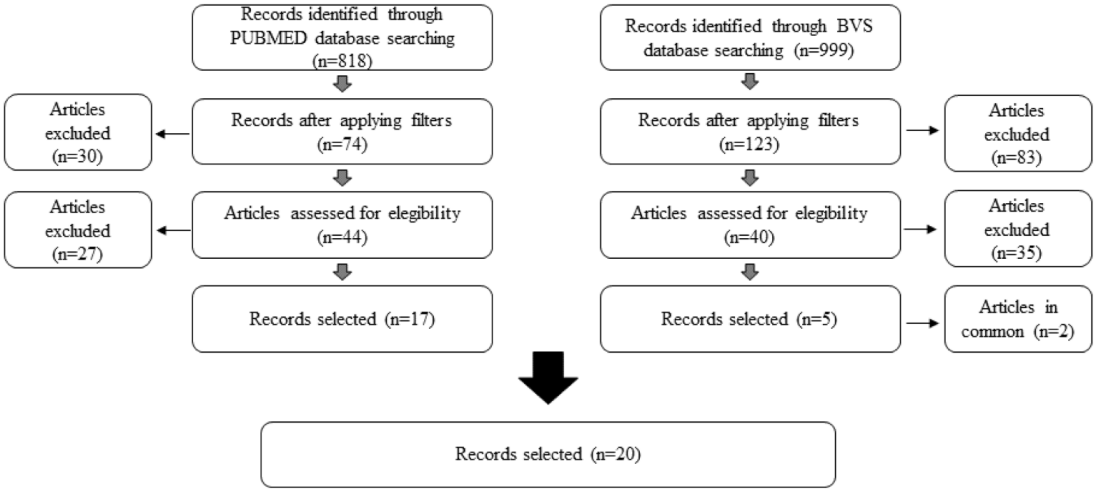


**Figure 1.** Study design detailing all steps for inclusion and exclusion of published manuscripts, as well as the specific searching databases



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in prevalence among adults aged 60 or over (41.0%). Hispanic (47.0%) and non-Hispanic (46.8%) adults had a higher prevalence of obesity than non-Hispanic white adults (37.9%).[14]

A study carried out with a population from Argentina, Chile and Uruguay (n = 7524) determined that the prevalence of obesity was 35.7% and central obesity was 52.9%. These data generally reflect trends in overweight and obesity for Latin America as a whole. These evidences reinforce that obesity and overweight configure a major problem of public health worldwide.[13,15]

In Brazil, the prevalence of obesity is about 20% in men and 20 to 30% in women [15], and has increased dramatically, reaching about ten-fold times in the past four decades. Comparatively, in 1975 it had a prevalence of 0.9 million obese men (2.6% of global obesity) and 1.9 million obese women (2.6% of global obesity), and in 2014 it changed to 11.9 million obese men (4.5% of global obesity) and 18 million obese women (4.8% of global obesity). Therefore, Brazilian population currently occupies the third place in the table of global prevalence of obesity among men and fifth place in terms of global prevalence of obesity among women[15] highlighting the high prevalence of obesity in the country.

Furthermore, obesity has been strictly related to the population incomes. People from high income countries are overweight or obese, with a considerable portion of individuals ranging between 35 to 40kg/m$^2$ BMI. It is observed that just a few high income countries have adult populations with a prevalence of overweight/obese less than 70%.[16] On the other hand, the low- and middle-income countries have more than 70% of the individuals with obesity or overweight and as the country economy evolves, obesity shifts mainly to the poor population.[17] Lastly, the Middle East and Latin America are the places in the globe that are among the highest prevalence of obesity, bringing to light that this condition is related to the income and the economically poor people, which are more prone to develop obesity than are the rich ones.[18]

Since obesity is a well-established condition worldwide, evidences become to point its role as a putative risk factor during the COVID-19 pandemic. It has been reported in many different articles that several patients that were positive to SARS-CoV-2 infection have obesity as a comorbidity. The compilation of the main findings is shown in table 1.

In Brazil, a study conducted in the city of São Caetano do Sul, state of São Paulo, detailed this scenario. A total of 1,583 patients were tested by RT-PCR to SARS-CoV-2, and 444 were found positive. In this group, the most frequent comorbidities were cardiovascular disease with 20.4% and diabetes mellitus with 11.1%, and the prevalent BMI was ranging between 25-26 kg/m$^2$ (41.2%), which corresponds to overweight, followed by a BMI between 30-35 kg/m$^2$ (17.9%), the grade I obesity. Individuals with obesity whose BMI between ranged between 30-35 kg/m$^2$, obtained the highest rate of hospitalization (12%).[19] Although this is an isolated study, the high number of patients enrolled allows to implicate obesity as a poor risk factor in Brazilian population.

In Europe, a large population study conducted in the United Kingdom, based on the U.K. Biobank data (n = 285,817 patients), showed that overweight may increase the risk for severe COVID-19 by 44.0% (relative risk [RR] = 1.44; 95% CI, 1.08–1.92; p = 0.01) while obesity almost doubled it (RR = 1.97; 95% CI, 1.46–2.65; p < 0.0001).[20]

Americas have demonstrated a similar pattern concerning the relation obesity and COVID-19. In New York city, a report showed that 41.7% (n=5700) of COVID-19 hospitalized patients were individuals with obesity, whereas the average prevalence of individuals with obesity in New York City was only 22.0%.[21] Despite many studies have reported COVID-19 hospitalization, just a few of them trace a parallel between obesity and hospitalization. These studies have shown significantly high prevalence of individuals with obesity among hospitalized patients than among patients not hospitalized or the general population.[21,23]

Another case study series with 477 patients that tested positive for SARS-CoV-2 in Metropolitan Detroit showed that most of the patients were African American (334 patients, 72.1%) and female (259 patients, 55.9%) with mean age of 57.5 (16.8) years. Among all patients, 355 (76.7%) required hospital admission, and the mean BMI was 33.6 kg/m$^2$. About 26% of severely obese patients from this study required intensive care, showing that SARS-Cov-2 infection may aggravate disease aggressiveness. A retrospective analysis of 124 intensive care patients from Detroit performed by another study demonstrated that almost one-half of them had a BMI greater than 30 kg/m$^2$, including 15% with BMI greater than or equal to 40. The mean BMI was 31 kg/m$^2$ (range, 27.3-37.5 kg/m$^2$) in patients requiring mechanical ventilation compared with 27 kg/m$^2$ (range, 25.3-30.8) in those who did not require (P < .001). Moreover, BMI greater than 35 was independently associated with the need for mechanical ventilation (OR, 7.36; 95% CI, 1.63-33.14; P = .02).[22]

In a Mexican case-control study, a total of 102,875 individuals who tested for SARS-CoV-2 by RT-PCR were analyzed, with 31,522 (30.6%) positive for COVID-19 and 71,353 (69.4%) with a negative test. The rate of positivity in individuals with comorbidities such as diabetes, obesity and hypertension was much higher than in individuals without these comorbidities, especially to diabetes (43% vs. 28.7%, p <0.001). For the risk of hospitalization due to COVID-19, diabetes (OR = 3.69, CI = 3.48-3.92, p <0.001), contributes more than hypertension (OR = 2.79, CI = 2.64 -2.95, p <0.001), and hypertension more than obesity (OR = 1.47, CI = 1.39-1.55, p <0.001). In this study, obesity was the second most important risk factor for SARS COV-2 infection; however, it was not such an important factor for hospitalization. Finally, the highest risk of infection in obese people is also in line with the findings from China, in which obesity remained a significant risk factor, even after adjusting for age, sex, smoking, diabetes, hypertension and dyslipidemia.[24]

Besides, among patients with symptoms, those with severe or critical conditions had much higher BMIs and,



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**Table 1.** Detailment of publications included in the study as evidence for discussion about the relationship obesity and COVID-19.

| Publication | Authors | Publication date | Country | Results and Conclusion |
|---|---|---|---|---|
| COVID-19 pandemic, coronaviruses, and diabetes mellitus | Muniyappa R, Gubbi S | May 2020 | United States | Hyperglycemia, hyperinsulinemia, and hypoglycemic agents affect pathogenesis of COVID-19. |
| Molecular immune pathogenesis and diagnosis of COVID-19 | Li X, Geng M, Peng Y, et al | April 2020 | China | The pathogenesis of SARS-CoV-2 depend on the interaction between the virus and the individual's immune system. The individual's immune system factors include genetics age, gender, nutritional status, immune regulation, and physical status. |
| Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China | Zhang JJ, Dong X, Cao YY, et al. | July 2020 | China | Allergic diseases, asthma, and COPD are not risk factors for SARS-CoV-2 infection. Older age, high number of comorbidities, and more prominent laboratory abnormalities were associated with severe patients. |
| Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China | Zhou F, Yu T, Du R, et al. | March 2020 | China | The potential risk factors of older age, high SOFA score, and d-dimer greater than 1 μg/mL could help clinicians to identify patients with poor prognosis at an early stage. |
| Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area | Richardson S, Hirsch JS, Narasimhan M, et al. | May 2020 | United States | In this case series that included 5700 patients hospitalized with COVID-19 in the New York City area, the most common comorbidities were hypertension, obesity, and diabetes. |
| Obesity could shift severe COVID-19 disease to younger ages. | Kass DA, Priya D, Cingolani | May 2020 | United States | Obesity can restrict ventilation by impeding diaphragm excursion, impairs immune responses to viral infection, is pro-inflammatory, and induces diabetes and oxidant stress to adversely affect cardiovascular function. |
| Factors association with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City | Petrilli CM, Jones SA, Yang J, et al. | April 2020 | United States | Strongest hospitalization risks were age ≥75, age 65-74, BMI>40, and heart failure Age and comorbidities are powerful predictors of hospitalization; however, admission oxygen impairment and markers of inflammation are most strongly associated with critical illness |
| COVID 19 in Northern Italy: An integrative overview of factors possibly influencing the sharp increase of the outbreak | Goumenou M, Sarigiannis D, Tsatsakis A, et al. | July 2020 | Italy | The purpose of this work is to discuss some of the possible contributing factors and their possible role in the relatively high infection and death rates in Northern Italy compared to other areas and countries. |
| Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships | Popkin, BM, Du, S, Green, WD, et al. | August 2020 | United States | Pooled analysis show individuals with obesity were more at risk for COVID-19 positive, >46.0% higher for hospitalization, 113% higher for ICU admission, 74% higher and for mortality, 48% increase in deaths. |
| Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit | Suleyman G, Fadel RA, Malette KM, et al. | June 2020 | United States | Of 463 patients with COVID-19, 55.9% were female, and 72.1% were African American. Most patients (94.0%) had at least 1 comorbidity, including hypertension (63.7%), chronic kidney disease (39.3%), and diabetes (38.4%). |
| What factors increase the risk of complications in SARS-CoV-2 positive patients? A cohort study in a nationwide | Yanover C, Mizrahi B, Kalkstein N, et al. | August 2020 | Israel | Our analysis suggests that cardiovascular and kidney diseases, obesity, and hypertension are significant risk factors for COVID-19 complications. |
| Obesity a risk factor for increased COVID 19 prevalence, severity and lethality. | Petrakis D, Margină D, Tsarouhas K, et al. | July 2020 | Greece | Obesity is a medical condition with complex pathophysiology, comprising various mechanisms, which now emerges as a significant risk factor for COVID-19. |
| The Perfect Storm: Coronavirus (Covid-19) Pandemic Meets Overfat Pandemic. | Maffetone PB, Laursen PB. | April 2020 | United States | The Covid-19 and overfat pandemics are two serious public health concerns that are correlated, despite having very different horizons and timescales. |
| Obesity and its Implications for COVID-19 Mortality. Risk Factors Associated With Acute Respiratory Distress | Dietz W, Santos-Burgoa C. | June 2020 | United States | The proportion of patients with obesity, severe obesity, and COVID-19 infections will increase compared with the H1N1 experience, and the disease will likely have a more severe course in such patients. |
| Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China | Wu C, Chen X, Cai Y,et al. | July 2020 | China | Older age was associated with greater risk of development of ARDS and death likely owing to less rigorous immune response. |
| SARS-CoV-2 infection and obesity: Common inflammatory and metabolic aspects | Michalakis, K, Ilias, I. | July-August 2020 | Greece | Obesity and SARS-CoV-2 share common elements of the inflammatory process (and possibly also metabolic disturbances), exacerbating SARS-CoV-2 infection in the obese. |
| Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. | Onder G, Rezza G, Brusaferro S | May 2020 | Italy | Within Italy, COVID-19 deaths are mainly observed among older, male patients who also have multiple comorbidities. |
| Obesity a Risk Factor for Severe COVID-19 Infection: Multiple Potential Mechanisms | Sattar N, McInnes IB, McMurray JJV. | July 2020 | United Kingdom | There are multiple pathways by which obesity (or excess ectopic fat) may increase the effect of COVID-19 infection. These include underlying impairments in cardiovascular, respiratory, metabolic, and thrombotic pathways in relation to obesity, all of which reduce reserve and ability to cope with COVID-19 infection and the secondary immune reaction to it. |
| High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. | Simonnet A, Chetboun M, Poissy J, et al. | July 2020 | France | The present study showed a high frequency of obesity among patients admitted in intensive care for SARS-CoV-2. Disease severity increased with BMI. Obesity is a risk factor for SARS-CoV-2 severity, requiring increased attention to preventive measures in susceptible individuals. |
| Obesity in patients younger than 60 years is a risk factor for Covid-19 hospital admission | Lighter J, Phillips M, Hochman S, et al. | August 2020 | United States | Though patients aged < 60 years are generally considered a lower-risk group of COVID-19 disease severity, based on data from our institution, obesity appears to be a previously unrecognized risk factor for hospital admission and need for critical care. |



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especially, individuals with obesity prevalence than normal population or patients who were COVID-19 negative. Thus, being an obese individual and infected by SARS-CoV-2 can promote a worse outcome when compared to non-obese infected individual. These findings also evidence that obesity may be a risk factor that may transcend individual´s ancestrally, since it has been reported in all continents.

Considering the high incidence of COVID-19 in obese patients globally, it is necessary to evidence which mechanisms are enrolled in this process that help to understand why disease goes so aggressively under these conditions. Obesity is a chronic disease that related to the dysregulation of the immune system's functioning.[25] In obese people, visceral fat acts as a substrate to pro-inflammatory and chemotactic compounds production, and is often infiltrated by macrophages and lymphocytes that contribute to the propagation of the inflammatory process.[26]

Adipose tissue has an important endocrine function, since adipokines are secreted by adipocytes, and regulate critical processes as appetite, energy balance, immunity, insulin sensitivity, angiogenesis, inflammation and acute phase response, blood pressure, and lipid metabolism.[25]

The main immunomodulatory adipokines are leptin, adiponectin and pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β. Chronic challenging from pro-inflammatory cytokines can desensitize immune cells to trigger adequate inflammatory responses during infectious challenges. Adiponectin has an anti-inflammatory function, as it reduces the cytotoxicity of NK cells (natural killer) and decreases the production of other cytokines, and is significantly reduced in obesity.[27] The action of leptin on monocytes is to positively regulate the production of proinflammatory cytokines, IL-6, IL-12 and TNFα, in addition to inducing the production of reactive oxygen species and increasing oxidative capacity. Thus, it plays a fundamental role in innate immunity, as it directly influences the differentiation, proliferation, activation and activity of NK cells. In adaptive immunity, it acts on the proliferation of T cells and on the activation of TCD4 + and TCD8 + cells. Its increased level in obesity influences negatively, because it increases the resistance of T

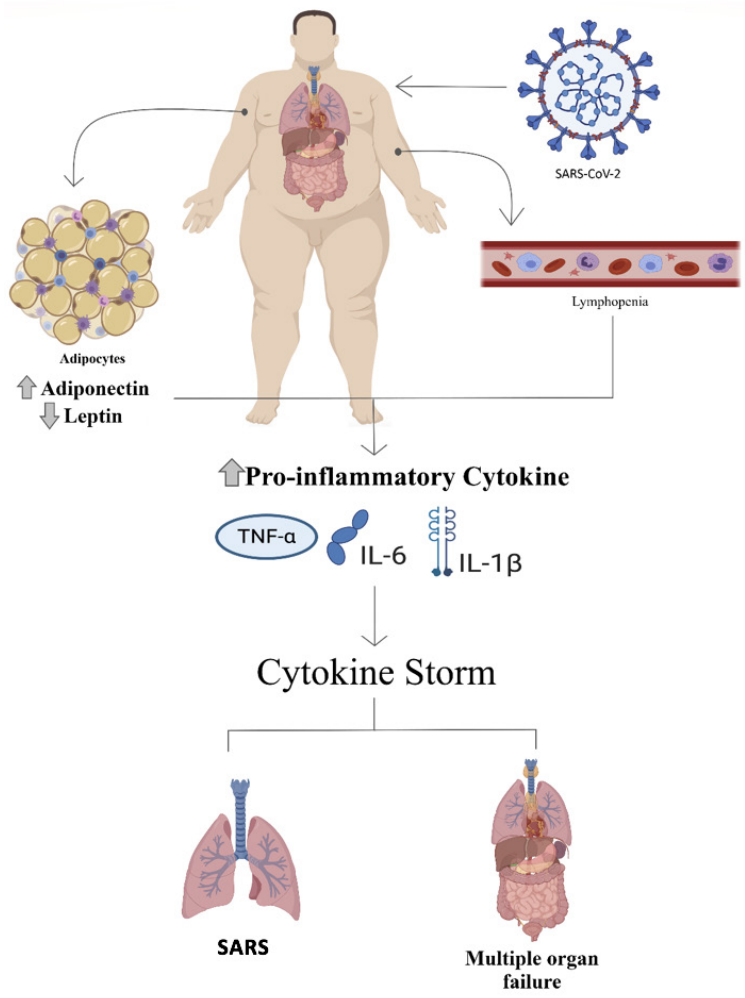


**Figure 2.** Immunological mechanisms shared between obesity and COVID-19. The hormonal regulation of adipocytes in obesity produces pro-inflammatory and chemotactic compounds, such as IL-6, IL-1β, TNF and chemokines. On the other hand, the SARS-CoV-2 infection leads to a condition of lymphopenia that consequently triggers pro-inflammatory responses. In the end, the confluence of these mechanisms causes a storm of cytokines, generating ARDS (acute respiratory distress syndrome), multiple organ failure or death as an outcome. Created with biorender.com.



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cells and NK.[25-27] Therefore, obesity - particularly central obesity - is strongly associated with a pro-inflammatory state, with an increase in reactive oxygen species and the pro-oxidative capacity of the immune system. Adipocytes from abdomen, intramuscular fat, liver and pericardium can produce pro-inflammatory and chemotactic compounds, such as IL-6, IL-1β, TNF and chemokines, as well as hormones that modulate inflammation, such as adiponectin and leptin.[26]

The strong relationship between obesity and complications of viral infections has already been pointed out through studies on the influenza virus, and also with the family history of the coronaviruses, SARS and MERS.[28] In the analysis of the role of obesity in viral infection, the genetic similarity of SARS and MERS viruses with SARS-CoV-2 is respectively, 80% and 50%.[1]

During and after the 2009 H1N1 influenza pandemic, BMI was recognized as an independent risk factor for influenza, in particular the severity of the disease, hospitalization, increased risk of disease spread and death. The causes identified were that hosts with excess fat may have a collapse of the respiratory epithelium, leading to the influx of fluid into the airway space and may have increased viral spread to other respiratory areas, reducing lung function and increasing mortality.[29] An American study carried out in California during the influenza A (H1N1) pandemic covered a group of hospitalized or died patients (n = 1088) diagnosed with influenza in the laboratory and admitted to California hospitals during the period from April to August 2009. This study included 268 patients over 20 years old, and, of these, 58% were obese (BMI> 30 kg/m$^2$). In addition, 60% of these individuals still had other underlying diseases, such as chronic lung disease, including asthma, diabetes and heart disease.[30]

Thus, the disproportionate impact between SARS-CoV-2 and H1N1 in patients with obesity or severe obesity seems similar, since this chronic condition has an important impact on lung function. After all, it is known that overweight results in a state of chronic inflammation, with systemic implications for immunity, which ultimately decreases the antiviral response, thus worsening the infectious condition.[31,32]

Obesity is classified as one of the conditions that exponentially increase the mortality of patients with SARS-CoV-2.[10] This risk is evidenced by the Center for Disease Control and Prevention (CDC), which determined the groups at greatest risk for the evolution of a severe illness, including asthma, chronic lung disease, diabetes, heart problems, chronic kidney disease, age over 65, immunosuppressed, obesity and severe obesity. The analysis of these risk groups reveals that most of these conditions are directly or indirectly related to weight gain.[11,33]

Both SARS-CoV-2 and obesity seem to share some common metabolic and inflammatory reaction pathways (Figure 2). For example, obesity causes hyperglycemia via insulin resistance, while COVID-19 infection can also cause hyperglycemia, however the pathophysiological mechanisms have not yet been elucidated. In addition, obesity represents a state of low-grade inflammation that shares many molecules and common pathways with those seen in SARS-CoV-2 infection.[34]

A recent publication from the Journal of the American Medical Association (JAMA), shown in Italy a high proportion of patients aged 70 years or older diagnosed with COVID-19 (37.6% cases) when compared to those from China (11.9%). This would explain, at least in part, the 7.2% fatality observed in Italy when compared to China (2.3%), which is mostly characterized by elderly male patients with multiple associated comorbidities. However, the authors pointed that these data are limited and derived from the first documented month of COVID-19 cases in Italy, which may then undergo changes in this pattern.[35] In that occasion, this publication failure to mention obesity as one of the pre-existing diseases associated with mortality from the virus. Apparently, the increased prevalence of this condition in older patients in Italy, when compared to China, may be one of the factors that differentiate mortality from SARS-CoV-2 between both countries.[31] Still, it is suggested that in obese patients with COVID-19 it may be caused by the reduction of the cardiorespiratory protection reserve, as well as the enhancement of immune dysregulation, which at least partially contributes to the progression to the critical stage of the disease, associated with multiple organ failure.[36]

A French study showed that the need for invasive mechanical ventilation in patients with COVID-19 infection treated in intensive care was more than 7 times higher for those with a BMI> 35 kg/m$^2$ when compared with individuals with BMI <25 Kg/m$^2$.[37] In another study from New York, those with a BMI between 30-34 kg/m$^2$ and over 35 kg/m$^2$ were 1.8 and 3.6 times more susceptible to requiring intensive care than those with a BMI over 30 kg/m$^2$.[38]

In relation to Brazil, the epidemiological bulletin of the Ministry of Health, on April 11, 2020, showed that among the deaths confirmed by COVID-19, 75% were over 60 years old, and 74% of them had at least one risk factor. Heart disease was the main associated comorbidity and was present in 463 of the deaths, followed by diabetes (in 342 deaths), pneumopathy (112), neurological disease (74) and kidney disease (71). In all risk groups, most individuals were 60 years of age or older, except for obesity.[39] This pattern remained present in the epidemiological bulletin of the Ministry of Health on June 23, 2020, in which 1,674 deaths were recorded by COVID-19 in which obesity was a risk factor, and 51% of these were individuals with less than 60 years.[40]

## CONCLUSION

In spite of the management decisions of some governments on quarantining, social isolation, screening methods, and flight suspensions due to the severity and aggressiveness of COVID-19, directed to all people, the proposal of specific decisions driven to obese individuals are neglected. It is proven that obesity has an intimate relationship with the worst clinical outcomes of SARS-CoV-2 infection, especially in places where the population has a



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BMI over 30kg/m$^2$. Moreover, the increased secretion of cytokines, such as TNF-α, IL-6 and IL-1β, which characterize the state of chronic obesity, aggravate coronavirus infection, increasing the need for hospitalization in the intensive care unities and invasive mechanical ventilation. Such patients, under these critical conditions, are still overloading hospitals and the health system care, with a considerable rate of death. Therefore, it is indispensable that current health promotion strategies must at least involve obesity as a key risk factor, which must be analyzed as a poor prognosis condition for people infected by SARS-CoV-2, as well as a specific segment of population that deserves specific public policies and conducts for protection against COVID exposure.

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## AUTHORS' CONTRIBUTIONS

**Maria Eduarda Oliveira Ferraz and Matheus Ricardo Garbim** contributed to the conception, design of the article, analysis and writing of the article;

**Carolina Panis** contributed to the planning and design of the article, review and final approval of the article.

All authors have approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and completeness.



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