Literature Review

Impact of COVID-19 on the gravity and prognosis of individuals with obesity: a systematic review

Impacto da COVID-19 na gravidade e prognóstico de indivíduos com obesidade: uma revisão sistemática

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ABSTRACT | INTRODUCTION: A marked proportion of patients with obesity has insulin resistance and hyperactivity of the renin-angiotensin-aldosterone system, which may be related to the worse results caused by SARS-CoV 2. In addition, the angiotensin 2-converting enzyme has greater expression in adipose tissue when compared to the lung, being susceptible to the entry of the virus in the adipocytes making it an important viral reservoir allowing the spread to too many organs. **OBJECTIVE:** To identify whether obesity can be a more serious predictor and worse prognosis for Coronavirus Disease 2019 (COVID-19). **MATERIALS AND METHODS:** Systematic review under the code CRD42020200617 with observational studies through the PubMed databases, the VHL Regional Portal, SciELO, Science Direct and Cochrane, and manual searches using the "Prognosis" OR "Patient Acuity" AND " Coronavirus Infections " AND " Obesity ". Observational studies that assess the impact of COVID-19 in common with obesity of both sexes that assess a score ≥7 on the Newcastle-Ottawa scale were included. RESULTS: 9 studies were included, totaling a sample of 179,047 adult patients aged 18 to 80 years, with a minimum BMI <24 kg / m2 and a maximum> 35 kg / m2. It was found that with obesity, he wishes to present an increase in the admission rates for acute and mandatory care, invasive mechanical necessity IMV), pneumonia and develop severe COVID-19, thus increasing their hospital stay. **CONCLUSION:** Individuals with obesity develop greater severity and worse prognosis for COVID-19, since there is an increase in admission rates for acute and mandatory care, need for IMV, length of hospital stay, severity and lethality.

DESCRIPTORS: Prognosis. Patient acuity. Coronavirus infections. Obesity.

RESUMO | INTRODUÇÃO: A maioria dos pacientes com obesidade apresenta resistência à insulina e hiperatividade do sistema renina-angiotensina-aldosterona, o que pode estar relacionado aos piores resultados perante infecção pelo SARS-CoV 2. Além disso, a enzima conversora de angiotensina 2 tem maior expressão no tecido adiposo quando comparado com o pulmão, sendo suscetível a invasão do vírus nos adipócitos tornando-o um importante reservatório viral permitindo propagação para demais órgãos. **OBJETIVO:** Identificar se a obesidade pode ser preditor de maior gravidade e pior prognóstico da Doença do Coronavírus 2019 (COVID-19). **MATERIAIS E MÉTODOS:** Revisão sistemática sob o código PROSPERO CRD42020200617 com estudos observacionais através das bases de dados PubMed, Portal Regional da BVS, SciELO, Science Direct e Cochrane, e buscas manuais por meio do cruzamento "Prognosis" OR "Patient Acuity" AND "Coronavirus Infections" AND "Obesity". Foram incluídos estudos observacionais que avaliaram o impacto da COVID-19 em indivíduos com obesidade de ambos os sexos que apresentaram pontuação ≥7 na escala Newcastle-Ottawa. RESULTADOS: Foram incluídos 9 estudos totalizando uma amostra de 179.047 pacientes adultos com idade entre 18 a 80 anos, com IMC mínimo <24 kg/m2 e máximo >35 kg/m2. Verificou-se que indivíduos com obesidade apresentam aumento das taxas de admissão de cuidados agudos e críticos, necessidade ventilação mecânica invasiva (VMI), pneumonia e desenvolvem COVID-19 grave, aumentando assim seu tempo de permanência hospitalar. **CONCLUSÃO:** Indivíduos com obesidade desenvolvem maior gravidade e pior prognóstico da COVID-19, visto que apresentam aumento das taxas de admissão de cuidados agudos e críticos, necessidade de VMI, tempo de permanência hospitalar, gravidade e letalidade.

DESCRITORES: Prognóstico. Gravidade do paciente. Infecções por coronavírus. Obesidade.

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Introduction

The current pandemic of severe acute coronavirus respiratory syndrome (SARS-Cov-2), commonly known as Coronavirus Disease 2019 (COVID-19), poses a scenario with serious repercussions for health systems in Brazil and worldwide. This infection leads to severe hypoxemic respiratory failure, resulting in overcrowding of intensive care units (ICU), lack of equipment and professionals, and significant death toll, mainly in the population with previous chronic health conditions[1].

SARS-Cov-2 can penetrate human cells by direct binding to the angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface[2,3]. It subsequently promotes maladjustment of the expression of this enzyme, making it incapable of fulfilling its protective effects on the orbits[2,3]. It is known that a considerable number of obese patients present insulin resistance and hyperactivity of the renin-angiotensin-aldosterone system, and this fact may be related to the worst results in the face of infection by this virus[2]. Evidence has shown that COVID-19 can worsen insulin resistance in people with Type 2 and Type 1 Diabetes Mellitus, especially those with obesity. Even in the milder form, COVID-19 can induce a pro-inflammatory state, which may be responsible for a reduction in insulin sensitivity[4].

Even knowing that ACE2 participates to the renin angiotensin aldosterone system[5], it has not yet been demonstrated that people with obesity have some alteration (quantity and/or quality) of this enzyme. There is a hypothesis that the greater expressiveness of ACE2 in the adipose tissue of obese individuals may increase SARS-Cov-2 infection and receptivity to this tissue[5,6]. ACE2 can allow the virus to enter the adipocytes making it an important viral reservoir allowing it to spread to other organs[2].

Given that obesity is a public health problem, responsible for the increase in the incidence of hypertension, diabetes and other comorbidities[7], our study presents as clinical relevance greater clarification of the relationship between SARS-Cov-2 and obesity, allowing a better targeting of approaches to these patients. Therefore, this systematic review aims to identify whether obesity can be a predictor of greater severity and worse prognosis of COVID-19.

Methods

A systematic review conducted in accordance with the recommendations of PRISMA (Preferred Reporting items for Systematic Reviews and meta-analyses)[8], registered at PROSPERO (International Prospective Register of Systematic Reviews) under the code PROSPERO CRD42020200617, to answer the question through the PECO (Population/Exposure/Comparator/Outcome) strategy: Do individuals with obesity present greater severity and, consequently, worse prognosis in COVID-19?

Observational studies that assessed the impact of COVID-19 in obese individuals of both sexes, who scored 7 on the Newcastle-Ottawa[9] scale, were included. On the other hand, studies with individuals affected by another type of Corone virus or other respiratory viruses were excluded, as well as studies with incomplete data and literature reviews.

The bibliographic searches of the scientific articles were carried out in July 2020 on the virtual data platforms Pubmed, Regional Portal of the VHL, Scielo, Science Direct and Cochrane Library by two independent authors, along with manual search, with the following combinations of Health Science Descriptors (DeCS) and Medical Subject Headings (MeSH): "Prognosis" OR "Patient Acuity" AND "Coronavirus Infections" AND "Obesity". A new search was conducted in September 2020 for possible updates of new studies.

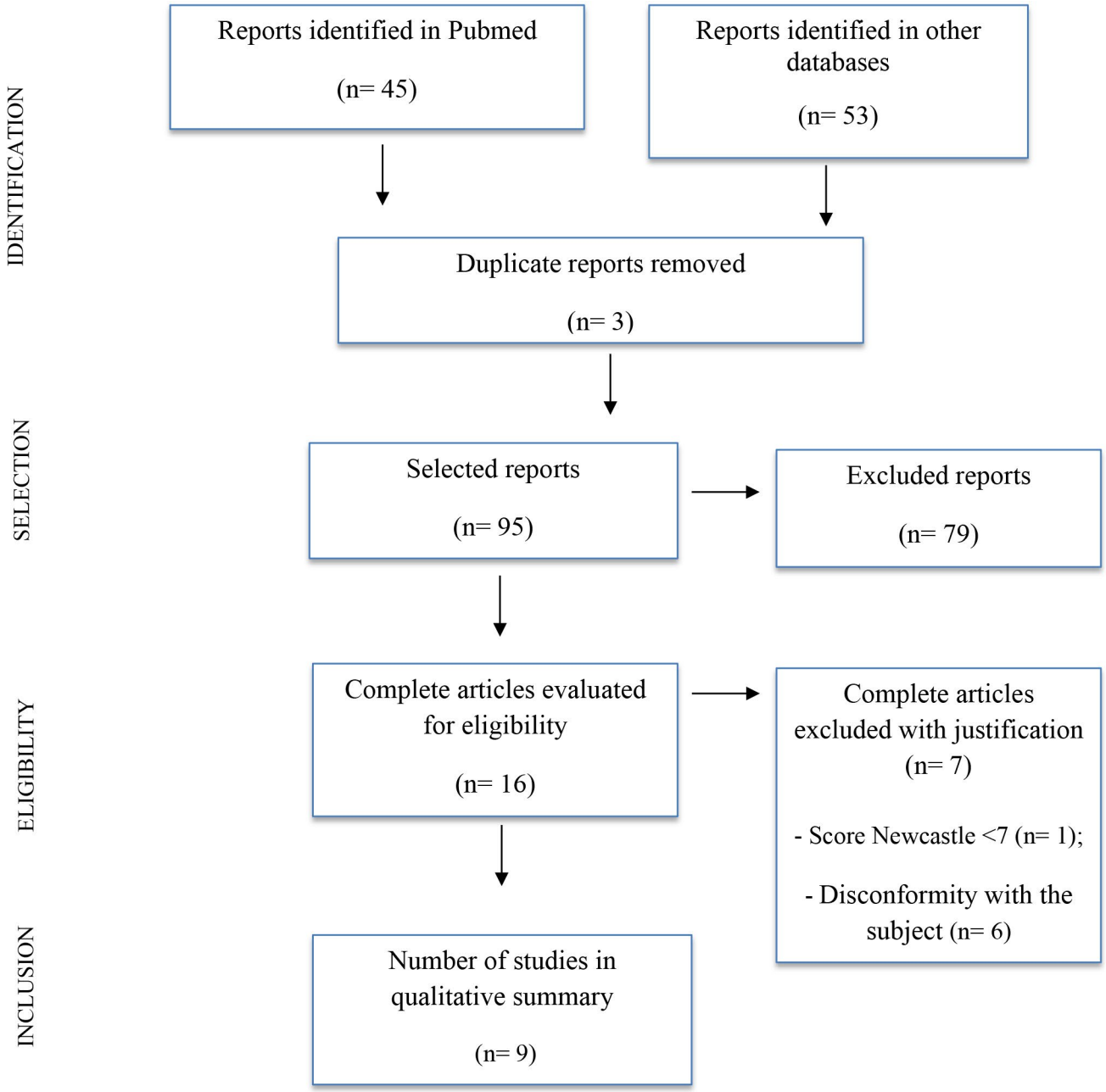
The evaluation of the quality of the included studies was performed by the Newcastle-Ottawa scale, its measurement was calculated in three components: selection of groups (zero to four points); comparability (zero to two points); and exposure/result (zero to three points). This measurement was presented numerically, and each asterisk (*) corresponded to one point, totaling from zero to nine points.

The screening process took place initially with the reading from the titles and abstracts of the articles, thus generating the first exclusion, soon after the reading of the manuscripts, occurred to the second exclusion, and then the extraction of the outcomes of interest, which include the study design, sample characteristics, the control group, the outcomes analyzed and the main results obtained that were shown in the table, with presentation of values and confidence interval or value "p" of significance, being considered significance when $p < 0.05$.

Results

Of the 98 references found through search strategies, only 3 were excluded by duplicity. Of the remainder, 79 were excluded after reading the titles and abstracts. Finally, 9 studies were included for analysis considering the eligibility criteria (Figure1).

Figure 1. Flowchart of screening and selection of articles that investigated the relationship of COVID-19 in obese individuals from July to September 2020



The included studies were conducted in Mexico, China, the United States, and France[10-18]. The follow-up time of the studies ranged from 1 to 2 months, with five articles[11-13,16,18] with 1 month of follow-up. All were observational retrospective cohorts, except for two that were prospective cohorts, and included a total of 179,047 adult patients, aged 18 to 80 years, mostly male, with varying severity and BMI scores, being considered >30 kg/m2, according to the World Health Organization and >25 kg/m2 considering the cut-off point for Asian populations[19].

The methodological quality of the included studies was high (Table 1). The scores ranged from 7 to 9 points. Meta-analyses cannot be conducted because the predominant methodological design of the studies included in this review is observational cohort.

Table 1. Quality evaluation of selected articles according to the Newcastle-Ottawa scale

AUTHOR	TYPE OF STUDY	ITEMS ASSESSED			TOTAL
		SELECTION	COMPARABILITY	EXPOSURE	
BELLO-CHAVOLLA et al.[10]	Cohort	****	**	***	9
CAI et al.[11]	Cohort	****	**	**	8
GAO et al.[12]	Cohort	***	**	**	7
HAJIFATHALIAN et al.[13]	Cohort	****	**	**	8
HU et al.[14]	Cohort	****	*	**	7
KALLIGEROS et al.[15]	Cohort	****	**	***	9
LIGTHER et al.[16]	Cohort	****	*	**	7
SIMONNET et al.[17]	Cohort	****	**	***	9
ZENG et al.[18]	Cohort	***	**	**	7

Evaluation of the quality of the studies included by the Newcastle-Ottawa scale, and each question answered corresponds to an asterisk.

The results found after data extraction from the included studies are described below.

Table 2. Results related to the impact of COVID-19 associated with obesity. (to be continued)

AUTHOR/YEAR	SAMPLE/ CHARACTERISTICS	VARIABLES ASSESSED	MAIN FINDINGS	
BELLO-CHAVOLLA et al.[10]	We obtained data from confirmed/negative cases of COVID-19 from the General Directorate of Epidemiology of the MH of Mexico. - Positive: (n= 51633). - Negative: (n= 98567). - Suspect: (n= 26933).	Clinical characteristics, predictive risk factors of COVID-19-related 30-day lethality, influence of obesity and diabetes on ICU admission, and need for IMV.	Chances of positivity for SARS-Cov-2 were higher for patients with diabetes, hypertension, obesity, age >65 years and male sex. Patients with early-onset diabetes (<40 years) and coexisting obesity showed an increased risk of lethality due to COVID-19 (p<0.001). Obese patients confirmed with COVID-19 presented higher rates	high, about 13.5%, mortality, hospitalization and pneumonia. In addition to presenting higher rates of hospitalization in the ICU, they were more likely to be intubated. COVID-19 increased the risk of mortality in obesity by five times. Obesity associated with any number of comorbidities significantly increased the risk of lethality (p<0.001).
CAI et al.[11]	A total of 96 patients infected with SARS-Cov-2 were included: BMI <24 kg/m2: (n= 59) BMI >24 kg/m2: (n= 37)	Clinical and demographic characteristics, CK levels, serum creatine and LDH, BP, lymphocyte and platelet count and factors associated with admission to the ICU.	Pneumonia: 75 patients were diagnosed and 21 patients were without findings based on CT. 25 patients were diagnosed with ARDS. Lymphocyte (p=0.027) and platelet count (p<0.001) were negatively correlated with BMI, while hemoglobin (p=0.008), CK (p=0.001), creatinine	serum (p<0.001) and LDH (p=0.001) showed a significant positive correlation with BMI. Older patients (p=0.009) and BMI ≥24 kg/m2 (p=0.005) were independent risk factors associated with ICU admission among COVID-19 patients. BMI ≥24 kg/m2 (p=0.007) were independent risk factors associated with radiographic exacerbation of the disease.
GAO et al.[12]	Adult patients with COVID-19 from three hospitals in China were selected and divided into: - Non-obese: (n=75). - Obese: (n=75).	Clinical features, plasma CRP levels, lymphocyte count, length of hospital stay and severity of COVID-19.	About 29 patients (19.3%) had diabetes. Obese patients were more likely to have diabetes than those without obesity (24.0% vs. 14.7%). At hospital admission, obese individuals had higher CRP levels and fewer lymphocytes (early indicators of severe COVID-19).	Obese patients also had longer hospital stay (p= 0.037) and a higher proportion had severe COVID-19 compared to non-obese patients (p=0.007). The presence of obesity was associated with a three times higher risk of severe COVID-19. Each 1-unit increase in BMI was associated with a 12% increase in the risk of severe COVID-19.

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Table 2. Results related to the impact of COVID-19 associated with obesity. (continuation)

AUTHOR/YEAR	SAMPLE/ CHARACTERISTICS	VARIABLES ASSESSED	MAIN FINDINGS	
HAJIFATHALIAN et al.[13]	Approximately 770 COVID-19-positive patients were included and categorized BMI <18,5 kg/m2: (n=28). BMI 18,5-30 kg/m2: (n=465). BMI ≥30 kg/m2: (n=277).	Demographic data, clinical characteristics, laboratory data and clinical outcomes were summarized (admission to the ICU with or without invasive mechanical ventilation and death).	Obese patients were more likely to have a previous diagnosis of asthma/COPD or OSA (p =0.007e p<0.001, respectively). They were also more likely to have a history of fever (78%, p<0.003), cough (73%, p=0.016) and dyspnea (78%, p<0.001). About 33% of obese patients had a higher risk of admission to the ICU and intubation (p = 0.001).	Obesity (BMI ≥30 kg/m2) was associated with increased risk of admission to the ICU or death (RR = 1.58, p = 0.002). The same analysis was repeated in the subset of patients aged 60 years or older. Obesity remained an independent predictor of admission to the ICU or death in this age group (RR = 1.48, p = 0.020).
HU et al.[14]	A total of 58 patients diagnosed with COVID-19 were included, and their clinical data were collected. Overweight/obesity: BMI ≥24 kg/m2 ALF: ALT > 40 U/L.	Anthropometric, BP and laboratory measurements (neutrophils, monocytes, lymphocytes, FPG, ALT, albumin, serum creatinine, UNB and CRP). Overweight/obesity were defined as BMI 24 kg/m2	A total of 29 patients (55.8%) were overweight/obese and 17 (29.3%) had ALF Compared to the control group, overweight/obesity patients had a longer hospitalization time (17.4 ± 6.1 versus 20.4 ± 4.4 days, p= 0.046) and a higher proportion	Prolonged hospitalization (26.1% versus 62.1%, p= 0.010)
KALLIGEROS et al.[15]	We identified 103 adult patients admitted with COVID 19 in two hospitals in the United States. BMI <25 kg/m2: (n=19) BMI 25-29,9 kg/m2: (n=35). BMI 30-34,9 kg/m2: (n=22). BMI >35 kg/m2: (n=27).	Demographic and epidemiological data, risk factors associated with admission to the ICU, and the need for IMV in the first 10 days of hospitalization.	The most common comorbidity was hypertension (64.0%), followed by diabetes (36.8%) and heart disease (24.2%). The prevalence of obesity was 47.5% in hospitalized patients, 56.8% in patients who needed ICU hospitalization, and 65.5% in patients who needed IMV. Although diabetes, heart and lung disease seem to increase the risk	of admission to the ICU, only severe obesity (≥35 kg/m2) reached statistical significance (aOR: 5.39, 95% CI: 1.13-25.64). Patients who needed IMV were more likely to have a diagnosis of preexisting heart disease (aOR: 3.41, 95% CI: 1.05-11.06) or obesity (aOR of 6.85 and 9.99 for BMI 30-34.9 kg/m2 and ≥35kg/m2, respectively).
LIGTHER et al.[16]	Patients who had positive polymerase chain reaction for COVID-19 were extracted and categorized: >60 years: BMI 30-34 kg/m2 (n=141) BMI >35 kg/m2: (n=99). <60 years: BMI 30-34 kg/m2: (n=173) BMI >35 kg/m2: (n=134).	Clinical characteristics, admission in acute and critical care.	Patients aged <60 years and BMI 30-34 kg/m2 were 2.0 (p<0.0001) and 1.8 (p=0.006) times more likely to be admitted to acute and critical care, respectively, compared to individuals with BMI <30 kg/m2. Similarly, patients with BMI ≥35 kg/m2 and with age <60 years had 2.2(p<0.0001) and 3.6 (p<0.0001) times	more chances of being admitted with BMI ≥35 kg/m2 and aged <60 years had 2.2 (p<0.0001) and 3.6 (p<0.0001) times more chances of being admitted to acute and critical care than patients of the same age group with BMI <30 kg/m2.

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Table 2. Results related to the impact of COVID-19 associated with obesity. (conclusion)

AUTHOR/YEAR	SAMPLE/ CHARACTERISTICS	VARIABLES ASSESSED	MAIN FINDINGS	
SIMONNET et al.[17]	About 124 patients were classified according to the need for IMV: - IMV: (n=85). - No IMV: (n=39).	Clinical characteristics and prevalence of need for IMV.	Moderate obesity and severe obesity were around 47.6% and 25.2%, respectively, more frequent among participants with COVID-19 (p<0.0001). A total of 85 of the 124 study participants (68.6%) required VMI, including 62 patients on admission, 13 on the 1st day, 4 on the 2nd day, and	6 patients remaining within 7 days. Those who needed IMV frequently had moderate and severe obesity (p<0.01).
ZENG et al.[18]	A total of 66 patients with COVID-19 with FLDAM were included in the analyses and divided into two groups: - Obese:(n=45). - Non-obese: (n =21).	A total of 66 patients with COVID-19 with FLDAM were included in the analyses and divided into two groups: -Obese: (n=45). - Non-obese: (n =21).	Among the 66 patients included, 12.1% were smokers, 24.2% had type 2 diabetes, 28.8% hypertension and 68.2% dyslipidemia. Compared to the non-obese group, obese patients had higher levels of aspartate aminotransferase, fasting glycemia, LDL and lower lymphocyte count.	They presented higher concentrations of PCR (p<0.001) and lower count of lymphocytes (p=0.005). The presence of obesity in FLDAM patients was associated with a 6 times higher risk of severe COVID-19.

MH: Ministry of Health; BMI: Body mass index; ICU: Intensive care unit; CK: Creatine kinase LDH: lactate dehydrogenase; BP: Blood pressure; CT: Computed tomography; ARDS: Acute respiratory distress syndrome; CRP: C-reactive protein; OSA: Obstructive sleep apnoea; COPD: Chronic obstructive pulmonary disease; ALF: Abnormal liver function; ALT: Alanine aminotransferase; FPG: Fasting plasma glucose; UNB: Urea nitrogen in the blood; IMV: Invasive mechanical ventilation; FLDAM: Fatty liver disease associated with metabolism; LDL: Low-density lipoprotein.

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Discussion

It was possible to observe that patients with obesity present a higher rate of hospitalization, acute care and admission to the ICU, pneumonia, acute respiratory discomfort syndrome and IMV (invasive mechanical ventilation) when compared to non-obese individuals[10,11,13-17]. These patients present a respiratory muscle overload, being three times higher, so that the total consumption of respiratory oxygen is raised by 14%. An acute viral infection can cause additional disharmonies between the capacity to generate respiratory muscle strength and the demands generated by breathing, leading to an increased risk of respiratory insufficiency[20]. There was a greater hospital stay in this public, which can be justified by the fact that obese patients are more predisposed to have severe COVID-19[12], in cases of obese patients with FLDAM this risk is six times higher[18]. In addition, it was observed that individuals with obesity and preexisting heart disease are more prone to need IMV.

In relation to lethality, obese individuals presented five times higher risk, when compared to non-obese individuals, this condition associated with comorbidities, regardless of the amount, significantly increased the risks. Early-onset diabetes (40 years of age) associated with coexisting obesity emphasized compatibility with higher mortality rates in individuals with COVID-19. This finding reflects the notion that early-onset type 2 diabetes can generate an increased risk of mortality in younger patients[10].

BMI was associated with higher admission rates in the ICU, the need for VMI, and the radiographic exacerbation of COVID-19[11,13-17]. In addition, obesity was associated with greater disease severity, since each BMI unit increases the risk of severe COVID-19[12], in the same way that obesity >35 kg/m2 can increase the risk of admission to ICU[15]. The disproportionate production of adipocins (especially leptin and adiponectin) has attracted attention, as they act as signaling molecules with broad effects in several systems, including the lungs, which may provide a mechanistic explanation related to the danger of the association of obesity with severe COVID-19. Adipose tissue also has the ability to produce a greater number of other adipocins, including resistin and visfatine, which affect the immune system and may be associated with adverse sepsis outcomes[21].

Advanced age was also shown to be an independent risk factor associated with admission to the ICU among patients with COVID-19[11]. In another study, it was identified that individuals with obesity with BMI 30-34 kg/m2 or more than 35 kg/m2, aged less than 60 years, were more likely to be admitted to acute and critical care than patients in the same age group with BMI >30 kg/m2[16]. On the other hand, other evidence shows that the association between obesity and admission to the ICU is true in all age groups, as well as in the subset of patients over 60 years of age, specifically[13].

With regard to laboratory parameters, such as lymphocyte counts[11,12,18] and platelets, it was observed that these were negatively correlated with BMI, while hemoglobin, CK, serum creatinine and LDH were significantly correlated[12]. In addition, obese individuals present higher levels of CRP, aspartate aminotransferase, fasting glycemia and LDL[12,18]. Both high CRP levels and lower numbers of lymphocytes are considered early indicators of severe COVID-19, thus confirming the vulnerability of these individuals to a greater severity and worse prognosis for the disease in question[18].

It is important to note that some of the studies included in this review presented obesity associated with other comorbidities[10,12,13,15,18], especially diabetes, which may lead to a higher risk for the most severe form of COVID-19 involvement. Among the limitations found for this review are the small number of studies that evaluated the severity and prognosis of individuals with obesity diagnosed with COVID-19, in addition to the scarcity of evaluation of pulmonary variables. Another limitation would be that few studies have evaluated the association of obesity with other comorbidities, it is plausible that this fact may result in a more severe impairment of COVID-19 and consequently a worse prognosis.

Studies are still needed to investigate the long-term impact of obesity as a factor for a greater severity and worse prognosis of COVID-19. However, our study contributes significantly to clinical practice, as it shows that COVID-19 associated with obesity generates longer hospital stay, need for IMV, as well as higher mortality rates. These results are important and allow a better targeting of approaches to these patients.

Conclusion

Individuals with obesity develop more severity and worse prognosis of COVID-19, as they have increased rates of admission of acute and critical care, need for IMV, longer hospital stay, severity and lethality, in addition to presenting changes in laboratory parameters such as lymphocytes, platelets and hemoglobin, CK, serum creatinine, LDH, CRP, aspartate aminotransferase, fasting glycemia and LDL. Therefore, new studies are needed for greater evidence and better targeting of approaches to these individuals.

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Author contributions

Araújo TA, Moura RF and Almeida NO participated in the conception, design, search and analysis of research data, interpretation of results, writing of the scientific article and approval of the final version.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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