CHAPTER
45

Factors associated with the mortality of patients hospitalized by COVID-19 in a tertiary hospital

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ABSTRACT
The pandemic of COVID-19 generated a significant impact on health and socioeconomically globally due to lack of treatment, high transmission, and morbidity and mortality. In this sense, analyzing the epidemiological scenarios of the disease generates means for health management planning, identification of more susceptible groups, and physiopathological understanding. The objective of this study was to identify factors associated with death in patients hospitalized for COVID-19 in a tertiary care hospital. A cross-sectional study was carried out based on secondary data seen at the hospital unit covered by the 8th Health Regional of Paraná (8thRS), in the year 2020. Data related to the socio-demographic, laboratory, and clinical characteristics of patients were collected, and the outcome analyzed was hospital death (yes/no). Pearson's chi-square test or Fisher's exact test was used to analyze the data. ("Predictors of burnout syndrome in intensive care nurses") As of December 31, 2020, 185 patients with RT-PCR confirmed diagnosis for COVID-19 were recorded, with 113 discharges (61.1%; 95%CI;54.1 - 68.1) and 72 deaths (39%; 95%CI; 31.9 - 48.2). In summary, we identified higher mortality in the male group, longer periods of hospitalization, and comorbidities present: hypertension, obesity, diabetes, and cardiovascular diseases.

Keywords: COVID-19, Death, Hospitalization.

1 INTRODUCTION

In 2019, in Wuhan, China, a new virus capable of infecting humans, the SARS-CoV 2 virus, was discovered in Portuguese. The disease caused by SARS-CoV 2 was termed COVID-19 and in March 2020 due to the rapid spread of the disease, it was determined by the World Health Organization (WHO) as a pandemic. According to the Ministry of Health, Brazil had its first case reported on February 26, 2020. A year later, on February 27, 2021, the country recorded 10,517,232 cases and 254,221 deaths from the virus. Due to the high transmissibility, lack of treatment, number of deaths, and overload in hospital care, health agencies are concerned about transmission and mortality (BRAGA

et al., 2020; BRAZIL, 2021).

The ease of dissemination and contagion, associated with the severity of complications in the respiratory system and systemic, are pointed out as elements of the pathogenicity of SARS-CoV2. Spread occurs mainly through inhalation of saliva droplets and respiratory secretions that can be suspended in the air or on objects when the infected person coughs, sneezes, or speaks. The incubation period of COVID-19 can range from 1 to 14 days and results from respiratory tract infection, characterized by a broad spectrum of clinical manifestations and varying degrees of severity. Most infected people are asymptomatic or have mild symptoms of the disease, resembling a common cold, and will not need to be hospitalized (BAPTISTA; FERNANDES, 2020; MARTELLETO *et al*., 2021; SOUZA *et al*., 2020).

When mild, respiratory symptoms present as dry cough, fever, sore throat, body ache, diarrhea, conjunctivitis, headache, loss of taste (dysgeusia) or smell (anosmia), rashes on the skin, or discoloration of the fingers or toes. However, when it progresses to a more severe condition, complications may develop, such as pulmonary involvement (visualized on imaging - radiography or computed tomography of the chest - by bilateral opacification of the air space), interstitial pneumonia, dyspnea, acute kidney injury, septic shock and need for mechanical ventilation. It can progress to more alarming conditions such as acute respiratory distress syndrome (ARDS), multiple organ failure, and death due to the cascade of cytokines by excessive activation of the immune system (FEITOZA *et al*., 2020).

However, not every case of COVID-19 patients will be hospitalized. According to the Brazilian Society of Pulmonology and Phthisiology, Computed Tomography recommends that hospitalization cases of COVID-19 patients should be reserved for cases of alarm symptoms or in specific clinical situations (BAPTISTA; FERNANDES, 2020).

Studies reveal that some factors are significant in determining the worsening and clinical outcomes of COVID-19. The comorbidities that are related to higher hospital admission and development of the disease form were patients with pre-existing comorbidities, such as systemic arterial hypertension (SAH), diabetes *mellitus* (DM), and coronary heart disease. There is also a correlation, in smaller numbers, with other diseases such as hepatitis B, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), neoplasms, and immunodeficiencies. Smokers also had a greater predisposition to develop the severe form of the disease due to previous lung injury caused by the toxic substances of cigarettes (ALMEIDA *et al*., 2022).

Obesity is also considered a comorbidity with worse outcomes, being a predictor for the worsening of the disease. Deregulation of immunity, increased pro-inflammatory activity, decreased cardiorespiratory capacity, and expiratory volume is pointed out as one of the fiopathologies of obesity

that aggravate infection by the virus, increasing the risk of mortality (MOREIRA *et al.*, 2020).

In addition to these factors, the patient's age range was correlated with his clinical outcome. Studies show that age can be a predictive factor, being worse for older ages, while young people and children have a lower mortality rate due to the disease. Biophysical and immunological changes and a higher probability of previous comorbidities are some of the factors that justify this factor linked to higher virological morbidity and mortality (ALMEIDA *et al.* , 2022; FEITOZA *et al*., 2020).

Finally, the length of the patient's hospitalization is directly proportional to the risk of death. Patients with more severe conditions require longer hospitalization and, therefore, there may be a need for more invasive treatments, such as hospitalization in the Intensive Care Unit (ICU) and use of mechanical ventilation (invasive or not), resulting in the worsening of the evolution of the clinical picture. In addition to COVID-19 infection, longer hospital stays increase the likelihood of viral, bacterial, or fungal coinfections and superinfections, worsening the severity of the condition (FERNANDES *et al.*, 2021).

The severity of the disease and death described in the literature has shown great variability due to the differences in the periods analyzed, the sample size and the standardization of the data. The results of international and national studies converge regarding the worse prognosis in male patients, with increased age, longer hospitalization and ICU bed stay, and the presence of comorbidities.

The profile of death from COVID-19 in the 8th Regional of the Southwest of Paraná has not yet been reported and discussed extensively with the existing literature. Given the unique character of the pandemic, which has had a great impact on public health, it is important to describe the characteristics of the affected population and factors associated with the greater severity and lethality of this disease, contributing to the confrontation of current and/or future crises.

Thus, this research aims to identify the factors associated with the mortality of patients hospitalized for COVID-19 in a tertiary hospital.

2 MATERIAL AND METHODS

2.1 DESIGN

This is a quantitative and cross-sectional study, resulting from a larger research conducted by the Health Sciences Center of UNIOESTE, *Francisco* Beltrão campus. Secondary data were obtained from the research project 'Epidemiological and clinical characterization of the population exposed to COVID-19', obtained through the survey of medical records of suspected and confirmed cases of COVID-19, in the year 2020.

Data were collected through individual notification forms and electronic medical records of patients confirmed of COVID-19 by RT-PCR (*Reverse-Transcriptase Polymerase Chain Reaction*, or

reverse transcriptase reaction followed by polymerase chain reaction), and transcribed into a questionnaire focusing on the following surveys: sociodemographic characteristics (gender, age), presence of comorbidity (yes or no), for each category: cardiovascular disease (CVD), diabetes *mellitus* (DM), neoplasia, obesity, chronic neurological disease, chronic lung disease, chronic hematologic disease, chronic liver disease, human immunodeficiency virus (HIV) infection; use of intensive care (ICU: yes; no); ventilatory support (invasive; noninvasive; no support). The outcome analyzed will be hospital death or not.

2.2 SAMPLE

The sample was composed of individuals who participated in the cross-sectional study 'Epidemiological and clinical characterization of the population exposed to COVID-19', obtained through a survey of medical records of suspected and confirmed cases of COVID-19, attended at the hospital unit of the 8th Regional Health of Paraná (8th RS), in 2020. The 8th RS encompasses 27 municipalities, headquartered in the municipality of Francisco Beltrão - Paraná, with an estimated population of 357,174 inhabitants (IBGE, 2018). Those whose notifications and medical records of patients were not confirmed of COVID-19 by RT-PCR were excluded.

2.3 STATISTICAL ANALYSIS

Descriptive and inferential analyses were used to study factors associated with hospital death, using the SPSS program, version 23. For crude analysis, Pearson's chi-square test or Fisher's exact test was used for categorical variables. Comparisons of means were made by the U test<. Graphs were also used through network analysis, which showed associations between the variables according to the outcome (cure/death).

2.4 ETHICAL ASPECTS

The present study has as its methodology a cross-sectional analysis based on secondary data obtained by the survey of medical records, without any intervention of the patients and subjects in the research. The present study was approved by the Research Ethics Committee (CEP) of UNIOESTE, number 4,034,106, on May 18, 2020. In addition, it is noteworthy that measures have been taken to minimize the risk of exposure of the data of the patients involved, such as the use of digital cloud storage and controlled access to researchers.

3 RESULTS

During the study period, 185 patients with a diagnosis confirmed by RT-PCR for COVID-19 were hospitalized, of which 113 (61.1%; CI95%;54.1 – 68.1) were discharged and 72 (39%; 95%CI; 31.9 – 48.2) that evolved to death.

Of the total hospitalizations analyzed, 3 patients did not live in the 8th Regional Health of Paraná, 1 of the patients was visiting family members in the region and needed hospitalization, being their residence in Rio de Janeiro (RJ) and 1 patient of the 10th and 9th Regional Health of Paraná, for lack of hospital beds, 1 with residence in Cascavel (PR) and 1 in Santa Helena (PR). Of the 8th Regional Health of Paraná, the highest frequencies of hospitalized patients were in the municipalities of Francisco Beltrão (72), Dois Vizinhos (33), Barracão (10), Enéas Marques (9) and Salto do Lontra (7).

Table 1 presents the characteristics of patients hospitalized with COVID-19 in 2020 in a hospital unit in the area covered by the 8th Regional Health of Paraná.

Table 1 – Demographic and clinical characterization of patients hospitalized for COVID-19 in a hospital unit, according to outcomes (discharge/death).

	DENOUEMENT		
Variable	**Death N=72 (%)**	**Loud N=113 (%)**	**P value**
Sex			
Male	46 (64,8)	66 (58,4)	0,388
Female	25 (35,2)	47 (41,6)	
Place of Internment			
Clinical	10 (13,9)	32 (28,3)	**0,022***
UTI	62 (86,1)	81 (71,7)	
Obesity			
Yes	25 (39,1)	31 (47)	0,363
No	39 (60,9)	35 (53)	
Cardiovascular Diseases			
Yes	13 (18,3)	12 (10,6)	0,138
No	58 (81,7)	101 (89,4)	
Systemic arterial hypertension			
Yes	48 (67,6)	65 (57,5)	0,171
No	23 (32,4)	48 (42,5)	
Diabetes Mellitus			
Yes	22 (30,6)	26 (23)	0,254
No	50 (69,4)	87 (77)	
Fever			
Yes	25 (34,7)	36 (32,1)	0,717
No	47 (65,3)	76 (67,9)	
Cough			
Yes	35 (48,6)	66 (58,4)	0,192
No	37 (51,4)	47 (41,6)	
Headache			
Yes	09 (12,5)	19 (16,8)	0,425
No	63 (87,5)	94 (83,2)	
Dispneia			
Yes	52 (72,2)	83 (73,5)	0,854
No	20 (27,8)	30 (26,5)	
Sore throat			

Yes No	04 (5,6) 67 (94,4)	05 (4,5) 107 (95,5)	0,737
Myalgia Yes No	 15 (20,8) 57 (79,2)	 25 (22,3) 87 (77,7)	0,811
Diarrhoea Yes No	 10 (14,1) 61 (85,9)	 13 (11,5) 100 (88,5)	0,606
Vomiting Yes No	 05 (6,9) 67 (93,1)	 06 (5,3) 107 (94,7)	0,647
Asthenia Yes No	 15 (21,1) 56 (78,9)	 27 (23,9) 86 (76,1)	0,663
Inappetence Yes No	 09 (12,7) 62 (87,3)	 12 (10,6) 101 (89,4)	0,669
Hospitalization Up to 7 days 8 to 14 days 15 to 21 days Over 21 days	 18 (25) 24 (33,3) 20 (27,8) 10 (13,9)	 73 (64,6) 31 (27,4) 06 (5,3) 03 (2,7)	**<0,001***

*Chi-square test.

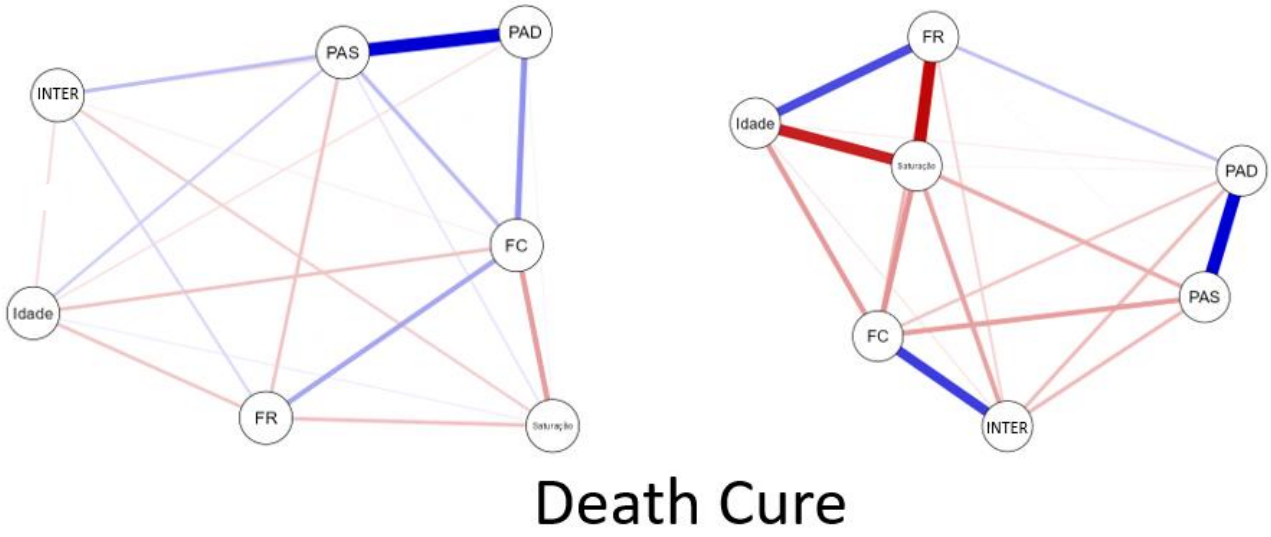
When performing the chi-square test, we identified an association between the outcome of death in the variables of hospitalization in the Intensive Care Unit (ICU) ($p = 0.022$) and length of stay longer than 7 days ($p < 0.001$). Hypertension and diabetes were the most frequent comorbidities among patients who died. Another associated factor was age ($p < 0.001$). These patients had slightly higher medians of respiratory rate, heart rate, and arterial oxygen saturation, but without statistical significance as shown in Table 2.

Table 2 – Characterization of the length of stay, age, and vital signs of patients hospitalized for COVID-19 in a hospital unit, according to death outcome, 2020.

			DEATH		
Variable	**n**	**Total (IQ50-Min-Max.) *****	**Yes (IQ50-Min-Max.)**	**No (IQ50-Min-Max.)**	**P value**
Length of Hospitalization	185	8 (1-68)	11,5 (2-46)	6 (1-68)	**<0,001****
Age (in years)	185	64 (0,0-96)	68,5 (27-91)	60 (00-96)	**<0,001****
Arterial oxygen saturation (SaO2)*	173	93 (35-125)	92 (35-99)	94 (70-125)	
Systolic blood pressure*	97	130 (70-201)	133 (70-201)	130 (90-186)	0,730
Diastolic blood pressure*	96	78 (40-123)	74 (40-107)	80 (50-123)	0,576
Respiratory rate*	112	21 (13-40)	22 (13-40)	20 (14-30)	0.592
Heart rate*	101	84 (31-150)	87 (52-128)	82 (31-150)	0,365

* Result of examinations on the admission of patients.
** Teste U de Mann-Whitney
IQ50 – Interquartile 50. Minimum and Maximum

Figure 1 – Network graph referring to the associations between the variables (vital signs, length of hospital stay, age) according to the clinical outcome of patients hospitalized for COVID-19 in a hospital unit, 2020.



HR: Respiratory rate
SBP: Systemic blood pressure
DBP: Diastolic blood pressure
INTER: Total length of hospital stay

Finally, we performed network analyses to understand the associations between the variables according to the outcome (cure/death). Evident differences can be seen in Figure 1. The central nodule related to death was the variable saturation, which was negative and strongly associated with age and respiratory rate. In the group of patients whose outcome was discharged, there was no central nodule and the only strong association found was between systolic and diastolic blood pressure; In this same group, it is possible to see that, although not significant, oxygen saturation was positive with the patient's age and indirectly negative when considering the respiratory rate.

4 DISCUSSION

It was announced by the World Health Organization (WHO) on January 30, 2020, that COVID-19 has been classified as a global pandemic, i.e. a public health emergency internationally. The high viral spread, lack of specific treatment, and high morbidity and mortality are some of the factors that have generated such concern and urgency of knowledge to cope with COVID-19. Thus, the purpose of this study was to analyze and identify the main factors associated with death in patients hospitalized for COVID-19 in the 8th Regional Health of Paraná (MARTELLETO *et al.*, 2021).

In the period analyzed, the lethality rate of the disease was 39%, corresponding to 72 cases. According to studies by Klosowski, Carraro, and Figueiredo (2022), the case fatality rate in the State of Paraná, during the year 2022, was 34%, with 14,352 cases and 4,870 deaths being reported in the 181 hospitals analyzed, the city with the lowest lethality Maringá (21%) and the highest in Apucarana (74%). In this context, the 8th RS has a higher case fatality rate in cases of hospitalization for COVID-

19 than the State of Paraná. Next, to propose a more structured discussion, the main results found in this research will be evaluated and discussed in comparison with the available scientific literature.

4.1 GENDER AND MORTALITY

There was a higher prevalence of deaths from COVID-19 in cases of hospitalization in males (64.8%) than in females (35.2%). This fact corroborates the data found in the literature, which demonstrates that men are more predisposed to mortality related to COVID-19 (BAPTISTA; FERNANDES, 2020).

One of the explanations for this fact is due to the greater predisposition to comorbidities in males, such as systemic arterial hypertension (SAH), diabetes *mellitus (*DM), and cardiovascular diseases (CVD). These are linked to higher morbidity and mortality of the virus (BAPTISTA; FERNANDES, 2020).

Another predisposing factor is due to male stigmas and social behaviors. The low demand for medical care, sedentary lifestyle, excessive alcohol consumption, and smoking, are some of the stigmatized male behaviors in society, worsening the prognosis if they get sick (BAMBRA *et al.*, 2020).

4.2 AGE AND MORTALITY

People over the age of 60 are considered a risk group due to extreme susceptibility to infection and worsening of the disease due to more deficient physiology and immune system. Lethality was higher in the elderly, with emphasis on those with preexisting diseases such as systemic arterial hypertension (SAH), cardiovascular diseases (CVD), and diabetes *mellitus (*DM) (MACIEL *et al.*, 2020).

The compromised immune mechanism causes the elderly to have worse prognoses in the face of infections. In addition, anatomical changes - such as degeneration in the muscles in the elderly - can cause changes in the respiratory tract, leading to atrophy in the repository anatomy, leading to a reduction in the clearance of the airways and pulmonary reserve. Given this, respiratory tract infections, as in the case of COVID-19, generate greater injuries and complications (COSTA *et al.*, 2020).

Another factor for the higher mortality rate is the lower energy intake in the elderly. Physiological variations with advancing age lead to a lower metabolic rate, generating risks regarding the evolution of malnutrition. In this context, they make them more vulnerable to infections and, consequently, increase the risk of greater complications in infections (BORGES *et al.* , 2021; OLIVE TREE; BRITO, 2021).

The elderly also had a longer period of hospitalization, and high rates of respiratory rate, heart rate and arterial oxygen saturation. However, in the present study, there was no statistical significance regarding the length of hospitalization, with the outcome of death. This data differs from the data pointed out by Walter *et al.* (2020), which found longer hospitalization time and higher death rates in the elderly (QUEIROZ *et al.*, 2020).

4.3 INTERNMENT REGIME

The results also demonstrate the association between hospitalization variables and clinical outcomes. Patients with a hospitalization period longer than 7 days had a worse prognosis ($p < 0.001$). In addition to the length of hospitalization, patients who were admitted to the Intensive Care Unit (ICU) had a higher mortality rate ($p = 0,022$).

Patients who require hospitalizations in ICU beds are due to the greater aggravation and worse prognosis of the disease. Usually, these patients require more aggressive measures such as ventilatory support (invasive and noninvasive), vasoactive drugs and pronation. In addition to the viral infection of COVID-19, the longer stay or in ICU increases the likelihood of coinfections and viral, bacterial or fungal superinfections, worsening the severity of the condition (FERNANDES *et al.*, 2021).

4.4 COMORBIDITIES

Obesity is considered a chronic non-communicable disease (NCD) and is correlated as a severity factor for COVID-19 infection. Obese patients have higher rates of hypoxemia, frequency and intensity of cough, dyspnea, admission to the Intensive Care Unit (ICU), severe complications, acute respiratory distress syndrome (ARS) and death. In the present investigation, obesity was identified as a factor associated with death, which converges with the study by Borges *et al.* (2021), which found a worse prognosis and morbidity and mortality of COVID-19 among obese people.

Some mechanisms are associated with the pathophysiology of obesity and explain the worsening of the hospitalized patient's condition. Initially, chronic inflammation occurs due to the increase of pro-inflammatory cytokines by adipocytes, generating a degree of immune impairment in the patient due to the decrease in innate and adaptive immunity. The worsening in ventilatory saturation and compensation in cases of virus infection in these patients is due to the injurious mechanism that occurs by the decrease in lung capacity, by the reduction of its compliance, expiratory volume and pulmonary function. Finally, the increase in circulatory demand in obese patients due to greater body vascularization demands a greater cardiovascular overload, thus increasing the vulnerability to cardiovascular and metabolic complications, such as atherosclerosis and microvascular lesions (MOREIRA *et al.* , 2020; BORGES *et al.* , 2021).

Feitoza *et al.* (2020) indicate that about 20% to 50% of those infected have some type of comorbidity and that can provide greater lethality of the disease. The main pre-existing comorbidities correlated with worse outcomes are systemic arterial hypertension (SAH), diabetes mellitus (DM) and coronary heart disease. One of the explanations for this association is due to the medications used in such comorbidities and that can aggravate the condition. For the treatment of SAH, DM and heart disease, medications that increase angiotensin-converting enzyme type 2 (ACE-2) are used, whose production occurs in cells of the lungs, kidneys, intestines and blood vessels. This enzyme has a high affinity for binding the virus to target cells, functioning as a functional receptor of COVID-19, which may aggravate the clinical picture of the patient infected by SARS-CoV-2 (SILVA JÚNIOR *et al*., 2021).

In the present study, there was a greater predisposition to worse outcomes in patients with preexisting comorbidities, especially obesity, systemic arterial hypertension (SAH), diabetes mellitus (DM), and coronary heart disease. This result is consistent with international data, in which these comorbidities were also associated with a worse prognosis. According to research conducted in January 2020 by Chen *et al.* (2020), referring to mortality from COVID-19 at *Jinyintan Hospital, Wuhan*, China, the most predominantly reported comorbidities associated with worse outcomes were hypertension (16.9%), followed by diabetes (8.2%), with other cardiovascular diseases also present.

4.5 ASSOCIATIONS BETWEEN VARIABLES

Finally, analyses were performed using network graphs to understand the associations between the variables according to the outcome (cure/death); Evident differences can be seen in Figure 1.

Regarding cure, Figure 1 shows that there was no central nodule, that is, no variable that centralizes the factors associated with cure. The only association that is more prominent in cured patients was between systolic and diastolic blood pressure. Although not significant in this same group, it is possible to see that oxygen saturation was positive with the patient's age and indirectly negative when considering the respiratory frequency.

Still referring to FIGURE 1, but in the outcome of death, the central nodule was saturation. This variable presents itself as a negative factor and is strongly associated with age and respiratory rate. This fact can be explained, according to Queiroz *et al.*, 2020, because when groups older than 60 years had higher death outcomes and, consequently, during the hospitalization period, presented complications from COVID-19, such as acute respiratory distress syndrome, co-infections, ventilatory support (invasive or not) and impaired immune response. All these aggravations reflect in the worsening of saturation and, consequently, as a compensatory response, in the respiratory rate.

5 FINAL CONSIDERATIONS

Due to the lack of an effective treatment against COVID-19, knowing the factors of higher risk of morbidity and mortality of the disease become crucial for the elaboration of care plans with groups of greater vulnerability in developing the severe form of the disease, aiming to reduce the rate of deaths from the coronavirus. In this study, it was found that the main variables for the outcome of death in patients hospitalized with COVID-19 were: older age groups, male patients, hospitalized for a hospitalization period longer than 7 days and if hospitalized in the Intensive Care Unit. In addition to these factors, patients who had some previous comorbidity or aggravation also had worse clinical outcomes, especially obesity, systemic arterial hypertension and diabetes *mellitus*.

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