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Overweight/obesity aggravates hospital complications in hospitalized patients with COVID-19: a systematic review

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Abstract. Coronavirus disease (COVID-19) has become a pandemic and patients with overweight and obesity have been reported to be at increased risk for complications from COVID-19. In this context, the objective of the present systematic review was to demonstrate the evidence relating the association or not of overweight and obesity with the prevalence of complications and worst prognosis in hospitalized COVID-19 patients.PubMed, Scielo, Lilacs, JMIR, ScienceDirect, Springer, Wiley and Web of Science were used to identify studies published in the period from 2020 to 2021. This work was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and PICOS approach. The review included non-randomized or randomized controlled clinical trials, cohort, case-control, cross-sectional and observational studies, and the patient's included in the studies should present overweight or obesity andCOVID-19. From 395 articles, 49 studies met the scope of the review and were selected to be evaluated in this systematic review.According to the selected articles, it was observed that most patients hospitalized with COVID-19 were overweight/obese, elderly (mean age between 60 and 65 years old) and male. Overweight and obesity significantly contributed to increase the incidence of complications as longer hospital stay, invasive mechanical ventilation, non-invasive ventilation, kidney injury, septic shock, heart injury and ICU admission, increasing the rate of deaths. It was observed that the overweight and obesity significantly contributed to increase the incidence of complications and promote a worst prognosis in those patients, being present in most hospital complications.
Keywords: Overweight, Obesity, Coronavirus disease, COVID-19, Comorbidities.

Introduction

Coronavirus diseases are pathologies developed by enveloped RNA virus responsible to several effects affecting respiratory, enteric, and neurologic systems and hepatic tissue. The literature recognizes six (6) species of human pathological coronaviruses. Four (229E, OC43, NL63 and HKU1) cause common flu-like symptoms, and two species, SARS-CoV and MERS-CoV, are associated with severe acute respiratory syndrome (SARS)(BELASCO; FONSECA, 2020).

In December 2019, from the investigation of a group of patients with pneumonia of unknown cause in Wuhan, China, a beta coronavirus was revealed, whose similarities with MERS-CoV and SARS-CoV identified it as a member of the family of coronaviruses that infect humans. It came to be called SARS-CoV-2, and its clinic, COVID-19 (ASSELAH et al., 2021).

SARS-CoV-2 is a single-stranded RNA virus, with a spherical or elliptical and pleomorphic molecular structure, with a diameter ranging from 60 to 140 nm, belonging to the subgenus sarbecovirus and subfamily Orthocoronavirinae(SILVA et al., 2021). The virus uses angiotensin-converting enzyme 2 (ACE2) as a receptor and mainly infects ciliary bronchial epithelial cells and type II pneumocytes (ASSELAH et al., 2021), (HUANG et al., 2020). The main routes of transmission are inhalation of respiratory droplets coming directly from infected people or from “fomites” (previously contaminated surfaces), direct contact with mucous membranes and by inhalation of suspended particles (ASSELAH et al., 2021), (LAUER et al., 2020), (ZHU et al., 2020a).

The clinical profile of COVID-19 ranges from an asymptomatic state to life-threatening complications that include acute respiratory distress syndrome (ARDS), multiple organ dysfunction and failure, septic shock, acute pulmonary edema, and severe pneumonia (ARBEL et al., 2020). The initial symptoms frequently reported by patients are fever, dry cough, fatigue, and dyspnea. Less common symptoms are rhinorrhea, malaise, expectoration, fatigue, nausea, vomiting, diarrhea, seizure, conjunctivitis, headache, myalgia and pain in the throat, chest and abdomen (ASSELAH et al., 2021).

There is no literary consensus on the incubation period, presenting values between 2 and 14 days. The mean time observed from the onset of the first symptoms to hospitalization ranges from 2 to 8 days, while the interval between the onset of symptoms and the need for mechanical ventilation corresponds to 11 to 23.7 days (PIETRI et al., 2021).

Regarding the risk factors for COVID-19, although all ages are vulnerable, age stands out, with the most diagnosed cases in the age group between 40 and 56 years old, and gender, demonstrating a high incidence in males (PIETRI et al., 2021).

Studies show that some patients fall into the risk group for complications arising from COVID-19, including elderly patients, pregnant women, obese patients, patients with chronic non-communicable diseases and cancer patients (ASSELAH et al., 2021).

In this context, the objective of the present systematic review was to demonstrate in accordance with analysis of selected articles from the literature, the evidences relating the association or not of overweight and obesity with prevalence of complications and worst prognosis in hospitalized COVID-19 patients.

Several published surveys are available that cover different aspects of the association between excess body weight and COVID-19 such as the literatures of Albashir (2020) (ALBASHIR, 2020), Huang (2020)(HUANG et al., 2020), and Wanqi Yu (2020)(YU et al., 2021). For example, in Huang's review it was shown that obese patients have a higher risk of hospitalization, respiratory complications, need for mechanical ventilation and death in the intensive care unit when compared to non-obese patients. Albashir (2020) (ALBASHIR, 2020) justified the increase in severity through overexpression in adipose tissue of the ACE2 receptor used by the SARS-CoV-2 spike protein and overexpression of angiotensin II (responsible for vascular permeability, development of pulmonary edema and ARDS) resulting from the balance in the angiotensin-aldosterone-system in the physiology of obesity. In 2020, Yu demonstrated that the worst prognosis was also attributed to the strong influence of obesity with other aggravating factors of COVID-19, such as diabetes mellitus, arterial hypertension, cardiovascular and chronic pulmonary diseases.

Although some studies have been demonstrated the effects of overweight and obesity and clinical profile of COVID-19 patients, more studies should be developed, and reviews should be published to demonstrate this impact for the health. Thus, the outline of the contributions of this paper relative to the recent literature in the field can be summarized providing the influences of overweight and obesity on development of complications, as necessity of mechanical ventilation, necessity of tracheostomy and deaths by hospitalized patients diagnosed with COVID-19, as well as the mechanisms associated.

To address these issues, general and specific questions related to the association between overweight/obesity and COVID-19 were proposed: Patients with overweight/obesity and diagnosed with COVID-19 presents more prevalence of other pre-existing chronic diseases, as diabetes and cardiovascular diseases? Does overweight/obesity increase the necessity of mechanical ventilation and/or tracheostomy in patients with COVID-19? Does overweight/obesity increase the incidence of complications, as renal injury, or cardiovascular events, in patients with COVID-19? Does overweight/obesity increase the necessity of intensive care unit (ICU) hospitalization by patients with COVID-19? Does overweight/obesity increase the rate of death in patients with COVID-19? These

questions helped in the analysis and discussion of articles related to the research topic.

Material and Methods

We conducted a systematic review of the literature to analyze the influence of overweight and obesity on development of complications in hospitalized patients diagnosed with COVID-19.

A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific question, that in this specific work aims to demonstrate the influence of excess body weight onhospital complicationsinpatients with COVID-19. In addition, it is appropriate to identify where new studies are needed, from the identification of areas of uncertainty where little or no relevant research has been performed, as well as to identify the mechanisms associated with these two pathologies, overweight/obesity, and COVID-19.

This work was conducted based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) proposed by (MOHER et al., 2009), (PAGE et al., 2021). PRISMA was conceived to improve the clarity and transparency in how systematic reviews are conducted, through a model that seeks to obtain a clear presentation of what was planned, done, and found (MOHER et al., 2009), (PAGE et al., 2021).

Research questions

Research questions contribute to know the influences and impact of overweight and obesity on complications in hospitalized patients with COVID-19. Answers will enable us to consolidate the studies carried out on this topic and will make it possible to list which ones are the challenges and areas that need to be explored.

All research questions were cited in the introduction section above.

Search strategy

The search string definition process was carried out by searching scientific databases, correlating known terms, such as synonyms, acronyms, and word combinations within the context of the work.

We used the PICOS approach proposed by (MOHER et al., 2009), (PAGE et al., 2021), to refine our research string. This is one of the suggested methods to support the definition of some subjects covered by PRISMA, such as objectives, search questions, and eligibility criteria, and each letter refers to a component: the participants (P), the interventions (I), comparisons (C), outcomes (O), and the study design chosen (MOHER et al., 2009), (PAGE et al., 2021), (MARQUES BERNARDO; ROBERTO CUCE NOBRE; BISCEGLI JATENE, 2004).

- Participants: adult men and women (age 18 years or older); patient diagnosed with COVID-19 and hospitalized in enfermary or in intensive care unit (ICU).
- Intervention: presence of overweight or obesity in hospitalized patients with COVID-19.
- Comparison: incidence of complications, as necessity of mechanical ventilation, necessity of tracheostomy, necessity of intensive care unit and incidence of deaths, among others, in overweight/obese patients diagnosed with COVID-19 and hospitalized.
- Outcomes: evaluate the incidence of complications during hospitalization period by COVID-19 in patients with overweight/obesity or not.
- Study design: the review included non-randomized or randomized controlled clinical trials, cohort, case-control, cross-sectional and observational studies. The patient's included in the studies should present overweight or obesity.

It was used this specific search string to be used in querying the databases based on the search strategy:

Search string in English - "SARS-CoV-2" and "COVID-19" and "overweight" and "obesity" and "complications".

Search string in Portuguese - "SARS-CoV-2" e "COVID-19" e "sobrepeso" e "obesidade" e "complicações".

To select the articles, studies from the years 2020-2021 (January 1st, 2020 to December 31st, 2021) were obtained from electronic databases and selected through searches using the search string. The electronic databases included in the survey were: MEDLINE/PubMed (n=66), Scielo (n=5), Lilacs (n=5), JMIR (n=5), ScienceDirect (n=41), Springer (n=77), Wiley (n=182) and Web of Science (n=14). We chose these databases because they are sources of relevant articles within the area covered in this paper, as overweight/obesity and COVID-19 (Figure 1).

Article selection

In the article selection process, inclusion and exclusion criteria were defined as shown below to ensure that the articles obtained were linked to the main objectives of the research. These criteria were proposed according to the terms defined in the intervention and participants in the PICOS method.

We used the Mendeley Desktop as a reference management software to organize the selected articles and to carry out the selection process. All articles were reviewed by three reviewers independently, who verified their relevance to the scope of this review.

Inclusion criteria: non-randomized or randomized controlled clinical trials, cohort, case-control, cross-sectional and observational studies; articles involving humans; articles that included groups of overweight or obese patients diagnosed with COVID-19 and hospitalized; articles that included some complications presented in these hospitalized patients diagnosed with COVID-19; articles published in English or in Portuguese; and articles published in 2020 or in 2021.

Exclusion criteria: patients diagnosed with COVID-19 and with less than 18 years old.

In the first stage, we removed duplicate articles. In the second stage, based on the titles and abstracts of the articles, we removed those that did not meet the intervention and participants criteria. In this period, we also removed articles not related to primary studies (theses, dissertations, opinions, criticism, protocols, books, posters, abstracts, oral presentations, and reviews). In the second phase of excluding articles, we were conservative in removing studies if there were any doubts regarding the tools used in the intervention or scope, as group of patients, participants, presence of overweight or obesity, complications, among others. These articles were also selected for the next stage. Only when the three reviewers confirmed that the article did not address the scope, it was excluded from the study (Figure 1).

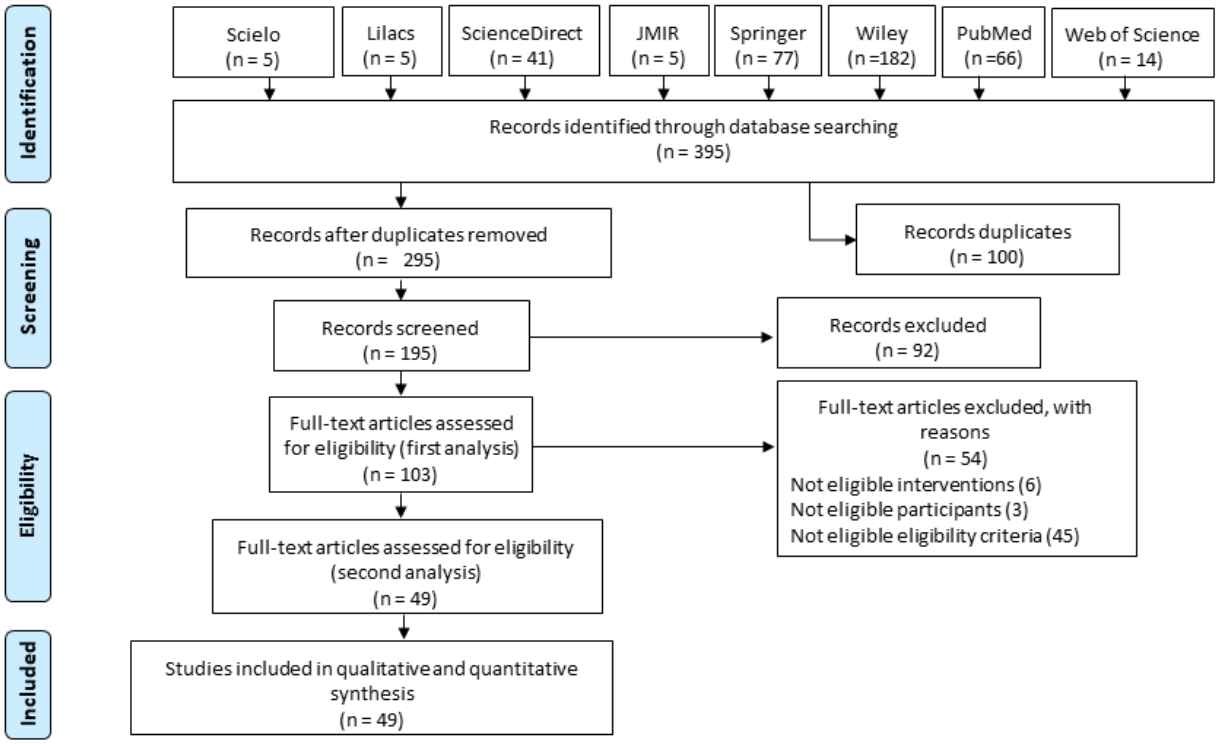

Figure 1. PRISMA flow diagram with the steps in the article selection process.

In the third stage, based on reading the full article, we excluded articles that did not address the intervention, study design, and participants inclusion criteria, as overweight or obese patients, and complications in COVID-19 patients. Moreover, the reviewers met to compare their article choices and discuss cases of disagreement. Subsequently, the reviewers, based on the mutual agreement, selected a final list of articles. If at least two reviewers assessed that the article did not address the scope, it was excluded from the study (Figure 1).

To limit our search, we only considered articles published within the years of 2020 and 2021 and written in English and Portuguese. The analysis and selection of articles were made in the period of February 01, 2022, to April 30, 2022.

Results and discussion

Patients with overweight/obesity and diagnosed with COVID-19 presents more prevalence of other pre-existing chronic diseases, as diabetes and cardiovascular diseases?

According to 10 out of the 49 selected articles, individuals with overweight orobesity and diagnosed with COVID-19 are more likely to have other pre-existing chronic diseases, such as diabetes, lung, hepatic, and cardiovascular diseases (CHEN et al., 2021), (MARTÍN-DEL-CAMPO et al., 2021a), (YANOVER et al., 2020).

Studies have been demonstrated that in COVID-19 patients, according with grade, duration and distribution of excess adipose tissue, obesity can progressively cause or exacerbate a variety of comorbidities including hypertension, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease and kidney disease (ALBASHIR, 2020), (MARTÍN-DEL-CAMPO et al., 2021a). The chronic inflammation related to adipose tissue may be a promoter for the occurrence of the cytokine storm that may be responsible for the variety of complications of COVID-19 (BETTINI et al., 2021). Some studies in this review related the complications of COVID-19 to immune dysfunction and the exacerbation of pre-existing diseases in conjunction with obesity, such as: hypertension and

diabetes mellitus (NAKESHBANDI et al., 2020), (YAN et al., 2021),(SAHIN et al., 2021), (ZHOU et al., 2020), (HEALY et al., 2022).

In 2021, Chen and collaborators (CHEN et al., 2021) demonstrated that obesity and COVID-19 both independently contribute to an increased risk of hepatic steatosis, and the combination of them may exacerbate the condition, that may increase the need of intubation, dialyses and poor outcomes.Also, in the year of 2020 Al-Sabah(AL-SABAH et al., 2020) and collaborators observed that people with diabetes, a chronic metabolic disorder characterized by high blood glucose levels due to insulin resistance or an insufficient production of insulin, are more likely to experience severe illness and complications from COVID-19, that can lead these patients to the ICU.

Martin-Del-Campo (2021)(MARTÍN-DEL-CAMPO et al., 2021a)also demonstrated the correlation between COVID-19 and obesity, associating with negative health outcomes. The study focuses on obesity class III (BMI $\geq$ 40 kg/m^2) and its association with mortality and kidney complications in COVID-19 patients hospitalized in Mexico during the first wave of the pandemic in 2020. The research involving 773 adult patients with confirmed COVID-19 diagnosis showed that individuals with obesity class III have a higher risk of mortality [OR = 3.54 (1.46–8.55), P = 0.005] and acute kidney injury (AKI) [OR = 2.70 (1.01–7.26), P = 0.05] than non-obese patients. The study also reveals that patients with obesity have a greater prevalence of risk factors and comorbidities. The findings suggest that obesity is a significant public health concern that needs to be addressed to improve COVID-19 outcomes.

Does overweight/obesity increase the necessity of mechanical ventilation and/or tracheostomy in patients with COVID-19?

Analyzing the selected studies (N=49), 6 of them investigated the relationship between patients with overweight and the need for mechanical ventilation in a more specific way (COSS-ROVIROSA et al., 2021), (CHIUMELLO et al., 2020), (KIM et al., 2021), (IANNELLI et al., 2021), (CHEN et al., 2021), (NAKESHBANDI et al., 2020). As a consensus, all articles confirmed that patients with these conditions had increased levels of hospitalization in specialized centers and, concomitantly, a greater need for assisted ventilation in addition to the use of high oxygen concentration. Furthermore, dependence on respiratory systems may be related to compromised physiological characteristics of each overweight or individual with obesity.

The formation of atelectasis in the lungs is due to the reduction of the respiratory functional capacity added to the impairment of the respiratory muscles, which makes the use of non-invasive ventilatory support unfeasible and induces the need for the use of mechanical ventilation and tracheostomy (ZHU et al., 2020b). Patients who fall into this context, in most cases, manifest frank respiratory symptoms, such as ARDS.

In this sense, the study of Chiumello et al. (2020)(CHIUMELLO et al., 2020) demonstrated that patients who required mechanical ventilation due to ARDS mostly had a BMI ≥ 25 kg/m^2. Thus, it can be said that the pathophysiological mechanism of adipose tissue accumulation is an important parameter regarding the prognosis of patients with COVID-19.

In any case, chronic inflammation of adipose tissue proved to be a triggering and explanatory factor in most of the articles reviewed for this study, which is confirmed by the marked release of inflammatory cytokines that predict the worsening of severe respiratory disease (BUSETTO et al., 2020). In short, the increased need for mechanical ventilation and/or tracheostomy proved to be proportionally faithful to the classifications of obesity and body lipids accumulation, once, the individual with obesity class III has a greater chance of unfavorable evolution when compared to a patient with normal weight (eutrophic patients) (BUSETTO et al., 2020), (BETTINI et al., 2021), (EASTMENT et al., 2021).

Studies shown that the use of mechanical ventilation was prevalent in ICU patients with some degree of obesity (ALMEIDA et al., 2020), (ROD; OVIEDO-TRESPALACIOS; CORTES-RAMIREZ, 2020). Coss-Rovirosa et al. (2021)(COSS-ROVIROSA et al., 2021) also demonstrated that the risk of mechanical ventilation is increased in patients with obesity class II and III.

Patients with overweight and obesityoften present chronic low-grade inflammation, insulin resistance, compensatory hyperinsulinemia, hyperglycemia, oxidative stress, among other metabolic changes that may increase the risk of developing several other diseases and clinical complications (YU et al., 2021), (QUEIROZ et al., 2022).

It is known that overweight and obesity are indicative of a differentiated impact of the respiratory syndrome by COVID-19 when compared to a group of eutrophic people. This difference implies the accentuated manifestation caused by SARS-CoV-2, since excess adipose tissue is associated with a greater amount of ACE2 receptors and the virus has mechanisms that facilitate entry into the cells of the individuals using ACE2 (CHIUMELLO et al., 2020). Such viral behavior makes it clear that overweight and obesity is an accentuated risk factor for a worst prognosis of COVID-19 and patients are more likely to use mechanical ventilation.

Does overweight/obesity increase the incidence of complications, as renal injury, or cardiovascular events, in patients with COVID-19?

According to 7 of the 49 articles selected, obesity is related to complications mainly affecting the respiratory system and the most cited are ARDS and pneumonia, which have lung lesions, low saturation and the need for mechanical ventilation

when aggravated (CHIUMELLO et al., 2020), (BUSETTO et al., 2020), (SAHIN et al., 2021),(HEALY et al., 2022), (CAI et al., 2021), (OLIVAS-MARTÍNEZ et al., 2021), (WANG; SATO; SAKURABA, 2021), (WANG et al., 2020).

Septic shock was also a complication of COVID-19 with greater severity in patients with a high BMI (PAGE-WILSON et al., 2021). A study by Sahin et al., in 2021 (SAHIN et al., 2021), 675 patients with at least one positive SARS-CoV-2 RT-PCR test were evaluated, 248 patients were overweight and 162 were with obesity. Patients were grouped according to BMI values, 238 patients with normal weight (BMI <25 kg/m²)(Group A), 248 patients with overweight (BMI =25 to <30 kg/m²)(Group B), 102 patients with obesity class I (BMI =30 to <35 kg/m²)(Group C) and 60 patients with obesity class II (BMI ≥35 kg/m²)(Group D). The number of patients with pulmonary involvement in terms of COVID-19 was significantly lower in normal-weight patients than in overweight and obese patients (Group B vs. Group A [P = 0.001], Group C vs. Group A [P < 0.001] and Group D vs. Group A [P < 0.001]). In patients with obesity class II, BMI ≥ 35 kg/m², pulmonary involvement was greater than in overweight patients (Group D vs. Group B [P = 0.022]). Furthermore, the number of patients with low oxygen saturation was significantly higher in obese patients with BMI ≥ 35 kg/m² (Group D) (P < 0.001).

Pneumonia is a very recurrent complication. According to Cai et al. (2020)(CAI et al., 2021) in a study of 383 patients with COVID-19 from Shenzhen, overweight was associated with an 86% higher risk and obesity with a 142% higher risk of developing severe pneumonia than patients with normal weight.

Acute kidney injury (AKI) is one of the complications related to increased BMI in hospitalized patients with severe COVID-19 and is associated with renal replacement therapy and increased mortality (MARTÍN-DEL-CAMPO et al., 2021a), (PAGE-WILSON et al., 2021).

Obesity may increase the risk of AKI through several mechanisms that are not fully understood. However, the dysregulation of fatty acid and carbohydrate metabolism, the presence of comorbidities, oxidative stress and inflammation are likely the most important factors associated with kidney injury. This association is supported, since obese and morbidly obese patients (obesity class III) had significantly increased serum creatinine concentrations at the end of the segment, if compared with overweight and normal-weight patients (MARTÍN-DEL-CAMPO et al., 2021a).

The most relevant analysis regarding obesity and AKI is a retrospective cohort study by Martín-Del-Campo et al. in 2021 (MARTÍN-DEL-CAMPO et al., 2021a), in which data from 773 patients with COVID-19 admitted to a tertiary teaching hospital in the Mexican state of Jalisco were analyzed. The study recognizes the significant association between obesity in patients with COVID-19, especially severe obesity, and increased risk of AKI [odds ratio (OR) = 2.70 (1.01-7.26), P = 0.05], renal replacement therapy [OR = 14.4 (1.46-42), P = 0.02] and mortality [OR = 3.54 (1.46-8.55), P =0.005]. In addition, obesity is the factor most associated with the development of endothelial dysfunction. This is a condition in which blood vessels lose the ability to contract and relax properly, which increases the risk of events such as heart attack, thrombosis, and stroke (MARTÍN-DEL-CAMPO et al., 2021a).

A retrospective study by Zhang et al., in 2020 (ZHANG et al., 2020), with 13 young patients who died for COVID-19 and 40 matched survivors showed that patients who died had higher BMI values (OR = 1354; 95% confidence interval [CI] = 1075-1704; P = 0.010), inflammation-related C-reactive protein index (OR = 1014; 95% CI = 1003-1025; P = 0.014), cardiac injury biomarker hs-cTnI (OR = 1420; CI 95% = 1.112-1.814; P = 0.005) and increased D-dimer biomarker of clotting activity (OR = 418.7; P = 0.047), compared with survivors. These data support that obese young people with COVID-19 may have an aggravated inflammatory response, increased cardiac injury and increased coagulation, probably inducing high mortality.

Does overweight/obesity increase the necessity of ICU hospitalization by patients with COVID-19?

In the articles selected for this systematic review, 13 of them confirmed a higher rate of hospitalization of obese patients with COVID-19 in the ICU. In these articles, the causes related to SARS-CoV-2 infection most cited for hospitalization of obese people in the ICU are exasperation of pre-existing chronic comorbidities, pneumonia, acute respiratory distress syndrome, thrombosis, and acute kidney injury.

Besides that, Moriconi et al., in 2020 (MORICONI et al., 2020), states that obese individuals infected with COVID-19 experience longer hospital lengths of stay, more intensive and longer oxygen treatment, and may take longer to eliminate SARS-Cov-2. These characteristics may increase the severity of the disease, given the greater immunological fragility of the population and the well-established restrictive mechanical pattern imposed by high body weight to the dynamics of the respiratory system.

In 2020, Hajifathalian and collaborators (HAJIFATHALIAN et al., 2020),concluded that obesity is an important risk factor for the severity of COVID-19 disease, with the need for intensive care. This was a retrospective study of 770 adult hospitalized patients who had complete BMI data in their medical records. The mean age among them was 63.5 (SD = 17) years old with a mean BMI of 29 (SD = 8), with 61% being male. Obesity (BMI ≥ 30 kg/m²) was associated with a significantly higher rate of ICU admission (P = 0.001), intubation (P < 0.001) and death (P < 0.001), even after adjusting for age, race, and troponin level.

In another cohort study, Al-Sabah et al., in 2020 (AL-SABAH et al., 2020), demonstrated that

among 1,158 hospitalized patients, 271 were diabetic, 236 were hypertensive, and 104 required ICU admission. In patients with measurements available, 157 had a BMI ≥ 25 kg/m^2. Univariate analysis showed that overweight, obesity (obesity class I) and severe obesity (obesity class III) were associated with a higher number of ICU admissions. The median BMI of patients admitted to the ICU was also significantly higher than those who did not require ICU care (median [IQR]: 27.5 [25.3–31.4] kg/m^2 vs 26 [23– 29] kg/m^2, respectively; P < 0.001).

Likewise, another cohort study by Heyali et al., in 2020 (HEALY et al., 2022), was a retrospectively collected clinical data from 417 patients admitted between March and June 2020 at Al Kuwait Hospital, from Dubai in the United Arab Emirates. Patients with a BMI above 29 kg/m^2 as well as underlying comorbidities had a significant increase in admission to the ICU compared to patients below 29 kg/m^2 and with comorbidities (n = 13/60, 21.7% vs. n = 7/76, 9.2%), p = 0.042).

Lastly, in the study by Biscarini et al. (2020)(BISCARINI et al., 2020), 74 of the 331 patients had a BMI ≥ 30 kg/m^2. Among patients with obesity, 21 (28.4%) required ICU admission and 25 died (33.8%). The effect of obesity on ICU remained significant after controlling for sex, age, interstitial lung disease, heart disease, and serum C-reactive protein. The obese patients with COVID-19 were more likely to be admitted to the ICU than non-obese patients.

Factors related to the comorbidities of individuals infected with SARS-CoV-2 are important for the incidence of worsening in the clinical evolution of the disease (SIMONNET et al., 2020), and obesity exponentially increases the risk of hospitalization in the ICU and, consequently, increases the probability of death of infected individuals (BOLSONI-LOPES; FURIERI; ALONSO-VALE, 2021).

Obesity is associated with a higher risk of noncommunicable diseases such as diabetes mellitus, cardiovascular disease, cancer, non-alcoholic fatty liver disease, among others, and often these comorbidities co-exist in a single individual (PETERSEN et al., 2020), (OSUNA-PADILLA et al., 2021).

Above all things, the combination of adipose tissue-mediated immune and metabolic dysfunctions may play a key role in the pathophysiological pathways that lead to obesity influencing a worst COVID-19 prognosis in need for ICU admission (HUANG et al., 2020).

Hajifathalian et al. (2020)(HAJIFATHALIAN et al., 2020), proposes that the adverse respiratory outcomes seen in COVID-19 and other respiratory infections are the result of a systemic inflammatory response, initiated by immune pathways and cytokine production among them interleukin-6 (IL-6), IL-10, tumor necrosis factor alpha (TNF-α) and other pro-inflammatory factors, triggering a cytokine storm. The consequence of this syndrome includes apoptosis, vascular leakage, impaired viral clearance, altered tissue homeostasis, acute lung injury, cardiac dysfunction, and finally ARDS. Another study has showed that obesity decreases lung compliance and functional residual capacity, as well the respiratory muscle work (ZHU et al., 2020a). All these physiological alterations lead to an increase of oxygen consumption and respiratory effort.

Now it's also known that adiposopathy, standard pattern on obese patients, leads to systemic inflammation and upper regulation of Th17, increasing the risk of organic failure in those infected with COVID-19 (ZHU et al., 2020b). This evidence is supported by other studies that correlate dyslipidemia, obesity, and changes not only on systemic immune response, but also on local lung immune patterns, changing the local response to the virus (YANOVER et al., 2020).

Al-Sabah et al. (2020)(AL-SABAH et al., 2020), demonstrated that diabetes in overweight and patients with obesity and COVID-19 increased the risk of poor outcomes and ICU admission. Corroborating, Coss-Rovitosa et al. (2021)(COSS-ROVIROSA et al., 2021), also observed the presence of diabetes and hypertension in obese patients with COVID-19 who needed early intubation. Findings of this study also demonstrated that overweight and obese patients hospitalized for COVID-19 have an increased risk for respiratory failure, AKI, renal replacement therapy and septic shock (MARTÍN-DEL-CAMPO et al., 2021a), (PAGE-WILSON et al., 2021).

At last, it's reasonable to conclude that the main mechanisms leaded by obesity that increase complications in hospitalized COVID-19 patients, are mostly the systemic inflammation present in overweight/obese patients and the higher expression of ACE2 and angiotensin, both leading the body systems to cardiovascular and respiratory failure (Figure 2) (YANOVER et al., 2020).

Table 1. Intervention information and results of selected articles.

Article reference	Number of Patients	Participant Groups	Countries	Types of study	Main Findings
A. Albarrán-Sánchez et al. (2021). https://doi:10.1002/osp4.584	608	Patients of all BMI ranges.	México	Retrospective cohort	The patients in the underweight, overweight and grade 3 obesity categories are at higher risk of COVID-19 related mortality, compared to those with grade I or II obesity.
A. B. Heberto et al. (2020). https://doiorg/10.1016/j.ijcha.2020.100638	254	Hospitalized patients with Covid	México	Observational	Multivariate logistic regression analysis revealed that obesity, arterial oxygen saturation, systolic blood pressure were directly related to higher levels troponins. Multivariate Cox proportional hazards analysis showed that the primary outcome(mortality) was determined by overweight/obesity.
A. E. Malavazos et al. (2021). https://doi: 10.1007/s40519-021-01173-w	215	Patients with abdominal obesity	Italy	Retrospective cohort	Abdominal obesity phenotype is associated with a high Chest X-ray severity score better than BMI-based obesity in hospitalized patients with COVID-19. Therefore, in a hospital setting, waist circumference should be measured, and patients with abdominal obesity should be monitored closely.
A. Iannelli et al. (2021). https://doi: 10.1007/s11695-020-05120-z.	4 248 253	Obese (BMI ≥ 30 kg/m^2) and Morbid obese (BMI ≥ 40 kg/m^2)	France	Retrospective	This nationwide study showed that bariatric surgery (BS) is independently associated with a reduced risk of death and invasive mechanical ventilation in obese individuals with COVID-19.
A. Petersen et al. (2020). https://doi:10.1016/j.metabol.2020.154317.	30	Hospitalized patients with Covid	Germany	Concept Proof	CT-based visceral adipose tissue and chest CT-quantified upper abdominal circumference increase the likelihood of COVID-19 severity. Performing routine chest CT can be a tool for risk assessment in patients.
A. P. Rossi et al. (2021). https://doi: 10.1016/j.numecd.2020.11.012.	95	Hospitalized patients with Covid.	Iceland	Prospective cohort	Obese subjects showed longer time of hospital and ICU stay as compared with normal weight patients. Obesity showed significantly higher CRP and CPK levels than normal weight subjects.
A. Qureshi et al. (2021). https://doi:81510.9734/JPRI/2021/v33i27B31497.	7 036	Hospitalized patients with Covid and with comorbidities	USA	Retrospective Cohort	Ample mortality count was observed among obese patients, whereas, the second highest count was among overweight patients. The data shows that the frequency of mortality is highly dependent on patients' BMI.
A. Olivas-Martínez et al. (2021). https://doi:10.1371/journal.pone.0245772.	800	Hospitalized patients with Covid	México	Prospective cohort	In this study, they found similar risk factors for mortality compared to previous reports. However, 45% of patients who did not survive justified ICU admission but did not receive IMV/ICU care due to unavailability of ICU beds. Furthermore, the mortality rate over time was mainly due to the availability of ICU beds, indirectly suggesting that overcrowding was one of the main factors contributing to hospital mortality.

C. Yanover et al. (2020). https://doi: 10.2196/20872.	4 353	Patients with hypertension, diabetes, obesity and other diseases.	Israel	Base population	Of the 4 353 SARS-CoV-2 positive individuals, 173 (4%) patients experienced complications from COVID-19 (all ages ÿ18 years). This analysis suggests that cardiovascular and kidney disease, obesity, and hypertension are significant risk factors for complications from COVID-19.
C. Gazzaruso et al. (2020). https://doi: 10.1016/j.numecd.2020.07.040.	49	Hospitalized patients with Covid.	Italy	Retrospective	Our data first suggest that s interaction with antithrombin (AT) is strongly associated with mortality in COVID-19. Other studies should confirm whether AT may become a prognostic marker and a therapeutic target in COVID-19.
D. Chiumello et al. (2020). https://doi: 10.1016/j.bja.2020.07.006	355	Hospitalized patients with Covid.	Italy	Retrospective	Found strong associations between C-ARDS and male sex and with overweight/obese patients.
D. Freuer et al. (2021). https://doi: 10.1016/j.metabol.2021.154732.	--	Patients with obesity	Germany	Mendelian randomized	Two-sample Mendelian randomization (MR) approach univariate and multivariable, investigated the causal impact of body composition on susceptibility and severity of COVID-19.
D. Moriconi et al. (2020). https://doi: 10.1016/j.orcp.2020.05.009.	115	Hospitalized patients with Covid.	Italy	Observational	Patients with obesity affected by COVID-19 required extended hospitalization and more intensive and prolonged oxygen treatment. Still, they did not have an increased risk of mortality as compared to the subjects without obesity.
D. V. A. R. Carneiro et al. (2021). https://doi.org/10.20945/2359-3997000000351.	--	Patients with comorbidities and hospitalized.	Brazil	Ecological study	This study pointed out that, at the aggregate level, there is a concomitant and correlated increase in mortality rates due to COVID-19 and prevalence of obesity in Brazilian capitals. The data found may contribute to actions to cope with the pandemic aimed at this population.
E. Pérez-Cruz, et al. (2021). https://doi: 10.1016/j.orcp.2021.05.001.	115	Patients admitted to the ICU with SARS-CoV-2	México	Prospective cohort	Diabetes and obesity are risk factors for increasing severity of SARS-CoV-2 infection, and they are both associated with an increase in mortality.
F. Martín-Del-Campo et al. (2021). https:// doi: 10.1016/j.clnesp.2021.08.027.	773	Eutrophic, overweight, obese and morbidly obese	México	Retrospective cohort	Prevalence of obesity and morbid obesity was very high in these hospitalized patients with severe COVID-19. Morbid obesity was significantly associated with some complications.

F. Zhang et al. (2020). https://doi: 10.1002/jmv.26039.	285		China	Retrospective	Our data support that obesity could be a risk factor associated with high mortality in young COVID-19 patients, whereas aggravated inflammatory response, enhanced cardiac injury, and increased coagulation activity are likely to be the mechanisms contributing to the high mortality.
G. Sidhu et al. (2021). https://doi: 10.1016/j.jdiacomp.2021.108054.	425	Hospitalized patients with Covid.	USA	Case control	During a hospitalization for COVID-19, severely obese patients with at least one obesity related condition and morbidly obese patients have a high mortality rate.
G. Page-Wilson et al. (2021). https://doi: 10.1371/journal.pone.0255811.	1 019	Hospitalized patients with Covid.	USA	Retrospective cohort	Racial differences in severe extra-pulmonary complications are present and accordingly both BMI and race are central to considerations of risk stratification and resource allocation.
H. Bihan et al. (2021). https://doi: 10.1186/s12933-021-01329-z.	100	Hospitalized patients with Covid.	France	Retrospective cohort	Epicardial adipose tissue (EAT) is located between the myocardium and the visceral pericardium and is considered the heart's VAT. Our results suggest that measuring EAT volume on chest CT scans at hospital admission in patients with COVID-19 might help to assess the risk of disease aggravation.
H. Cai et al. (2021). https://doi: 10.1186/s12879-021-05818-0.	455	Overweight and Obese.	China	Retrospective cohort	Compared the patients of BMI < 24, and high proportion patients with BMI ≥ 24, especially those with elevated RCP and LDH, developed the severe type, with longer hospitalization duration and anti-virus course. Thus, high BMI is a risk factor for the progression and prognosis of imported COVID-19.
H. Yan et al. (2020). https://doi: 10.1002/edm2.215.	610	Covid 19 dead and survivors.	China	Retrospective cohort	The data indicate that a larger proportion of the effect of BMI on severity of COVID-19 is mediated by glycemia and LDH levels whereas less than half of it is mediated by systemic inflammation.
I. A. Osuna-Padilla et al. (2021). https:// doi: 10.20960/nh.03440.	112	Hospitalized patients.	Mexico	Retrospective cohort	High nutritional risk is related to mortality in COVID-19 ill patients. Overweight and obesity are common in this sample.
J. Robertson et al. (2021). https://doi: 10.1002/oby.23378.	4 315		Sweden	Cohort	Higher BMI in early adulthood was associated with severe COVID-19 many years later, with a risk increase starting already at BMI ≥ 22.5 kg/m2.
J. Wang et al. (2020). https://doi: 10.1002/oby.22979.	297	Overweight and obese	China	Retrospective study	The median days of hospitalization were longer in patients with obesity than lean patients were independent risk factors of severe illness.

K. Hajifathalian et al. (2020). https://doi: 10.1002/oby.22923.	770	Hospitalized patients with Covid.	USA	Observational	Patients admitted with COVID-19 and obesity were more likely to present fever, cough, and dyspnea and be younger than normal weight patients. Obesity was associated with a significantly higher rate of ICU admissionor death independent of age, race, and troponin I level.
L. Busetto et al. (2020). https://doi: 10.1002/oby.22918.	92	Hospitalized in a medical clinic COVID-19.	Italy	Retrospective cohort	Patients with overweight and obesity, despite their younger age, required more frequently assisted ventilation, and they were more prone to be admitted in an ICU or semi-intensive care.
L. Palaiodimos et al. (2021). https://doi.org/10.3390/jcm11030622	8 833	Hospitalized patients with Covid	USA	Base population	The association of overweight and obesity with death appeared to be stronger in men, younger patients, and individuals of Hispanic ethnicity. Furthermore, overweight and obesity were independently associated with in-hospital death.
L. Pietri et al. (2021). https://doi:(10.1016/j.metabol.2021.154703).	131	Hospitalized patients id.	France	Observational	Excess body weight was significantly associated with severe forms of the disease, independently of its classical associated comorbidities.
M. A Vultur et al. (2021). https://doi.org/10.22551/revmedchir. v125i3.2451	108	Patients hospitalized with covid and diabetes.	Romania	Cross-sectional	The study included 108 (33.4%) patients with known or unknown DM, from a group of 323 COVID-19. 92 (85.16%) from the first group and 174 (80.9%) in the second group also associated obesity/overweigh.
M. Cottini et al. (2021). https://doi: 10.1016/j.mayocp.2021.01.021.	338	Overweight and Obese.	Italy	Prospective cohort	Our data suggests that presence of underlying co-morbidities and high BMI work synergistically affect the clinical outcomes of COVID-19.
M. C. Eastment et al. (2021). https://doi: 10.1002/oby.23111.	276 564	Hospitalized patients with Covid.	USA	Cohort	BMI has a stronger effect on mortality particularly in those younger than 65 years of age compared with those who are older.
M. F. Coss-Rovirosa et al. (2021). https://doi:10.20945/2359-3997000000350 .	355	Hospitalized patients with Covid.	México	Cohort	Describe the demographic, clinical, and biochemical characteristics of overweight or obese people with severe COVID-19 pneumonia and evaluate its association with mechanical ventilation requirements in a Mexican cohort.
M. Hamer et al. (2020). https://doi: 10.1073/pnas.2011086117.	334 329	Community of in England.	England	Prospective cohort	General obesity is a risk factor for hospitalization due to COVID-19. Elevated risk was apparent even with modest weight gain.
M. Nakeshband et. al. (2020). https://doi: 10.1038/s41366-020-0648-x.	684	Eutrophic, overweight and Obese.	USA	Retrospective cohort	This study reveals that patients with overweight and obesity who have COVID-19 are at increased risk for mortality and intubation compared to those with normal BMI.

M. Sarmadi et al. (2021). https://doi: 10.1186/s12889-021-11715-7.	159 countries	Confirmed cases and deaths from Covid-19.	Iran	Ecological Study	Countries with higher BMI or cholesterol at aggregate levels had a higher ratio of COVID-19 incidence and mortality, especially in developing countries with younger populations.
N. Kamyari. et al. (2021). https://doi: 10.2196/22717.	100	Recovered patients and patients who died.	Iran	Observational	Obesity has affected increased death rates and reduced recovery rates. Although there are differences in dietary patterns, overall, unbalanced diets are a health threat across the world and affect not only death rates but also the quality of life.
N. Pettit et al. (2020). https://doi: 10.1002/oby.22941.	238	Hospitalized patients with Covid.	USA	Retrospective cohort	Obesity was found to be a significant predictor for mortality among patients with COVID-19 after adjusting for age, gender, and other comorbidities. Patients with obesity were also more likely to present with hypoxemia.
R. J. Thomson et al. (2020). https://doi: 10.1371/journal.pone.0243710.	156	Hospitalized patients with Covid.	England	Prospective Cohort	Age, obesity and degree of hypoxaemia were independently associated with increased odds of deathin patients admitted to an ICU in London with COVID-19.
S. Al Heialy, et al. (2021). https://doi: 10.1016/j.sjbs.2020.11.081.	417	Hospitalized patients with Covid.	UAE	Cohort	This study sheds light on the association between overweight/obese category and comorbidities and emphasizes the need to monitor these patients.And highlights the need for monitoring these patients.
S. Bettini et al. (2021). https://doi: 10.1159/000517851.	90	Patients <75 years old hospitalized.	Italy	Cross- sectional	Patients with overweight and obesity required more IMV and had higher peaks of CRP and ferritin than patients with normal weight during COVID-19.
S. Biscarini et al. (2020). https://doi: 10.1016/j.numecd.2020.07.047.	331	Patients of all BMI ranges.	Italy	Retrospective	Obese patients were more likely to be admitted to the ICU, but there were no significant differences in mortality among non-obese patients.
S. Al-Sabah et al. (2020). https://doi: 10.1111/cob.12414.	1 158	Hospitalized patients with Covid.	Kuwait	Retrospective cohort	In this study, diabetes and BMI were associated with severe COVID-19 outcomes as assessed by ICU admission of hospitalized patients.
S. Sahin et al. (2021). https://doi: 10.1159/000517180.	675	Eutrophic, overweight and Obese.	Peru	Cross-sectional	The lung involvement and presence of hypoxia were more common in people living with obesity, and acute inflammatory markers were lower in normal weight patients when compared with patients with obesity.
T. Kim et al. (2021). https://doi:10.1002/oby.23076.	10 861	Patients with BMI of all ranges.	USA	Base population	Patients who are underweight or with obesity are at a risk for mechanical ventilation and death, suggesting pulmonary complications (indicated by mechanic ventilation).
U. Fresánedoihttt al. (2021). https://doi: 10.1002/oby.23029.	433 995	Eutrophic and Obese	Spain	Cohort	Severe obesity is a relevant risk factor for COVID-19 hospitalization and severity in young adults, having a magnitude similar to that of aging.

V. Chen et al. (2021). https://doi: 10.1007/s10620-020-06618-3.	342	Hospitalized patients with Covid.	USA	Cohort	Metabolic disease was highly prevalent including nearly 90% overweight. Hepatic steatosis was associated with increased transaminitis and need for intubation, dialysis, and vasopressor.
Y. Arbel et al. (2020). https://doi: 10.1038/s41366-020-00680-7.	30 states	Total infected alive, dead and population of each state	USA	Regression	The reasons for the drop in infection and mortality rates with a high prevalence of obesity can be explained by several conditions, such as greater social distancing by obese people, increased metabolic reserves, more aggressive treatment, and unidentified factors that should be examined in researchfuture ones.
Z. Zhu. K. et al. (2020). https://doi: 10.1016/j.metabol.2020.154345.	489 769 Enrolled in the UK Biobank	Overweight and obese.	UK	Cohort	In this large population-based cohort, individuals with more severe obesity, central obesity, or a genetic predisposition to obesity are at greater risk of developing severe COVID-19.

Total of 49 articles. N = number of samples; BMI = body mass index; RCP = reactive C protein; CT = computational tomography; ICU = intensive care unit.

Table 2. Number of articles selected according to the variables: type of study, hospital complications resulting from Covid-19 and country where the research was carried out.

Variable	Number (Percentage)
Type of study	
Cohort Retrospective	16 (33.0 %)
Cohort	6 (12.0 %)
Cohort Prospective	5 (10.0 %)
Observational	6 (12.3 %)
Retrospective	4 (8.2 %)
Transversal	3 (6.1 %)
Ecological Study	3 (6.1%)
Population base	3 (6.1%)
Control case	1 (2.0 %)
Clinical study - Randomized	1 (2.0 %)
Concept proof	1 (2.0 %)
Hospital Complications	
Intensive care unit (ICU)	21 (43.0 %)
Death	18 (37.0 %)
Mechanical ventilation	11 (22.0 %)
Non-invasiveventilation	3 (6.1%)
Kidney Injury/ Hemodialysis	3 (6.1%)
Heart injury	2 (4.1%)
Septic shock	2 (4.1%)
Countries	
United States	11 (22.5%)
Italy	9 (18.4%)
México	7 (14.4%)
China	4 (8.2%)
France	3 (6.1%)
Germany	2 (4.1%)
Iran	2 (4.1%)
Israel	2 (4.1%)
Brazil	1 (2.0 %)
Kwuait	1 (2.0 %)
Turkey	1 (2.0 %)
England	1 (2.0 %)
Dubai	1 (2.0 %)
Iceland	1 (2.0 %)
Spain	1 (2.0 %)
United Kingdom	1 (2.0 %)
Romania	1 (2.0 %)

Does overweight/obesity increase the rate of death in patients with COVID-19?

In accordance with this present systematic review, it was observed that among the 49 selected articles 21 articles demonstrated the influence of overweight and obesity on patient death (KIM et al., 2021), (MARTÍN-DEL-CAMPO et al., 2021a), (ZHANG et al., 2020), (KAMYARI et al., 2021), (MARTÍN-DEL-CAMPO et al., 2021b). A recent study cleared out the correlation of higher body mass and AKI, that increase the risk of death. In addition, it's seemed that BMI itself, in young patients, is the most relevant risk factor to increase the mortality. Apparently its due to aggravated inflammatory responses, cardiac damage, and increased coagulation activity on this population (KIM et al., 2021), (MARTÍN-DEL-CAMPO et al., 2021a), (ZHANG et al., 2020), (KAMYARI et al., 2021).

Kim et al., in 2021 (KIM et al., 2021),demonstrated that the increase of BMI leads to more common pulmonary complications, and higher odds of death by COVID-19 infection. The authors demonstrated that 20.1% of obesity class I, 20.9% of obesity class II, and 21.9% of obesity class III died from SARS-CoV-II infection, with obesity class II and III having a p-value lower than 0.001 when compared with normal weight (KIM et al., 2021).

In the present study, in accordance with the selected articles, it was observed that overweight and obesity are associated with a more severe COVID-19 with increased risk for hospitalization and ICU admission among overweight and obese patients (AL-SABAH et al., 2020), (BUSETTO et al., 2020), (BETTINI et al., 2021), (KAMYARI et al., 2021), an increased risk of intubation and invasive mechanical ventilation and increased death rate (MARTÍN-DEL-CAMPO et al., 2021a), (NAKESHBANDI et al., 2020), (BUSETTO et al., 2020), (BETTINI et al., 2021), (EASTMENT et al., 2021).

Several studies have demonstrated the mechanisms associated with the hospital complications in overweight/obese COVID-19 patients, among them, are obesity-related

comorbidities; elevated ACE2 expression; chronic inflammation, leading to increased expression of cytokines (cytokine storm), which is related to acute respiratory syndrome; oxidative stress; and lipotoxicity, damaging the liver and pancreas, which leads to insulin resistance and metabolic syndrome. In addition, obese patients have poor pulmonary reserve and rapid O2 desaturation, contributing to early intubation. Upper respiratory tract can also be obstructed due to the excess adipose tissue and dyslipidemia can promote pulmonary inflammation and vascular damage (COSS-ROVIROSA et al., 2021), (CHIUMELLO et al., 2020), (AL-SABAH et al., 2020), (NAKESHBANDI et al., 2020), (CARNEIRO; HILLESHEIM; HALLAL, 2021).

COVID-19 complications in obese patients are followed by a greater activation of the inflammatory response and hypercoagulable state, causing vascular damage, accelerating hypertension, increasing the risks of pulmonary embolism, stroke, and thrombosis. On the other hand, there is also an attenuated innate immune response to viral infections (KIM et al., 2021), (NAKESHBANDI et al., 2020), (BETTINI et al., 2021). Finally, these findings demonstrated that obesity might be an important risk factor for COVID-19 complications.

In addition to the exacerbation of comorbidities, other complications resulting from COVID-19 in obese patients are: ARDS, respiratory failure, pneumonia, pulmonary embolism, need for artificial respiration, AKI, liver damage, thrombosis, need for hemodialysis, neurological lesions with encephalitis, cutaneous manifestations, myalgia, septic shock, acute myocardial infarction, cerebrovascular disease, cardiac arrest and even multiple organ failure (BIHAN et al., 2021), (MALAVAZOS et al., 2021), (QURESHI et al., 2021), (ROBERTSON et al., 2022), (SARMADI et al., 2021).

Some limitations of this review were: a) only studies published in English and in Portuguese were considered, so relevant studies published in other languages may have been disregarded; b) only studies that analyzed hospitalized patients for COVID-19 was considered, thus other relevant articles that analyzed general patients affected by COVID-19 may have been excluded.

Conclusion

In conclusion, it was observed that several articles described that overweight and obesity are related to a longer hospital stay, and other severe outcomes of COVID-19 such as invasive mechanical ventilation, non-invasive ventilation, kidney, lung, hepatic and heart injury, septic shock, ICU admission and deaths regardless of other risk factors (Figure 2). Thus, this population needs to be addressed with priority in actions to prevent and treat COVID-19.

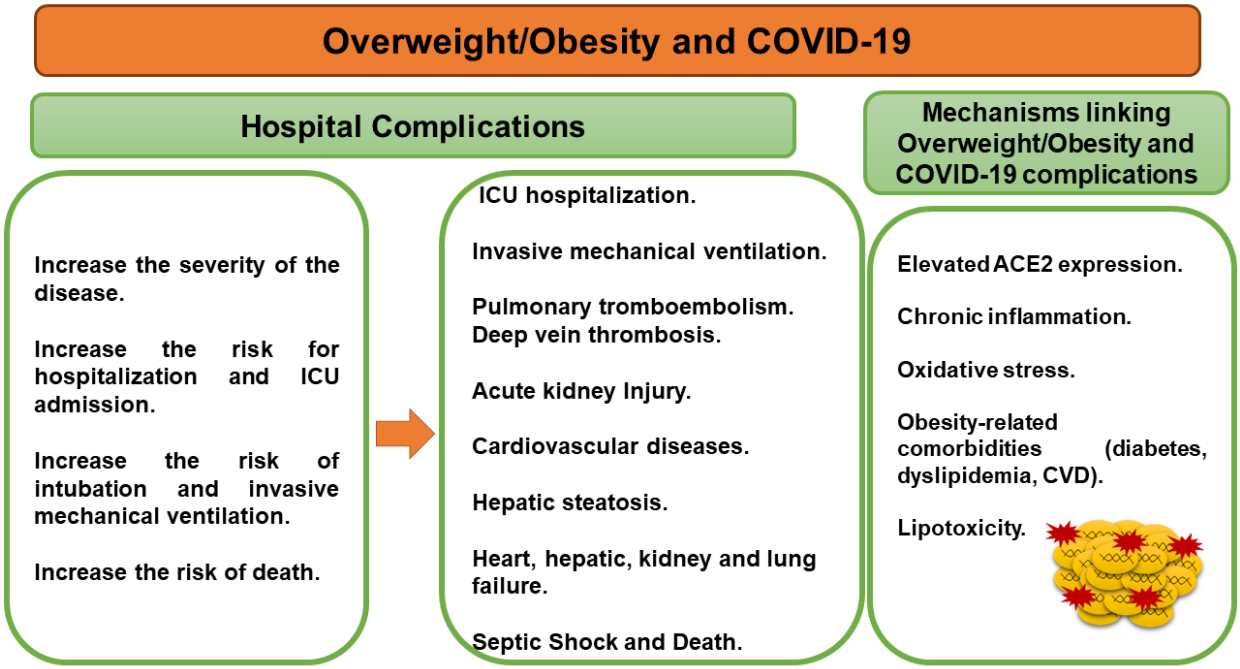

Figure 2. Schematic representation of the association between overweight/obesity and COVID-19. Hospital complications and mechanisms associated with this interrelation ship. ACE2 = angiotensin converting enzyme 2. CVD = cardiovascular diseases.

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Competing Interests

The authors declare no conflicts of interest.

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