



Obesity and comorbidities in COVID-19: a longitudinal observational retrospective study of the main relationships of life risk

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Abstract

Introduction: Currently, around 30% of the world's population is overweight or obese. By 2030, it is estimated that more than 60% of the world's population will be overweight or obese. The COVID19 pandemic has resulted in the worsening of obesity comorbidities. The primary increase in the inflammatory response in obese patients functions as a predictor for the hyperinflammatory state observed in COVID-19. Therefore, this primary increase can be amplified by SARS-CoV-2 infection, increasing the production of cytokines such as TNF- α , IL-1, and IL-6. **Objective:** It was to carry out a retrospective longitudinal observational study to quantitatively analyze how cardiovascular comorbidities such as diabetes, hypertension, obesity, smoking, and compromised immunity contribute to the increased risk of life of participants affected by COVID-19. **Methods:** This study followed a longitudinal observational retrospective design (STROBE). A total of 45 public and official documents from Brazil (ANVISA), WHO (World Health Organization), Pan American Health Organization (PAHO), EASO (The European Association for the Study of Obesity - The European Commission/ National Information on COVID-19, Lancet Resource Centre) and scientific articles were subjected to eligibility analysis and, after that, 32 documents dated from 2019 to 2022 were selected. **Results:** In total, 3,993,857 participants

were found from 32 documents. The highest incidence of deaths occurred in participants who were smokers, had compromised immunity, had diabetes, and were obese. The greatest risk of death was observed among participants who smoke (HR=2.5) and those with compromised immunity (HR=2.1). Despite this, other comorbidities such as diabetes, obesity, and hypertension also presented statistically significant results for the risk of life. It was observed that only the difference between the means of the comorbidities "obesity" and "diabetes" was not statistically significant, with $p < 0.05$, that is, both comorbidities have similar impacts on the worsening and death of participants in the presence of COVID-19. **Conclusion:** Cardiovascular comorbidities such as diabetes, hypertension, obesity, smoking, and compromised immunity contributed to the increased risk of life in participants affected by COVID-19, especially in those of an older age. The endothelial dysfunction caused by SARS-CoV-2 explains why participants with comorbidities related to blood vessels such as cardiovascular disease, hypertension, diabetes, and obesity are more likely to develop severe COVID-19, even death.

Keywords: Obesity. Comorbidities. Life risk. Public health. COVID-19.

Introduction

In the scenario of chronic non-communicable diseases, obesity stands out as a multifactorial disease that can cause several public health problems [1]. Currently, around 30% of the world's population is overweight or obese. By 2030, it is estimated that more than 60% of the world's population will be overweight or obese. Estimates suggest that the prevalence of severe obesity in 2030 will be 11%, approximately twice the current prevalence. In this context, there are 2.0 billion overweight and obese people in the world [1].

By 2025, Brazil will be in fifth place in the world ranking, with an estimated 18.0 million people, tending to reach more than 70.0 million. Furthermore, in Brazil, this chronic disease has increased by 67.8% in the last thirteen years, from 11.8% in 2006 to 19.8% in 2018. The highest growth rate was among adults aged 25 to 34 (84.2%) and 35 to 44 years old (81.1%). Today, in the country, 20.7% of women are obese and 18.7% of men [2,3].

In this context, the appearance of the new coronavirus (SARS-CoV-2), whose disease is COVID-19, resulted in the worsening of obesity comorbidities [3-11]. It is necessary to understand the mechanisms by which obese patients are at greater risk of progressing to severe forms of the disease, even death [12,13]. In this sense, immunity plays a decisive role in SARS-CoV-2 infection. The lack of regulation and excessive immune response to the viral stimulus produces exacerbated pro-inflammatory cytokines (cytokine storm), reaching a state of hyperinflammation, with consequent damage to various tissues in the obese person [14].

Therefore, the occurrence of immune dysfunction, greater predisposition to infection, and mortality from sepsis is a reality. Obesity was correlated with high leukocyte and lymphocyte counts (except NK, suppressor T, and cytotoxic T cells), with suppression of lymphocyte proliferation of T and B lymphocytes, and with higher rates of oxidative activity and phagocytosis by monocytes and granulocytes, demonstrating the consequences of this pathology on the immune system [14]. In addition to these changes, it is known that obesity initially favors the development of inflammation in adipose tissue, through increased production of pro-inflammatory adipokines, such as IL-6 and TNF- α . In this way, the proportion between pro-inflammatory and anti-inflammatory cytokines becomes unbalanced [15]. Consequently, damage occurs to the vascular system, promoting endothelial dysfunction, characterized by a decrease in the production of nitric oxide and an increase in the synthesis of reactive oxygen species, which establishes an inflammatory state and oxidative stress. Regarding innate immunity, in obese patients,

there is a modification of the immune environment in adipose tissue [16].

As a corollary, obesity induces a change in the macrophage profile, with an increase in the M1 (pro-inflammatory) phenotype. This effect corresponds to an upregulation in inflammatory genes, and a downregulation in anti-inflammatory genes. However, it is not only in adipose tissue that this change occurs in cells of the innate immune system. Thus, authors demonstrated that circulating mononuclear cells in obese individuals are also in a pro-inflammatory state, with an increase in intranuclear factor κ B (NF- κ B) and, consequently, with an increase in the transcription of pro-inflammatory genes. Inflammatory processes regulated by it. As a corollary, the innate immune response in patients with obesity is altered, resulting in an imbalance in the line of defense against infections, an increase in the inflammatory response, and an abnormal activation of T lymphocytes. Furthermore, the primary increase in the inflammatory response in obese patients works as a predictor for the hyperinflammatory state observed in COVID-19. Therefore, this primary increase can be amplified by SARS-CoV-2 infection, increasing the production of cytokines such as TNF- α , IL-1, and IL-6 [13,17,18].

Therefore, the present study aimed to carry out a longitudinal observational retrospective study to quantitatively analyze how cardiovascular comorbidities such as diabetes, hypertension, obesity, smoking, and compromised immunity contribute to the increased risk of life in patients affected by COVID-19.

Methods

Study Design

This study followed a longitudinal observational retrospective model, following the clinical research rules of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), available at: <https://www.strobe-statement.org/>.

Search Strategy and Data Sources

After literary search criteria using MeSH Terms (descriptors): *Obesity; Cardiovascular diseases; Diabetes; Hypertension; Smoker; Impaired immunity; COVID-19*. A total of 45 public and official documents from Brazil (ANVISA), WHO (World Health Organization), Pan American Health Organization (PAHO), EASO (The European Association for the Study of Obesity - The European Commission/ National Information on COVID-19, Lancet Resource Centre) and scientific articles were subjected to eligibility analysis and, after that, 32 documents dated from 2019 to 2022 were selected.

Participant Eligibility

The inclusion criteria were participants with a positive result confirmed by rtPCR or qPCR for COVID-19, presenting comorbidities such as obesity (BMI of 30 to 45 kg/m²), diabetes under treatment, hypertension, smokers and compromised immunity, with ages varying from 40 to 80 years old and of both genders. The exclusion criteria were data that did not meet the proposed objective of the present study.

Ethical Approval

Not applicable, as the present study consulted public information and statistical databases such as WHO, PAHO, Ministry of Health, ANVISA, and EASO.

Statistical Analysis

For data analysis, a database was built in a Microsoft Excel spreadsheet, which was exported to the statistical program Minitab 18® (version 18. Minitab. LLC. State College. Pennsylvania, USA). The variables were presented as percentages, mean, and standard deviation. Logistic regression analysis was performed to determine the risk of life [Hazard Risk (HR)] about the variables diabetes, hypertension, obesity, smokers, and compromised immunity in the presence of COVID-19, with p<0.05 being significant. Tukey analysis (ANOVA-One-Way) was also performed with p>0.05 with a statistical difference in the 95% CI between the variables of the present study in the 95% CI.

Results

In total, 3,993,857 participants were found from 32 documents, 1,165,897 with diabetes, 934,958 with hypertension, 858,374 with obesity (BMI, 30-45 kg/m²), 47,096 smokers and 987,532 with compromised immunity. The highest percentages of deaths occurring in descending order were smoking (11,333, 24.1%), compromised immunity (191,000, 19.3%), diabetes (198,491; 17.0%), obesity (145,605; 16.9%) and hypertension (113,243; 12.1%), with a Hazard Risk of 2.5; 2.1; 1.75; 1.7; 1.3, respectively. All cases had a p-value <0.05 (Table 1).

Furthermore, participants with diabetes had a 56% higher risk of death from COVID-19 compared to participants without diabetes; those with hypertension had a 45% increased relative risk of death from COVID-19 compared to participants without hypertension and those with obesity had a 47% increased relative risk of death from COVID-19 compared to non-obese participants. Additionally, current and past smoking was associated with a 31% relative risk of death in participants with COVID-19. In addition, it was observed that each 5 kg/m² increase in BMI is associated with a

10% higher risk of death from COVID-19, especially in older participants.

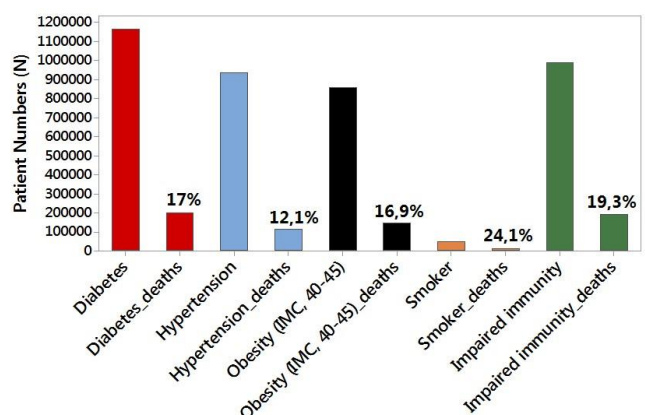
Table 1. Life risk attributable to diabetes, hypertension, obesity, smoking, and compromised immunity in participants with COVID-19 of both genders. Confidence Interval (CI) 95%.

Comorbidities	Nº Participants	Nº Deaths	Hazard Risk (HR)	CI (95%)	p-value
Diabetes	1,165,897	198,491 (17.0%)	1.75	(1.44-2.23)	0.002
Hypertension	934,958	113,243 (12.1%)	1.3	(1.13-1.87)	0.004
Obesity (IMC. 30-45 kg/m ²)	858,374	145,605 (16.9%)	1.7	(1.55-2.21)	0.0022
Smoker	47,096	11,333 (24.1%)	2.5	(1.89-3.14)	0.0012
Compromised immunity	987,532	191,000 (19.3%)	2.1	(1.91-3.10)	0.0021

Source: Own Authorship.

Figure 1 shows the graphic representation of the number and percentage of death events (deaths) of participants with diabetes, hypertension, obesity, smokers, and compromised immunity in the presence of COVID-19. The highest incidence of deaths occurred in participants who were smokers, had compromised immunity, had diabetes, and were obese.

Figure 1. Graphical representation of the number and percentage of death events (deaths) of participants with diabetes, hypertension, obesity, smokers, and compromised immunity in the presence of COVID-19.

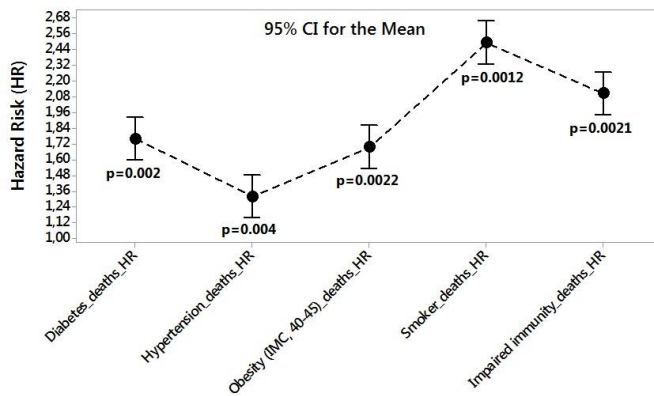


Source: Own Authorship.

The risk of life (Hazard Risk-HR) was determined by the logistic regression analysis tool and showed statistical significance with p<0.005 for all relationships of comorbidity events in the presence of COVID-19, with the highest HR being observed among smokers

(HR=2.5) and immune-compromised participants (HR=2.1). Despite this, other comorbidities such as diabetes, obesity, and hypertension also presented statistically significant results, as shown in Table 1 and Figure 2.

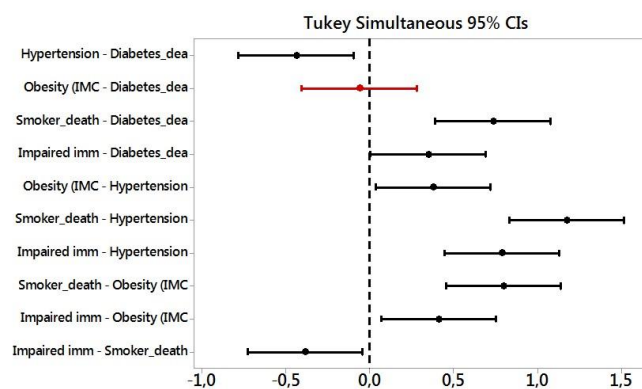
Figure 2. Risk of life (Hazard Risk-HR) determined by the logistic regression analysis tool, adopting $p < 0.005$ with statistical significance at the 95% CI.



Source: Own Authorship.

Using Tukey's statistical analysis (One-Way ANOVA), it was observed that only the difference between the means of the comorbidities "obesity" and "diabetes" was not statistically significant, as the interval highlighted in red in Figure 3 includes the number zero, with $p < 0.05$.

Figure 3. Tukey statistical analysis (One-Way ANOVA) of the difference between the means of comorbidities, with $p < 0.05$ without statistically significant difference in the 95% CI.



Source: Own Authorship.

Discussion

The present study analyzed how cardiovascular comorbidities such as diabetes, hypertension, obesity, smoking, and compromised immunity contributed to the increased risk of life in participants affected by COVID-

19, resulting in evidence that these comorbidities can increase mortality in infected participants, especially in those of an older age. The highest incidence of deaths occurred in participants who were smokers, had compromised immunity, had diabetes, and were obese. The greatest risk of death was observed among participants who smoke (HR=2.5) and those with compromised immunity (HR=2.1). Despite this, other comorbidities such as diabetes, obesity, and hypertension also presented statistically significant results for the risk of life. It was observed that only the difference between the means of the comorbidities "obesity" and "diabetes" was not statistically significant, with $p < 0.05$, that is, both comorbidities have similar impacts on the worsening and death of participants in the presence of COVID-19.

In this scenario, in Brazil and around the world, obesity is recognized as the most important non-infectious epidemic, being considered a chronic disease of increasing incidence, severe, and multifactorial [2,3]. Overweight and obesity are already seen from the age of five, in all income groups and regions of Brazil, although socioeconomic factors are also determining factors [10-12]. Studies highlight that obesity is related to several diseases, such as type II diabetes, hypertension, cardiovascular diseases, dyslipidemia, atherosclerosis, and some forms of cancer, among others. In people with a BMI between 18 and 25 (ideal weight), there are around 8.0% diabetics. In individuals with a BMI above 40 (severe obesity), this percentage reaches 43.0% [16].

The highest incidence of dyslipidemia is in obese participants, being a "trigger" for cardiovascular diseases (CVD) and stroke. Obesity-related hypertension accounts for 65% to 75% of hypertension [13]. The mechanisms of hypertension in participants with obesity are not completely understood, but there is strong evidence that it is related to the kidneys. There is evidence that the increased incidence of chronic kidney disease (CKD) is closely related to obesity, affecting 20% of adults. In participants with hypertension and no history of smoking, alcohol consumption, chronic obstructive pulmonary disease, or cardiovascular disease, the lowest mortality occurs with a BMI of 23-26.9 kg/m² [12]. Furthermore, end-stage renal disease increases with increasing BMI, with a relative risk of 3.57 for participants with obesity. Thus, proposed mechanisms for obesity-related hypertension include hyperleptinemia, activation of angiotensin II, hyperinsulinemia, and compression of the kidney by fat accumulation [13,17].

Additionally, as abdominal fat increases, fat also accumulates around the heart. There is evidence that an

increase in visceral fat, increased leptin production, and reduced adiponectin, may be the signal that accelerates the accumulation of atherosclerotic plaques and causes plaques to be distributed locally in the coronary arteries. With heart failure, the heart rate is increased, blood vessel contraction occurs, blood pressure increases and the circulation of free fatty acids and cytokines increases [19,20].

In this context and to support the findings of the present study, Du et al suggested that participants with obesity had a 2.68 times higher risk of mortality from COVID-19 compared to non-obese participants (n=7 studies) [21] and that for every 1 kg/m² increase in BMI, the risk of death increased by 6%. Participants with COVID-19 and pre-existing obesity may have an overactivated inflammatory response, which can induce an excessive inflammatory response [22]. Obesity is also strongly associated with increased risk of diabetes, hypertension, and several other chronic diseases [23] that increase the risk of COVID-19 mortality [24].

Additionally, one study showed that a current or former smoker may have a 25% increased relative risk of death in participants with COVID-19 compared to those who have never smoked. Smokers are more likely to get a severe COVID-19 infection due to their poor mucociliary clearance, which can lead to the release of pro-inflammatory markers and oxidative stress and thus contribute to higher mortality rates [25].

In the scenario of the new coronavirus (SARS-CoV-2), the COVID-19 disease is associated with vascular inflammatory processes, myocarditis, and cardiac arrhythmias, thus, its mortality is associated with cardiovascular diseases, diabetes, and hypertension. These disorders share underlying pathophysiology related to the renin-angiotensin system (SARS) [26]. In this context, four different mechanisms can contribute to increasing the virulence of the coronavirus in the lungs and heart. Thus, the mechanisms are that cardiovascular disease and pharmacological inhibition of SARS can increase ACE2 levels, as well as coronavirus infection can decrease ACE2, leading to excess toxic accumulation of angiotensin II, which induces respiratory distress syndrome. acute and fulminant myocarditis [27]. Added to this, a recent study showed that Fe²⁺ and Fe³⁺ ions can attack lung and heart tissues [28].

Thus, the association between obesity and inflammatory disease stands out. There are three possibilities, the first reflects production and release from organs other than adipose, mainly the liver (and immune cells). The second explanation is that white adipose tissue secretes factors that stimulate the production of inflammatory markers by the liver and

other organs. The third possibility is that adipocytes themselves are a ready source of some, or several, of these inflammatory markers [14,15].

In addition, effects such as sensors of energy balance have been attributed to cytokines. Among all the adipokines related to inflammatory processes, interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), leptin, and adiponectin stand out [15]. In this context, some studies have shown low concentrations of the anti-inflammatory adipokine (adiponectin) associated with the occurrence of several types of cancer and high concentrations with the inhibition of tumor growth. 3-5 Adiponectin and leptin are the most abundant adipokines synthesized by adipose tissue. , although there are others such as TNF- α , IL-6, IL-1, CC-chemokine ligand 2 (CCL2), a visceral adipose-tissuederived serine protease inhibitor (vaspin), and retinol-binding protein 4 (RBP4) [13].

Also, it is noteworthy that the adipose tissue of obese individuals presents an upregulation of the expression of the angiotensin-converting enzyme 2 (ACE2), which functions as a receptor for SARS-CoV-2 to enter the cell. Thus, adipose tissue functions as a potential viral reservoir and target. Thus, obesity is a pathology that causes damage to the immune system and amplifies inflammatory responses and this contributes to understanding the interaction between COVID-19 and obesity [13,27].

Meta-inflammation describes the combination of inflammation and metabolic changes that occur in the body of obese participants [14]. Several toxic mediators that contribute to the inflammatory state and tissue damage are present in obesity, such as free fatty acids (FFA), toxic lipid derivatives, such as diacylglycerol, toxic nitric oxide metabolites, and inflammatory mediators, such as protein C reactive, cytokines, chemokines, macrophages, and TNF- α . The imbalance in inflammatory mediators induced by excess nutrients is the basis of meta-inflammation in obesity, considered a low-grade chronic inflammatory state. Similar to that observed in acute inflammatory diseases, obesity can cause multiple organ dysfunction. Meta-inflammation leads to myocardial dysfunction through direct damage to inflammatory mediators, as well as through dysfunction of other organs [15].

Therefore, the endothelial dysfunction caused by SARS-CoV-2 explains why participants with comorbidities related to blood vessels such as cardiovascular disease, hypertension, diabetes, and obesity are more likely to develop severe COVID-19, even death [29,30]. Furthermore, obesity produces hemodynamic changes that contribute to the development of structural and functional cardiac

abnormalities. These changes can cause heart failure (HF), even in the absence of other comorbidities, such as hypertension and coronary artery disease (CAD). Therefore, HF related to severe obesity is called obesity cardiomyopathy. In this context, inflammatory mediators produced by adipose tissue are direct mechanisms of cardiac dysfunction, and hypertension, diabetes, and CAD are indirect mechanisms [14,31,32].

Conclusion

It was concluded that cardiovascular comorbidities such as diabetes, hypertension, obesity, smoking, and compromised immunity contributed to the increased risk of life in participants affected by COVID-19, especially in those of an older age. The endothelial dysfunction caused by SARSCoV-2 explains why participants with comorbidities related to blood vessels such as cardiovascular disease, hypertension, diabetes, and obesity are more likely to develop severe COVID-19, even death.

Acknowledgement

Not applicable.

Ethical Approval

Not applicable, as the present study consulted public information and statistical databases such as WHO, PAHO, Ministry of Health, ANVISA, and EASO.

Informed consent

Not applicable.

Funding

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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It was applied by Ithenticate@.

Peer review process

It was applied.

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