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Coronavirus Pandemic

Factors associated with deaths from COVID-19 in a region of northeastern Brazil

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Abstract

Introduction: There is a need to improve knowledge and understanding of the factors associated with mortality from COVID-19 so that managers and decision-makers can implement strategies to mitigate and control the severe forms of the disease. This study aimed to determine the factors associated with deaths from COVID-19 in the state of Maranhão, in northeastern Brazil.

Methodology: This is a cross-sectional and analytical study with patients with a confirmed diagnosis of COVID-19 who died from March 2020 to January 2022. Simple and multiple logistic regression models were used to assess the association between clinical-epidemiological characteristics and death. The odds ratios were expressed using a 95% confidence interval and a 5% significance level.

Results: A total of 386,567 cases of COVID-19 were registered in the period, of which 10,986 died. Risk factors associated with deaths from COVID-19 were male sex, age over 30 years, positive reverse transcriptase–polymerase chain reaction (RT-PCR) result, positive CT scan, and having one or more associated comorbidities. The three comorbidities linked to the highest propensity to die were diabetes mellitus, neurological disease, and obesity.

Conclusions: The study findings support the implementation of strategic actions by health care and surveillance professionals and managers towards reducing the incidence of the risk factors for mortality by COVID-19 in Maranhão.

Key words: SARS-CoV-2; death; COVID-19; risk factors.

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Introduction

The SARS-CoV-2 virus, the causative agent of COVID-19, an infectious respiratory disease with high morbidity and mortality [1], has caused health, social, psychological [2], and financial [3] implications worldwide. Although increasing immunization against the disease has reduced the severe forms and decreased deaths [4,5], many lives were lost in the last two years due to the pandemic.

Epidemiological data on mortality from COVID-19 show that until June 19, 2022, Brazil ranked second in the world in COVID-19 deaths with 668,693 records, surpassed only by the United States, which surpassed the mark of one million deaths (at the moment, there are 1,002,946 registered deaths) [6].

Considering the accumulated data on deaths from COVID-19, from February 26, 2020, to the epidemiological bulletin released on June 18, 2022, Brazil had 315.5 deaths per 100,000 inhabitants. Among the federative units, the highest accumulated mortality rate was registered in Rio de Janeiro with 425.4 deaths per 100,000 inhabitants, followed by Mato Grosso with 415.5 per 100,000 inhabitants. The state of Maranhão, in northeastern Brazil, accounts for 153.1 deaths per 100,000 inhabitants [7].

It is noteworthy that the mortality from COVID-19 has been decreasing in Maranhão [8]. This decline is believed to be linked to the increasing immunization against the disease, given that vaccines against SARS-

CoV-2 have effectively reduced hospitalizations and deaths in the Brazilian territory [4,9].

On the other hand, the remarkably low mortality rates in Maranhão raise the question of underreporting of deaths [10]. Studies have shown that, in Brazil, there is a great underreporting of COVID-19 cases and a deficit in laboratory tests to confirm cases [11,12], a phenomenon that is further accentuated in states with lower socioeconomic conditions and human development indexes (HDI), such as Maranhão [13] - the second state with the worst HDI in the country, only behind Alagoas [14].

Research carried out in 185 countries identified that mortality from COVID-19 was associated with age over 65, chronic health conditions, and social and income inequalities1. Other associated factors reported in a study with 3,108 counties in the United States were socioeconomic conditions and the environment/climate [15].

Studies developed in Brazil and the United States show that male sex, advanced age, and pre-existing diseases are risk factors associated with disease worsening and unfavorable outcomes [16-18]. Furthermore, an integrative literature review shows that age of 60 years or older, diabetes mellitus, and systemic arterial hypertension are risk factors for death from COVID-19 [19].

Studies on the deaths caused by COVID-19 in the different regions of Brazil are still incipient, especially in Maranhão State. Among the studies, there was a description of the epidemiological profile and an analysis of the spatio-temporal distribution of deaths from COVID-19 in a short time frame (the first months of the pandemic) [20,21]. We have found no prior studies examining the association between clinical-epidemiological characteristics and unfavorable outcomes (such as death from COVID-19) in Maranhão.

There is a need to improve knowledge and understanding of the factors associated with mortality from COVID-19 so that managers and decision-makers can implement strategies to mitigate and control the severe forms of the disease. This study aimed to determine the factors associated with deaths from COVID-19 in the state of Maranhão, in northeastern Brazil.

Methodology

A cross-sectional, retrospective, and analytical study was carried out with confirmed cases of COVID-19 who died. In this type of epidemiological study, the factor and the effect are observed at the same time frame [22].

The study was carried out in the state of Maranhão, whose capital is the city of São Luís. The state has an area of 329,642,170 km^2, approximately 7,075,181 inhabitants, and 217 municipalities [23].

All cases of COVID-19 registered in the Maranhão COVID-19 Notification System, linked to the State Department of Health (SES/MA), were considered. Data were collected in February 2022 and comprised the period from March 20, 2020 (the date of the first death in the state) to January 31, 2022.

The clinical-epidemiological variables analyzed included age, sex, race/color, COVID-19 diagnostic criteria, laboratory type (public or private), type of COVID-19 exam requested, type of healthcare facility (public or private), and presence of comorbidities (yes/no). Among the comorbidities, we investigated the register of prior diagnoses, including systemic arterial hypertension, diabetes mellitus, obesity, heart, respiratory, neurological, renal, and other diseases or conditions (cancer, autoimmune, dermatological, digestive, hematological, metabolic, psychiatric, rheumatological or urological disease, hepatitis, leprosy, HIV, alcoholism, chemical dependence, and smoking).

After checking for errors and inconsistencies in the database, a descriptive analysis was conducted, and the absolute and relative frequencies of all clinical-epidemiological variables of interest were calculated. Simple and multiple logistic regression models were used to assess the association between clinical-epidemiological characteristics and death from COVID-19 [24]. A univariate (crude) logistic regression was initially performed, considering all variables with a p-value ≤ 0.20 to identify the main risk factors. Subsequently, a multivariate (adjusted) logistic regression was carried out to estimate the odds ratios, using a confidence interval (CI) of 95% and a significance level of 5%. All statistical tests were performed in IBM SPSS software (version 16) [25].

Results

This study identified 386,567 cases of COVID-19 in Maranhão between March 2020 and January 2022, of which 10,986 died. Most deaths occurred in male patients (59.09%) of a mixed race/color (64.10%), diagnosed by the laboratory criterion (99.09%), tested at public laboratories (89, 97%) through rapid testing (56.54%), treated at public hospitals (84.92%), and in subjects with comorbidities (74.39%). A relevant number of deaths occurred in individuals aged over 70

years (45.99%), and the most frequent comorbidities were systemic arterial hypertension (47.41%) and diabetes mellitus (29.45%). It was also observed that the type of healthcare facility (5.47%) and race/color (3.50%) were the variables with the highest percentage of unreported data (Table 1).

In the crude analysis, the variables significantly associated with death ($p \leq 0.20$) were: male sex, age of 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 70 years, and over 70, presence of positive CT scan, positive reverse transcriptase–polymerase chain reaction (RT-PCR) result, and presence of comorbidities (systemic arterial hypertension, diabetes mellitus, obesity, and respiratory, neurological, and renal diseases). All the variables above behaved as risk factors for death. Age between 10 and 19 years was the only protective factor found in the study at this stage of the analysis.

In the adjusted analysis, the variables significantly associated with death ($p \leq 0.05$) were: male sex (OR = 1.83, 95% CI = 1.72–1.94), age of 30 to 39 years (OR = 2.49, 95% CI = 1.71–63), 40 to 49 years (OR = 4.21, 95% CI = 2.91–6.10), 50 to 59 years (OR = 6.87, 95% CI = 4.76–9.93), 60 to 69 (OR = 13.44, 95% CI = 9.31–19.38), and over 70 (OR = 28.38, 95% CI = 19.70–40.89), positive CT scan (OR = 7.24, 95% CI = 5.71–9.18), positive RT-PCR result (OR = 2.45, 95% CI = 2.29–2.68), presence of comorbidities (OR = 17.40, 95% CI = 15.45–19.65), systemic arterial hypertension (OR = 2.10, 95% CI = 1.75–3.65), diabetes mellitus (OR = 5.75, 95% CI = 4.45–7.15), obesity (OR = 4.80, 95% CI = 3.78–6.65), respiratory disease (OR = 1.96, 95% CI = 1.11–2.99), neurological disease (OR = 5.09, 95% CI = 3.90–6.65), and renal disease (OR = 3.14, 95% CI = 2.49–3.96). The variables above behaved as risk factors for death (Table 2).

Discussion

The fight against COVID-19 is still challenging for health systems and services [26], and efforts have been made to achieve the lowest possible impact on patients. Thus, studies on the understanding of the factors associated with mortality are important, providing the basis for decision-making in healthcare settings.

The descriptive analysis of the clinical-epidemiological characteristics associated with deaths from COVID-19 in Maranhão showed a greater incidence of death in males, subjects with advanced age (60 years or older), with comorbidities, and of a mixed race/color. This profile was also reported in international [27] and national [28-30] studies and the state of Maranhão in the first months of the pandemic [20,21].

Table 1. Clinical-epidemiological characterization of deaths from COVID-19 in Maranhão, Brazil, from March 2020 to January 2022.

Variables	N = 10,986 (%)
Sex	
Male	6,492 (59.09)
Female	4,494 (4.91)
Age	
0 to 9 years	39 (0.35)
10 to 19 years	42 (0.38)
20 to 29 years	167 (1.52)
30 to 39 years	517 (4.71)
40 to 49 years	910 (8.28)
50 to 59 years	1,516 (13.80)
60 to 70 years	2,729 (24.84)
70 years and older	5,052 (45.99)
Not informed	14 (0.13)
Race / Color	
Yellow	546 (4.97)
White	2060 (18.75)
Indigenous	67 (0.61)
Mixed	7042 (64.10)
Black	886 (8.06)
Not informed	385 (3.50)
COVID-19 diagnostic criteria	
Clinical signs and symptoms	16 (0.15)
Positive CT scan	83 (0.76)
Positive laboratory results	10,886 (99.09)
Not informed	1 (0.01)
Laboratory type	
Public	9,884 (89.97)
Private	968 (8.81)
Not informed	134 (1.22)
Type of COVID-19 test	
Serological test	202 (1.84)
Rapid test	6,212 (56.54)
RT-PCR	4,494 (40.91)
Not informed	78 (0.71)
Type of health care facility	
Public	9,329 (84.92)
Private	1,036 (9.43)
Not informed	621 (6.65)
Presence of comorbidities	
Yes	8,172 (74.39)
No	2,814 (25.61)
Comorbidity type*	
Systemic arterial hypertension	5,208 (47.41)
Diabetes mellitus	3,235 (29.45)
Heart disease	1,310 (11.92)
Obesity	15,978 (8.15)
Lung disease	13,440 (6.85)
Neurological disease	527 (4.80)
Renal disease	477 (4.34)
Other comorbidities	1,170 (10.64)

Note: A record may have more than one comorbidity assigned. RT-PCR: positive reverse transcriptase–polymerase chain reaction.

Table 2. Crude and adjusted analysis of clinical-epidemiological variables associated with death from COVID-19 in Maranhão, Brazil, from March 2020 to January 2022.

Variables	DEATH FROM COVID-19			
	Univariate analysis (crude) Odds ratio (95% CI)	*p value*	Multivariate analysis (adjusted) Odds ratio (95% CI)	*p value*
Sex				
Female	1	-	1	-
Male	1.88 (1.81 - 1.96)	< 0.001	1.83 (1.72 - 1.94)	< 0.001
Age				
0 to 9 years	1	-	1	-
10 to 19 years	0.47 (0.30 - 0.73)	0.001	0.61 (0.37 - 1.03)	0.061
20 to 29 years	0.88 (0.62 - 1.26)	0.502	1.27 (0.85 - 1.89)	0.236
30 to 39 years	2.10 (1.51 - 2.90)	< 0.001	2.49 (1.71 - 3.63)	< 0.001
40 to 49 years	4.49 (3.25 - 6.20)	< 0.001	4.21 (2.91 - 6.10)	< 0.001
50 to 59 years	10.33 (7.52 - 14.21)	< 0.001	6.87 (4.76 - 9.93)	< 0.001
60 to 70 years	25.47 (18.56 - 34.96)	< 0.001	13.44 (9.31 - 19.38)	< 0.001
70 years and older	69.67 (50.80 - 95.53)	< 0.001	28.38 (19.70 - 40.89)	< 0.001
Color/race				
Indigenous	1	-	-	-
White	0.94 (0.73 - 1.20)	0.620	-	-
Mixed	0.91 (0.71 - 1.17)	0.488	-	-
Black	1.21 (0.95 - 1.53)	0.330	-	-
Yellow	0.85 (0.61 - 1.13)	0.311	-	-
COVID-19 diagnostic criteria				
Positive laboratory results	1	-	-	-
Clinical signs and symptoms	1.12 (0.83 - 1.35)	0.301	1.21 (0.92 - 1.41)	0.100
Positive CT scan	6.14 (4.67 - 8.01)	< 0.001	7.24 (5.71 - 9.18)	< 0.001
Laboratory type				
Private	1	-	-	-
Public	0.94 (0.88 - 1.06)	0.225	-	-
Type of COVID-19 test				
Rapid test	1	-	-	-
Serological test	0.78 (0.61 - 1.04)	0.265	0.81 (0.67 - 1.15)	0.198
RT-PCR	4.93 (4.74 - 5.13)	< 0.001	2.45 (2.29 - 2.68)	< 0.001
Type of health care facility				
Private	1	-	-	-
Public	0.89 (0.72 - 1.10)	0.325	-	-
Comorbidities				
No	1	-	-	-
Yes	21.11 (18.45 - 24.96)	< 0.001	17.40 (15.45 -19.65)	< 0.001
Systemic arterial hypertension				
No	1	-	-	-
Yes	14.54 (12.62 - 16.96)	< 0.001	2.10 (1.75 - 3.65)	< 0.001
Diabetes Mellitus				
No	1	-	-	-
Yes	18.32 (16.45 - 23.96)	< 0.001	5.75 (4.45 - 7.15)	< 0.001
Obesity				
No	1	-	-	-
Yes	15.11 (12.45 - 18.96)	< 0.001	4.80 (3.78 - 6.65)	< 0.001
Heart disease				
No	1	-	-	-
Yes	0.91 (0.69 - 1.22)	0.22	-	-
Respiratory disease				
No	1	-	-	-
Yes	10.11 (8.95 - 12.96)	< 0.001	1.96 (1.11 - 2.99)	< 0.001
Neurological disease				
No	1	-	-	-
Yes	15.52 (12.95 - 19.16)	< 0.001	5.09 (3.90 - 6.65)	< 0.001
Renal disease				
No	1	-	-	-
Yes	21.11 (18.45 - 24.96)	< 0.001	3.14 (2.49 - 3.96)	< 0.001
Other comorbidities				
No	1	-	-	-
Yes	0.78 (0.45 - 1.93)	0.591	-	-

RT-PCR: positive reverse transcriptase–polymerase chain reaction.

Most subjects were treated at public health care facilities, screened through rapid testing, and diagnosed by the laboratory criterion. It is known that serious conditions and hospitalizations have a high financial cost, which leads many patients to rely on public health facilities. Thus, it is not uncommon for most deaths to occur in public healthcare settings.

The rapid test was the most used option among the deceased, and this finding may be due to the test's low cost and ease of the procedure, despite its low specificity [31,32]. Concerning the medical diagnosis of COVID-19, the laboratory criterion was the most used. The use of laboratory testing for antibody detection is not the most sensitive method to detect the virus, but it is more accurate than the rapid test [32-33]. Besides, laboratory testing can be used to confirm the disease, thus helping in the diagnostic process [33].

In this investigation, men were almost twice as likely to die than women. Studies carried out in national [26,34] and international [29,35] scenarios identified similar findings. The fact that women's immune response to the virus is more robust compared to men may explain our results [36].

Furthermore, sex hormones also influence the outcome described above, as testosterone inhibits the innate immune response, while estrogen has an immunomodulatory action [37]. In addition, men are more affected by heart and cerebrovascular diseases than women, and these comorbidities also corroborate the occurrence of death [38,39].

Regarding the age group, individuals over 30 years were more likely to die from COVID-19, and the chances of dying increased with age, from 2.5 times in the age group of 30 to 39 years to 28.38 times in subjects aged 70 or older.

Research carried out with patients hospitalized in the state of Paraná, Brazil, identified that patients over 65 were 58 times more likely to die from COVID-19 than younger adults [28]. Such findings are related to the fact that aging generates many physiological changes [39] leading to a decline in the immune system, making it difficult to fight infections, added to the fact that pre-existing diseases related to advanced age such as cardiac and pulmonary diseases, dementia, and diabetes potentiate unfavorable SARS-CoV-2 infection outcomes [28,40].

We have also found an association between positive CT scans and death. Patients diagnosed by CT scan were about seven times more likely to die than those diagnosed by laboratory testing. It is noteworthy that imaging testing alone is not indicated for COVID-19 screening and diagnosis but to assess the evolution and complications caused by the disease [41,42]. Individuals with a chest tomography showing extensive pulmonary involvement are considered severe cases.

Patients who underwent the RT-PCR test were almost two and a half times more likely to die than patients who underwent the rapid test. Prior studies in Maranhão [20] and Paraíba [43] have found similar results and may be related to the fact that RT-PCR has greater specificity and sensitivity for identifying individuals with SARS-CoV-2 infection [44].

Comorbidities have negatively influenced the course of SARS-CoV-2 infection [45,46]. In our study, as in other national [35,47] and international [16,18,48] studies, comorbidities were associated with death from COVID-19 and behaved as important risk factors. The adjusted analysis revealed that people with one or more pre-existing conditions were about 17.50 times more likely to die.

Chronic diseases increase the risk for unfavorable COVID-19 outcomes, whether admission to the ICU or death [47]. The SARS-CoV-2 virus invades cells by binding to Angiotensin Converting Enzyme-2 (ACE-2) receptors on the surface of host cells. Some comorbidities cause greater expression of these receptors and increased protein release convertase, thus favoring the entry of the virus into the host's cells [49].

The most frequent comorbidities were systemic arterial hypertension, diabetes mellitus, obesity, and respiratory, neurological, and renal diseases. Diabetes mellitus had the highest risk of death, as diabetic individuals were almost six times more likely to die from COVID-19. The glycemic increase compromises the immune function, altering the cellular, humoral and antioxidant functions [44,49]. Besides, diabetic patients are more vulnerable to infections, as the capacity of phagocytic cells is compromised in these patients, leading to a greater susceptibility to infections [49].

Subjects with systemic arterial hypertension often have several dysfunctions compromising the cardiac, renal, and pulmonary functions at admission, increasing their susceptibility to negative COVID-19 outcomes [50,51]. Our study corroborates prior studies that also found a relationship between systemic arterial hypertension and death from COVID-19 [52,53]. In our study, systemic arterial hypertension increased the chances of death by more than twice, similar to a study conducted in China [50].

Obesity proved to be the third disease with the highest odds ratio for death from COVID-19, increasing the risk of dying by more than four times. A study carried out in Mexico [54], and two cohort studies

carried out in England [55,56] also reported this association.

Obesity is an important precursor for the emergence of other comorbidities such as systemic arterial hypertension, diabetes mellitus, and cardiovascular diseases [57]. In addition, excess adipose tissue favors chronic inflammation leading to a cytokine storm, increasing pro-inflammatory cytokines [58], and favoring the development of a higher viral load [57].

As COVID-19 is a respiratory disease, it is expected that the disease cause more deleterious effects in people who already have respiratory comorbidities. In our study, having an associated respiratory condition resulted in a 1.96-fold greater risk of progressing to death. Pulmonary diseases have already been reported as a risk factor for death from COVID-19. In Indonesia, among hospitalized patients who died from the disease, 4.00% had chronic obstructive pulmonary disease [52], and in the United States, in-hospital deaths among patients with prior respiratory diseases accounted for 24.09% of in-hospital deaths [26].

Neurological diseases were also evidenced as risk factors for mortality from COVID-19, increasing approximately five times the chance of dying. Studies carried out in the states of Espírito Santo [47] and Ceará [59], Brazil, showed that patients with this type of comorbidity were also more vulnerable to death from COVID-19.

The mechanisms used by SARS-CoV-2 to enter the central nervous system (CNS) are poorly understood. An experimental study suggests that the virus takes over brain cells when it breaks the blood-brain barrier. Thus, when invading the CNS, the virus causes direct damage to it, and neuroinflammation may also occur [60]. The impairment of the nervous system, when already aggravated by another associated neurological disease, influences a worse prognosis.

Renal diseases also behaved as risk factors for death by COVID-19, increasing the risk of death by 3.14 times. Many studies have demonstrated this association [17,61,62]. There is a greater expression of ACE-2 in kidney tissue in these patients, and the virus binds to these cells [46]. In addition, there is a tropism of SARS-CoV-2 for renal tubular cells [63]. The mechanisms above explain the severe COVID-19 outcomes in patients with renal dysfunctions.

The population of Maranhão State was severely affected by COVID-19 due to the syndemic aspects established by the disease in this territory. Studies suggest that the interaction and results of the association of chronic noncommunicable diseases with COVID-19 characterize this pandemic as a syndemic, as the mutual occurrence of different events affects the course and outcome of COVID-19 and other diseases [64,65]. Furthermore, this federative unit is marked by unfavorable socioeconomic conditions [13] and vulnerabilities enhanced by the global economic crisis, increasing the clinical and social impacts [65].

The current context indicates the need to expand the healthcare model in Maranhão articulated with the Chronic Care Model, aiming at broader healthcare for the population, covering the other endemic and epidemic processes, and preparing the healthcare system for future pandemics that may occur.

Regarding the study's limitations, it was not possible to investigate the association between some variables such as education and main associated symptoms and the outcome of death from COVID-19 due to the unavailability of some information in the database used in our study. Another relevant limitation is the possibility of underreported cases and deaths, an issue reported in prior studies in Brazil [4,66], the European continent, and South Africa [67]. Mortality information is crucial in understanding the spread of COVID-19. However, the significant underreporting of deaths in official documents makes this understanding less clear and reliable [67].

In addition, it was impossible to assess all variables relevant to the population's context. It is known that the disease's lethality is influenced by conditioning factors, including access to health care services [3], and some of these factors are not easily accessed.

Conclusions

This study has shown that the main risk factors associated with death from COVID-19 in a sample of patients from Maranhão were: male sex, age (mainly over 70 years), positive RT-PCR results, positive CT scan, and having one or more comorbidities (three of which were highly associated with the risk of death - diabetes mellitus, neurological diseases, and obesity). Hypertension, respiratory, and renal diseases also behave as risk factors for death.

The study findings support the implementation of strategic actions by health professionals, health surveillance professionals, and managers toward reducing the incidence of the risk factors for mortality by COVID-19 in Maranhão.

Authors' contributions

RAO and MSN conceived the study. MSN provided supervision throughout. All authors were involved in the implementation of the study. JCS, LFSS, FSS, and GGSS

extracted data from the Information System. LHS, JSML, FBAA, LMP, and ILTPR performed statistical analysis. MY, JMB, FAASS, and ACPJC analyzed the data. RAO and MSN wrote the manuscript. All authors edited the manuscript. All authors reviewed and approved the final version of the manuscript.

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Ethical approval

The Research Ethics Committee of the Federal University of Maranhão granted ethical approval for the study under opinion no. 4,227,396.

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