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Predictors of Death for Hospitalized Patients with COVID-19 in the First Year of the Pandemic in Northern Brazil - A Retrospective Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Identified predictors of death for hospitalized patients with COVID-19 in the First Year of the Pandemic in Northern Brazil.

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Methods: A longitudinal retrospective cohort study was carried out, using data from the Brazilian Ministry of Health's COVID-19 severe case and hospitalization notification forms, considering the period from January 1, 2020 to December 31, 2020. The extracted variables were related to the epidemiological profile and outcome of the disease. Data were analyzed using SPSS software, with chi-square test by contingency table, binary logistic regression, and survival analysis.
Results: Those vaccinated against influenza were associated with survivors in univariate and multivariate analysis, as well as survival analysis. The predictors of lethality were invasive ventilation (OR 6.627; CI 5.780–7.597), other pneumopathy (OR 1.901; CI 1.439–2.510), dyspnea (OR 1.899; CI 1.737–2.076), immunodeficiency (OR 1.905; CI 1.493–2.431), hospitalized in ICU (OR 1.764; CI 1.588–1.959), chronic kidney disease (OR 1.753; CI 1.396–2.203), diabetes mellitus (OR 1.210; CI 1.108–1.321), and male sex (OR 1.198; CI 1.111–1.293).
Conclusion: Those vaccinated against influenza were associated with survival; namely, they showed a lower risk of death in the regression and showed longer survival in the survival analysis, when compared to those who were not vaccinated. The lethality was higher than the other studies, while the predictors were similar. Evidencing that COVID-19 had more impact on deaths, which may be associated with the vulnerability factors of the region.

Keywords: Severe acute respiratory syndrome; Brazil; pandemic; COVID-19; SARS-CoV-2.

1. INTRODUCTION

Severe Acute Respiratory Syndrome (SARS) is a serious respiratory tract disease that can be caused by viruses, bacteria, and so on. Viral etiologies are capable of causing major epidemics in some regions of the world, specifically those caused by two coronaviruses (CoV), such as that caused by SARS-CoV, which emerged in 2003 and was termed by SARS in China, which spread to 29 countries and regions, as well as MERS-CoV (Middle East respiratory syndrome), in 2012 in Saudi Arabia. The transmission of both of these viruses is characterized by respiratory droplets directly and indirectly; and, in most cases, the resulting diseases have been shown to be mild, only with flu-like symptoms and without the evolution of SARS [1].

Six sub-groups of CoV are human pathogens: the α-coronavirus sub-group includes 229E and NL229E, while the β-coronavirus sub-group includes OC43, HKU1, SARS-CoV, and MERS-CoV [2]. The pathophysiological mechanism of SARS-CoV and MERS-CoV involves binding in the angiotensin converter enzyme 2 (ACE2) of the host, which is expressed in many tissues of human organs and highly expressed in the lungs, heart, and small intestine; however, the presence of ACE2 may not be the only requirement for tropism [3,4].

In 2009, a pandemic occurred due to a respiratory virus called H1N1. It started in the United States, with swine-origin (S-OIV), and was declared a pandemic of H1N1 influenza type A. On April 25, the World Health Organization (WHO) declared a public health emergency of international interest and, on April 26, the United States declared a public health emergency. On April 29, the WHO increased the phase of the influenza pandemic from 4 to 5, indicating that transmission of the virus from person to person was already occurring in at least two countries in a region of the world. This infection highlights the higher incidence of cases in children and adolescents, with a clinical picture that resembles other acute respiratory syndromes; however, a vaccine was developed, which reduced its transmission and incidence in the world. It became a seasonal disease in Brazil, for example, and since the influenza pandemic in 2009, Brazil has maintained surveillance for SARS in hospitalized cases, with nasopharyngeal sampling and molecular investigation using the SIVEP-GRIPE platform, through the completion of an investigation form [5–7].

In December 2019, cases of severe pneumonia of unknown etiology appeared in Wuhan, China, with an association of cases that had contact in a market in the region. In January 2020, the causative infectious agent was isolated, being from the coronavirus family. Thus, it was classified as SARS-CoV-2, having several similarities to SARS-CoV including its genome, pathophysiology, and transmission mechanism. The associated disease was named COVID-19 [8].

Studies have shown that trivalent influenza vaccine can offer a form of protection against mortality and severity in COVID-19 [9,10], Even a study in Brazil showed lower chances of

admission to the Intensive Care Unit (ICU) and death in those vaccinated against influenza [11].

In March 2020, the World Health Organization declared the outbreak of SARS-CoV-2 as a pandemic, with the first confirmed case in Brazil in February 2020. In the state of Pará, the first case was confirmed in March 2020, which was characterized as an imported case [12–14].

In Brazil, as of March 3, 2021, there had been 10,869,227 confirmed cases and 262,770 deaths, with a lethality of 2.4% [15]. Regarding the state of Pará, on March 3, 2021, there had been 372,388 confirmed cases and 8875 deaths, with a lethality of 2.38%. It should be highlighted that this information refers to data of both flu syndrome (mild cases) and acute respiratory syndromes (severe cases) [16].

The Amazon macro-region encompasses practically all of the states with Amazonian vegetal cover. In the last few decades, the North, as a whole, has been undergoing major alterations in its natural landscape. This region is still sparsely populated and industrial activity is restricted. In general, all of the States that make up the macro-region lack infrastructure and social services (e.g., access to education, health, security, employment, transportation, and many others) as, in these areas, there is a huge absence of the state and, often (as in Pará), the power is centered in the hands of large landowners and loggers who act according to their own interests, on the basis of force. The occupation without planning and state presence have contributed to the emergence of profound impacts on the environment, in which the main agents of devastation are the extraction of wood, mining, and especially the growing expansion of agricultural and pastoral areas [17–19].

Given this context, the northern region has the second-highest incidence of COVID-19 in Brazil, with 6481.9 cases per 100,000 inhabitants, as well as presenting the highest mortality rate in the country of 152.0 deaths per 100,000 inhabitants (data referring to the date March 3, 2021). The increase in cases and deaths in January and February 2021 highlights record death rates since the beginning of the pandemic in Brazil, showing that, despite the pandemic having begun a year ago, the country is at its worst moment [16]. Thus, there exists a need to specifically determine the clinical and epidemiological characteristics of SARS by COVID-19 in the state of Pará—due to the unique characteristics of this population—that, based on evidence of the factors associated with lethality, can be used to subsidize strategies for the reduction of deaths in this region of Brazil. Our objective was to identify the predictors associated with the lethality of 16,375 severe and hospitalized cases of COVID-19 in the state of Pará, northern Brazil.

2. METHODS

2.1 Type of Study

This was a longitudinal retrospective cohort study using data from COVID-19 severe and hospitalized cases for the surveillance of acute and severe respiratory syndromes by the SIVEP-GRIPE information system, made publicly available on the OpenDataSUS platform of the Brazilian Ministry of Health [20]. We followed the recommendations of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE; https://www.strobe-statement.org/checklists/) [21].

2.2 Study Site and Population

The study was conducted with a database in the state of Pará, which is located in the northern region of Brazil (Fig. 1).

The study population consisted of all cases reported and confirmed for COVID-19 in the SIVEP-GRIPE Epidemiological Surveillance Information System [22]. The Database (BD) has been made publicly available through the OpendataSUS (https://opendatasus.saude.gov.br/) platform of the Ministries of Health and DataSUS, referring to notifications made between January 1, 2020, and December 31, 2020.

The inclusion criteria were confirmed cases of COVID-19 and residents in Pará, with confirmation criteria completed (confirmed or discarded for COVID-19). Only confirmed cases for COVID-19 were included, as well as case evolution (hospital discharge for cure or hospital discharge for death). Exclusion criteria were notifications with at least one blank essential field for confirmation and/or evolution criteria.

The gold standard confirmation criterion in Brazil is the molecular test, following the protocols established by the guidelines and recommendations of the Brazilian Ministry of Health and the Central Laboratories (LACEN) [23].

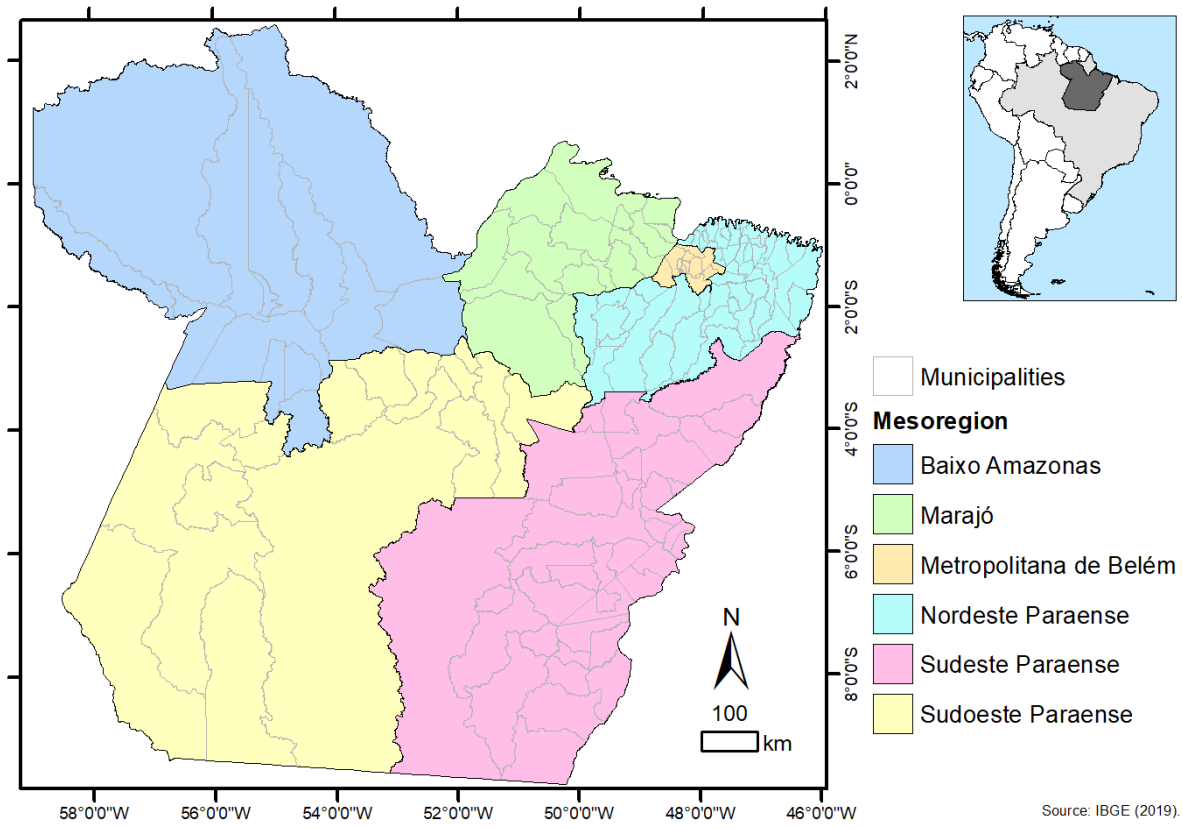

Fig. 1. Spatial location of the mesoregions and municipalities of the state of Pará, Amazon, Brazil

Source: Sardinha 2021

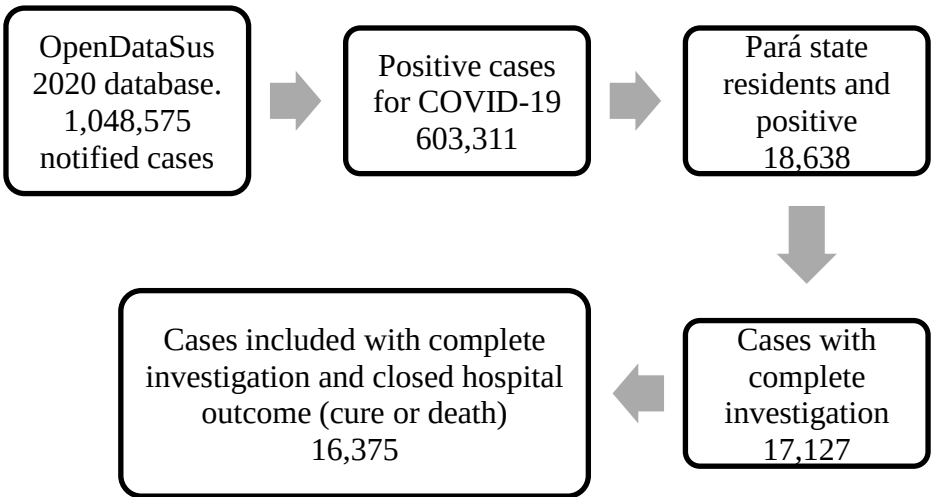

Fig. 2. Flowchart of participant selection

2.3 Data Collection and Case Definition

The eligibility criteria were based on the selection of cases confirmed for COVID-19 and residents in Pará, with confirmation criteria (item 72), evolution (item 74) and date of evolution (item 75), according to the notification and investigation form [24]. The form describes that SARS is defined for individuals with influenza syndrome (IS) who have: dyspnea/respiratory distress OR persistent chest pressure OR O_2 saturation lower than 95% on room air OR bluish coloration of the lips or face. IS is defined as an individual with an acute respiratory condition

characterized by at least two (2) of the following signs and symptoms: fever (even if referred), chills, sore throat, headache, cough, runny nose, and smell or taste disturbances. For notification in SIVEP-GRIPE, hospitalized cases of SARS or deaths from SARS, regardless of hospitalization, should be considered [24].

The time-zero of the cohort was defined by the date of symptom onset, and the delta-time (ΔT) corresponded to the period from the date of symptom onset to the outcome (cure or death) for cases with a confirmed diagnosis of SARS by COVID-19. The follow-up time was until the outcome.

The definition of cardiovascular diseases was according to the COVID-19 Brazilian epidemiological surveillance guide, which cites the following diseases: Myocardiopathies of different etiologies (heart failure, ischemic myocardiopathy, etc.) Hypertension; Cerebrovascular disease, valvulopathies and cardiac arrhythmias [25].

The same surveillance guide cites the other comorbidities and their definitions: Severe or decompensated lung diseases (moderate/severe asthma, pulmonary disease obstructive lung disease); Immunodepression and immunosuppression; Advanced stage chronic kidney disease (grades 3, 4 and 5); Diabetes mellitus, type 1 or 2, according to clinical judgment; Chromosomal diseases with immunological fragility state (example Down's syndrome); Malignant neoplasia (except non-melanotic skin cancer); Chronic liver disease (non-alcoholic fatty liver disease, autoimmune hepatitis and cirrhosis); Some hematological diseases (including sickle cell anemia and thalassemia). The form was filled out by the medical professional or nurse at the time of the patient's hospitalization, based on the investigation of the health history and physical examination [25].

A more detailed definition of comorbidities is available in the basic health care booklets, which are the technical references for health professionals in Brazil to act in health services [26].

The BD was made available in Excel 2019 format, with variables corresponding to the notification form of the SIVEP-GRIPE, which is composed of 80 variables referring to sociodemographic and clinical–epidemiological data. The variables extracted, according to the form, were: gender (item 8), age (item 10), pregnancy (item 11), race (item 12), municipality of residence (item 19), signs and symptoms (item 35), has risk factors/comorbidities (item 36), had flu vaccine (item 37), hospitalized in the ICU (item 47), used ventilatory support (item 50), tomography aspect (item 50), chest x-ray (item 51), final classification (item 72), closure criterion (item 73), and evolution (item 74).

2.4 Statistical Analysis

The dependent variable of this cohort was deaths from SARS by COVID-19 (6955). A comparison of the clinical–epidemiological and outcome variables of SARS by COVID-19 in the deceased and survivor groups was performed, in order to identify the predictors associated with deaths.

The data were organized in Excel 2019 and the analysis was performed using the statistical program Statistical Package for the Social Sciences 20.0. The chi-square test of independence by contingency table (LxC) was used to compare the variables of survivors and deceased, and to identify the independent variables. To verify the age difference between survivors and deceased, the Shapiro Wilk normality test was applied to verify which test to use. The Kolmogorov-Smirnov test was significant <0.01 and thus the sample does not have normality, and we used the Mann-Whitney test to verify the difference between the groups. The results were presented in tables.

The binary logistic regression was performed with the dependent variable death, and a univariate model with clinical, epidemiological, and outcome covariates was performed. After the identification of statistically significant variables ($p < 0.01$), a multivariate regression model was performed only with the significant variables, considering the fit of the model by the Hosmer–Lemeshow, Nagelkerke's R^2, and -2 log-likelihood tests.

Survival analysis was performed using the outcome of death and hospital discharge, considering the date of symptom onset, date of death, and date of hospital discharge, associated with the variable's ICU stay, invasive ventilatory support, and not being vaccinated against influenza, by the Kaplan–Meier method.

For all tests, the alpha significance level of 0.05 was considered.

3. RESULTS

The study population totaled 16,375 cases, the criteria for confirmation of COVID-19 in the hospitalized cases in this cohort were 8717 (53.23%) by Real-Time Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR), 6450 (39.39%) serological, 550 (3.36%) clinical epidemiological, 481 (2.94%) clinical, and 177 (1.08%) by clinical imaging. Of these cases, 9420 (57.53%) survived, and 6955 (42.47%) died. Therefore, the lethality of SARS due to COVID-19 in this study was 42.47%. Regarding the demographic data, there were 9670 (59.05%) male cases and 6705 (40.95%) females, with an overall average age of 58 years. Regarding the survivors, the majority were male (n = 5344; 56.73%), and they had a mean age of 51.1 years. For the deceased, the mean age was 67 years. The Mann-Whitney test was significant for deaths. (<0.01) (Table 1).

In relation to signs and symptoms, cough (n = 13,050; 79.69%), fever (n = 12,775; 78.02%), dyspnea (n = 12,196; 74.48%), respiratory distress (n = 10,319; 63.02%), O_2 saturation ≤95% (n = 8001; 48.86%), and sore throat (n = 5569; 34.01%) were more recurrent in cases of SARS. The signs and symptoms associated with survivors were cough (82.15% vs 76.36%; <0.01), fever (80.22% vs 75.03%; <0.01), sore throat (38.82% vs 27.49%; <0.01), diarrhea (19.45% vs 11.93%; <0.01), vomiting (10.37% vs 6.77%; <0.01), abdominal pain (3.76% vs 1.90%; <0.01), fatigue (7.65% vs 5.62%; <0 .01), loss of smell (6.59% vs 3.35%; <0.01), loss of taste (6.46% vs 3.48%; <0.01), and others (29.94% vs 19.80%; <0.01). The signs and symptoms associated with mortality were dyspnea (69.28% vs 81.52%; <0.01), respiratory distress (61.48% vs 65.10%; <0.01), and O_2 saturation ≤95% (43.57% vs 56.03%; <0.01) (Table 2).

In the evaluation of comorbidities and risk factors, the most recurrent and representative were chronic cardiovascular disease (n = 3972; 24.26%) and diabetes mellitus (n = 3555; 21.71%). For survivors, the only comorbidity associated with survival was asthma (2.46% vs 1.29%; <0.01). However, most comorbidities were associated with death, including chronic cardiovascular disease (19.00% vs 31.37%; <0.01), diabetes mellitus (17.76% vs 27.06%; <0.01), chronic kidney disease (1.70% vs 4.24%; <0.01), another chronic pneumopathy (1.00% vs 3.16%; <0.01), immunodeficiency (1.80% vs 3.01%; <0.01), chronic neurological disease (1.30% vs 2.24%; <0.01), chronic liver disease (0.40% vs 0.83%; <0.01), and others (16.07% vs 19.32%; <0.01); Table 2.

In the variable "Vaccinated against influenza", 1975 (12.06%) of the population were vaccinated, but when the test was applied to compare survivors and deceased, significant results were observed for the survivors (13.46% vs 10.17%; <0.01) (Table 2).

For the binary logistic regression models, the following results were obtained. Multivariate: -2 log-likelihood 16,856.204, p-value <0.01; R^2 Nagelkerke = 0.382; Hosmer–Lemeshow test, p-value 0.06. In the multivariate adjusted model, the predictors of lethality were invasive ventilation (OR 6.627; CI 5.780–7.597), other pneumopathy (OR 1.901; CI 1.439–2.510), dyspnea (OR 1.899; CI 1.737–2.076), immunodeficiency (OR 1.905; CI 1.493–2.431), hospitalized in ICU (OR 1.764; CI 1.588–1.959), chronic kidney disease (OR 1.753; CI 1.396–2.203), diabetes mellitus (OR 1.210; CI 1.108–1.321), and male sex (OR 1.198; CI 1.111–1.293); Table 3.

In the ICU survival analysis, the test was significant (p < 0.01), indicating that ICU inpatients had a lower survival rate than non-ICU inpatients: the mean survival days for non-ICU inpatients was 60 days, while that for ICU inpatients was 31 days (Fig. 3).

The survival test concerning the cases that used invasive ventilatory support presented lower survival, compared with the cases that did not use it—the Kaplan–Meier test was also significant (<0.01)—with a median survival of 57 days in cases not using invasive ventilation and 24 days in those with invasive ventilation (Fig. 4).

Survival analysis was also performed to identify whether unvaccinated cases had shorter survival, and the test was significant (<0.01), compared with vaccinated cases, with mean survival of 50 and 43 days for vaccinated and unvaccinated cases, respectively (Fig. 5).

4. DISCUSSION

In this study, we analyzed the severe and hospitalized COVID-19 cases in the state of Pará that occurred in the year 2020, as reported and investigated in the SIVEP-GRIPE platform of the Ministry of Health, which carries out surveillance of acute and severe respiratory syndromes of hospitalized patients, regardless of the etiological agent.

Table 1. Demographic characteristics of SARS cases by COVID-19 in the state of Pará in 2020

Characteristics	Total (16,375)	%	Survivors (9420)	%	Deaths (6955)	%	p-value (survivors vs. deaths)
Age							
Minimum – Maximum	0–114		0–103		0–114		
Average	58		51.1		67		
Median	61		52		70		<0.01*
Standard Deviation	20.44		20.27		16.59		
Sex							
Male	9670	59.05	5344	56.73	4326	62.20	<0.01
Female	6705	40.95	4076	43.27	2629	37.80	<0.01
Race							
White	1630	9.95	924	9.80	706	10.15	0.49
Black	606	3.70	359	3.80	247	3.55	0.41
Yellow	136	0.83	71	0.75	65	0.93	0.24
Parda	11,016	67.27	6530	69.32	4486	64.50	<0.01
Indigenous	107	0.65	60	0.64	47	0.68	0.84
Ignored	1583	9.67	886	9.41	697	10.02	0.20
Not filled in	1297	7.92	590	6.26	707	10.17	<0.01

*Source: Ministry of Health, Sivep-Gripe/OpenDataSUS, 2020. *Mann-Whitney*

Table 2. Clinical characteristics, risk factors, and comorbidities in cases of SARS by COVID-19 in the state of Pará in 2020. Belém, Pará, Brazil, 2020

Variable Studied	Total (16375)	%	Survivors (9420)	%	Deaths (6955)	%	p-value (survivors vs. deaths)
Clinical characteristics							
Fever	12.775	78.02	7557	80.22	5218	75.03	<0.01
Cough	13.050	79.69	7739	82.15	5311	76.36	<0.01
Sore throat	5569	34.01	3657	38.82	1912	27.49	<0.01
Dyspnea	12.196	74.48	6526	69.28	5670	81.52	<0.01
Respiratory distress	10.319	63.02	5791	61.48	4528	65.10	<0.01
O_2 saturation ≤95%	8001	48.86	4104	43.57	3897	56.03	<0.01
Diarrhea	2662	16.26	1832	19.45	830	11.93	<0.01
Vomit	1448	8.84	977	10.37	471	6.77	<0.01
Abdominal pain	486	2.97	354	3.76	132	1.90	<0.01

Variable Studied	Total (16375)	%	Survivors (9420)	%	Deaths (6955)	%	p-value (survivors vs. deaths)
Fatigue	1112	6.79	721	7.65	391	5.62	<0.01
Loss of smell	854	5.22	621	6.59	233	3.35	<0.01
Loss of taste	851	5.20	609	6.46	242	3.48	<0.01
Other	4197	25.63	2820	29.94	1377	19.80	<0.01
Risk Factors and Comorbidities							
Pregnant	138	0.84	127	1.35	11	0.16	<0.01
Puerpera	41	0.25	26	0.28	15	0.22	0..54
Chronic cardiovascular disease	3972	24.26	1790	19.00	2182	31.37	<0.01
Chronic hematological disease	80	0.49	34	0.36	46	0.66	<0.01
Down syndrome n	49	0.30	26	0.28	23	0.33	0.63
Chronic liver disease	96	0.59	38	0.40	58	0.83	<0.01
Asthma	322	1.97	232	2.46	90	1.29	<0.01
Diabetes Mellitus	3555	21.71	1673	17.76	1882	27.06	<0.01
Chronic neurological disease	278	1.70	122	1.30	156	2.24	<0.01
Another chronic pneumopathy	314	1.92	94	1.00	220	3.16	<0.01
Immunodeficiency	379	2.31	170	1.80	209	3.01	<0.01
Chronic kidney disease	455	2.78	160	1.70	295	4.24	<0.01
Obesity	254	1.55	144	1.53	110	1.58	0.84
Other	2858	17.45	1514	16.07	1344	19.32	<0.01
Flu vaccinated	*1975*	*12.06*	*1268*	*13.46*	*707*	*10.17*	*<0.01*

Source: Ministry of Health, Sivep-Gripe/OpenDataSUS, 2020

Table 3. Association of clinical, epidemiological, and outcome variables in the univariate and multivariate models adjusted for the odds ratio for death in SARS by COVID-19 in hospitalized in northern Brazil, 2020

Univariate regression			CI* for OR**		Multivariate regression		CI* for OR**	
	p-value	OR	Lower	Upper	p-value	OR	Lower	Upper
Invasive ventilation	<0.01	6.552	5.711	7.516	<0.01	6.627	5.780	7.597
Other pneumopathy	<0.01	1.900	1.438	2.510	<0.01	1.901	1.439	2.510
Dyspnea	<0.01	1.873	1.707	2.054	<0.01	1.899	1.737	2.076
Immunodeficiency	<0.01	1.855	1.452	2.369	<0.01	1.905	1.493	2.431
Hospitalized in ICU	<0.01	1.755	1.579	1.950	<0.01	1.764	1.588	1.959
Chronic kidney disease	<0.01	1.736	1.381	2.183	<0.01	1.753	1.396	2.203
Chronic liver disease	0.34	1.685	1.039	2.731				

Univariate regression			CI* for OR**		Multivariate regression		CI* for OR**	
	p-value	OR	Lower	Upper	p-value	OR	Lower	Upper
Chronic hematological disease	0.112	1.567	0.901	2.723				
Obesity	0.168	1.240	0.913	1.682				
Diabetes Mellitus	<0.01	1.198	1.095	1.310	<0.01	1.210	1.108	1.321
Male gender	<0.01	1.194	1.106	1.289	<0.01	1.198	1.111	1.293
O_2 saturation ≤95%	0.90	1.074	0.989	1.167				
Chronic neurological disease	0.661	1.068	0.797	1.429				
Vomit	0.701	1.028	0.892	1.185				
Chronic cardiovascular disease	0.901	1.006	0.921	1.098				
Respiratory distress	9.937	1.003	0.921	1.093				
Fever	0.946	0.997	0.906	1.096				
Age	<0.01	0.954	0.952	0.956	<0.01	0.954	0.951	0.956
Down syndrome	0.657	0.862	0.447	1.662				
Sore throat	<0.01	0.827	0.761	0.898	<0.01	0.827	0.762	0.897
Cough	<0.01	0.794	0.719	0.876	<0.01	0.794	0.722	0.873
Influenza Vaccinated	<0.01	0.705	0.629	0.791	<0.01	0.714	0.637	0.801
Diarrhea	<0.01	0.695	0.623	0.775	<0.01	0.703	0.633	0.781
Asthma	0.16	0.690	0.510	0.934				
Constant	0.73	0.357			2.06	0.737		

*Multivariate: -2 log-likelihood 16,856.204, p-value < 0.01; R^2 Nagelkerke = 0.382; Hosmer–Lemeshow test, p-value 0.06. * Confidence Interval, ** Odds Ratio. Source: Ministry of Health, Sivep-Gripe/OpenDataSUS, 2020*

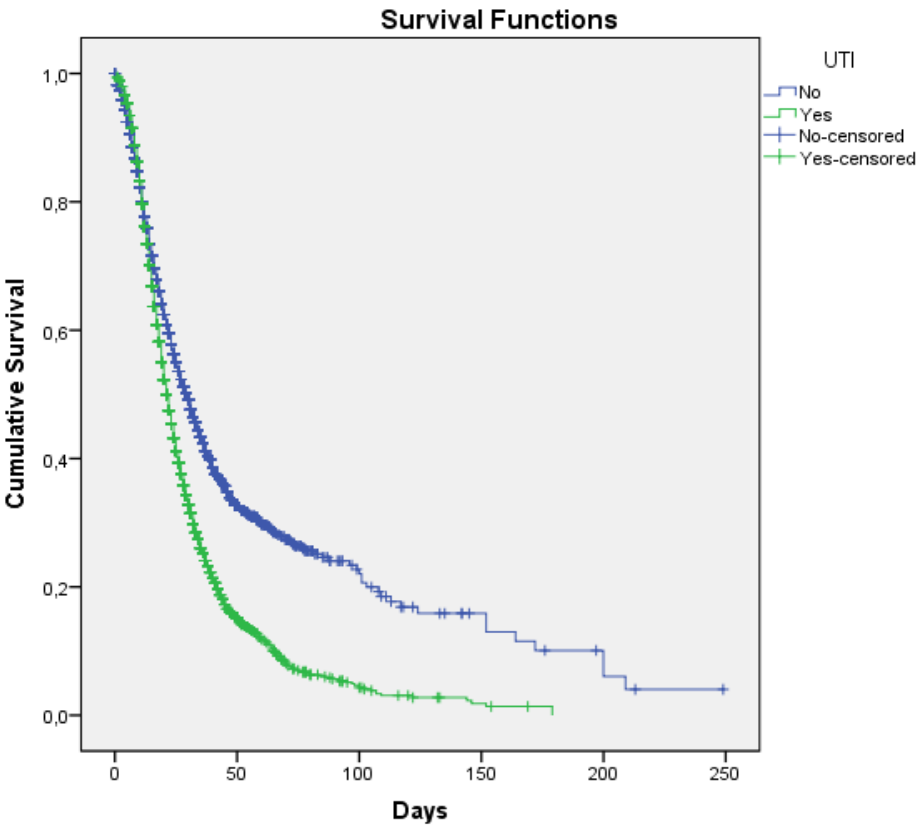

Fig. 3. Survival analysis of SARS by COVID-19 cases in the ICU
Source: Ministry of Health, Sivep-Gripe/OpenDataSUS, 2020. Long Rank (Mantel-cox) X^2 211.207 – p <0.01

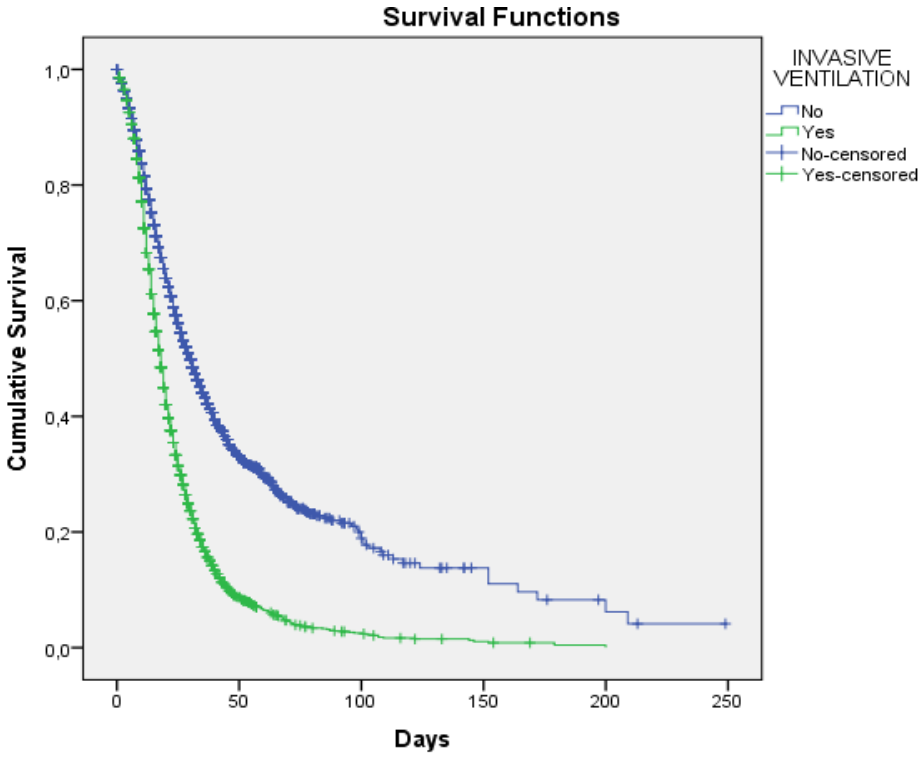

Fig. 4. Survival analysis of SARS by COVID-19 cases that used invasive ventilatory support
Source: Ministry of Health, Sivep-Gripe/OpenDataSUS, 2020. Long Rank (Mantel-cox) X^2 688.455 – p <0.01

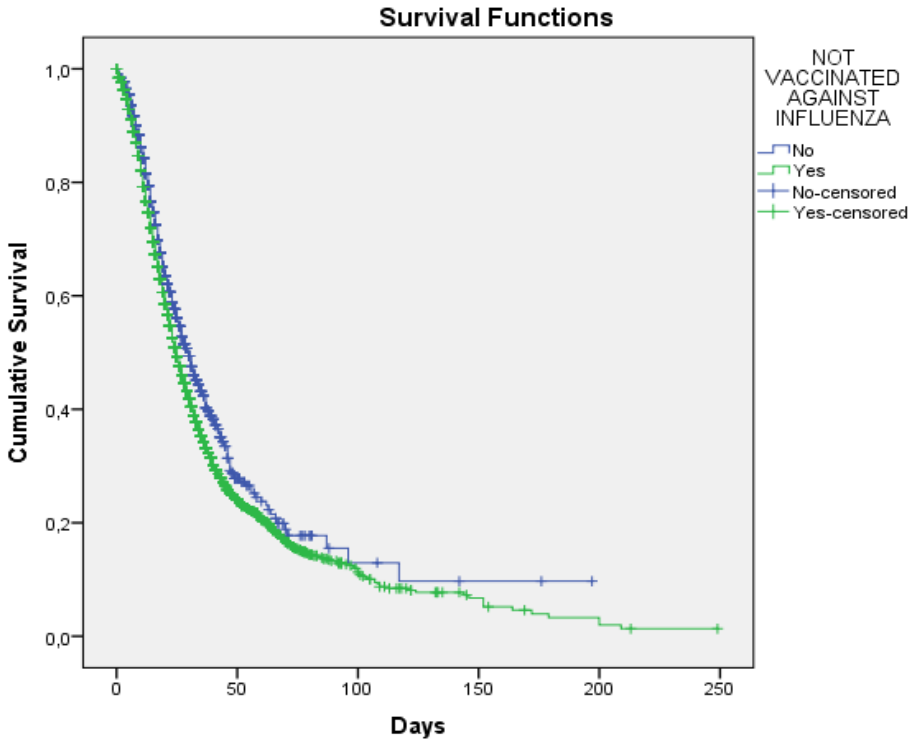

Fig. 5. Survival analysis of SARS by COVID-19 cases not vaccinated against influenza
Source: Ministry of Health, Sivep-Gripe/OpenDataSUS, 2020. Long Rank (Mantel-cox) X^2 24.287 – p <0.01

The study population presented lethality in 42.47% of hospitalized patients, much higher than that for Brazil (32.35%) [27], with a predominance of males in general (59.05%) and in the deceased group (62.20%), with higher odds of death (OR 1.198: CI 1.111–1.293). It is noteworthy that several studies have shown that the incidence of infected women is most often higher when evaluating all cases (i.e., mild, moderate, and severe); however, these same studies show that, in terms of deaths, the predominance is in males [28–30], corroborating the results herein that severe cases were more common in men, as well as deaths.

One study has cited that the higher occurrence of severity and death in men is associated with greater expression of ACE2, which may explain how SARS-CoV-2 can have a greater impact on this gender [31].

Two meta-analyses have shown that the lethality of COVID-19 is concentrated in older individuals [32,33], similar to the results observed in this study by the Mann-Whitney test, but in the multivariate regression model, older age was not associated with death. We believe that the other variables influenced. Studies have indicated that older people have more chronic diseases, which are most often risk factors for complications of COVID-19, as well as a weakened immune response due to immunosenescence; which is a natural deterioration of the immune response, causing changes in immune memory, as well as in the production and actions of certain defense cells such as T-cells. Thus, clinical presentations are atypical, such as an absence of fever, which is the main sign of infection, impairing adequate screening of the disease in this age group [34]. A study has highlighted that being aged over 60 years is a risk factor for mortality and can still be potentiated in the presence of some chronic diseases. Thus, advanced age is associated with most causes of death from chronic and infectious diseases, and it is no different for COVID-19 [35].

The predominant clinical features in the study population included cough (79.69%), fever (78.02%), dyspnea (74.48%), respiratory distress (63.02%), O_2 saturation ≤95% (48.86%), and sore throat (34.01%), being similar to the results of other studies evaluating severe and hospitalized cases [36,37]. In terms of the clinical characteristics associated with mortality, we observed dyspnea (81.52%), respiratory distress (65.10%), and O_2 saturation ≤95% (56.03%); in addition, the odds ratio dyspnea (OR 1.899; CI 1.737–2.076) presented almost twice as many chances for death. This result has also been observed in other studies [38,39].

Respiratory distress and oxygen saturation changes can occur without the presence of dyspnea; however, dyspnea usually occurs as a consequence of respiratory distress and oxygen saturation changes, which may indicate pulmonary hypoxia in COVID-19. The O_2 saturation below 95% already indicates signs of severity directly associated with the pathological process of SARS-CoV-2, which causes a cytokine storm or macrophage activation syndrome, which leads to an inflammatory cascade causing a state of generalized pulmonary hypercoagulability, causing hypoxia and injury to lung tissue. Thus, for the management of cases, laboratory markers such as D-dimer, prothrombin time, platelet aggregates, macro platelets, C-reactive protein, lactate, ferritin, serum amyloid A, and liver enzymes become essential, with changes in the levels of these markers having been cited in studies as predictors for mortality [40,41].

In the chi-square test, all comorbidities were associated with mortality except for asthma; while those in the regression were being a carrier of another lung disease, kidney disease, diabetes, and immunodeficiency. Similar to the results of other studies, we also highlighted that the presence of chronic diseases is an important predictor of mortality [42–44]. One study has highlighted that, in diabetic individuals, the highest rate of inflammatory processes is due to the constant recognition of glucose by type C lectin receptors. Hypertensives, usually grouped with other diseases, are treated with drugs to reduce blood pressure mainly by Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB), leading to increased ACE2 expression, which is used by SARS-CoV-2 to enter human cells. To date, studies have shown that individuals with these conditions and affected by COVID-19 have a controlled release of pro-inflammatory cytokines and unbalanced immune response, leading to the cytokine storm phenomenon [45].

Having another chronic pneumopathy, such as Chronic Obstructive Pulmonary Disease (COPD), increases the chances of severe COVID-19 forms by up to five times, according to a meta-analysis [46]. In terms of immunodeficiency, a study has shown the chances of progression to severity in COVID-19 being increased by up to 3.39 times, as directly associated with opportunistic infections that can cause other systemic complications, influenced by severity and mortality, as b-lymphocyte deficiency prevents the storm of inflammatory cytokines; however, it facilitates secondary infections, such as bacterial infections, with chances of sepsis [47,48].

It has been shown that asthma is not significantly associated with mortality. A study in 1526 patients with COVID-19, both hospitalized and non-hospitalized, showed the prevalence of only 14% of asthma patients in hospitalized patients, finding no association between asthma and disease severity and longer hospitalization time; furthermore, the continuous use of initiatory corticosteroids did not influence mortality, severity, and/or hospitalization [49]. A meta-analysis provided no clear evidence of increased risk of COVID-19 diagnosis, hospitalization, severity, or mortality due to asthma [50].

This study also identified that people vaccinated against influenza died less than the unvaccinated (13.46%, $p < 0.01$). The OR showed a lower risk in the vaccinated (OR 0.714; CI 0.637–0.801), confirmed also in the survival analysis, showing shorter survival period in the unvaccinated cases ($p < 0.01$). In a study in Italy that analyzed data from elderly people over 65 years who were vaccinated or not vaccinated against influenza, a simple linear regression was performed to predict the percentage of deaths from COVID-19. They showed a moderate to strong negative correlation ($r = -0.5874$, $n = 21$, $P = .0051$), which means that where there were higher rates of influenza vaccination, there were fewer deaths from COVID-19. A significant regression equation was found [$F(1.19) = 10.01$, $P = 0.01$], with an R^2 value of 0.3450. The percentage of COVID-19 deaths in each region decreased by 0.3450 for each percentage unit of elderly people over 65 years of age vaccinated against influenza [51], similar to the results of this research.

A study in Brazil with a sample of 92,664 patients having COVID-19, of whom about one-third received the influenza vaccine, showed that influenza-vaccinated patients were 8% less likely to be in the intensive care unit, 18% less likely to require mechanical ventilation, and 17% less likely to die [11]. The research by Yang et al. [52] showed that COVID-19 patients who had not received an influenza vaccination in the last year had a 2.44× chance (95%CI: 1.68–3.61) of hospitalization and a 3.29× chance (95%CI: 1.18–13.77) of longer ICU stay, when compared to those who were vaccinated. The results were also controlled to take into account age, race, gender, hypertension, diabetes, chronic obstructive pulmonary disease, obesity, coronary

artery disease, and congestive heart failure. These analyses suggest that influenza vaccination is potentially protective against moderate to severe cases of COVID-19 infection. This protective effect is valid regardless of the presence of comorbidity.

Another study in Brazil considering 472,688 hospitalized cases of COVID-19 showed, in a regression, almost twofold higher odds ratios for invasive ventilation, ICU admission, and death in unvaccinated cases [53].

Concerning the deceased group, ICU admission (38.71%) and invasive ventilatory support (32.05%) had high significance. For predicting mortality, it was observed that invasive ventilatory support presented an OR of 6.627 (CI 5.780–7.597) and admitted to ICU boarding school had an OR of 1.764 (CI 1.588–1.959). In a study of 164 critically followed patients admitted to the ICU in Mexico, the majority were men (69%), with mean age of 57.3 years. A total of 38.4% presented hypertension and 32.5% presented diabetes; all received invasive ventilation for an average time of 11 days, with lethality of 51.85%, death before 30 days, and a median survival of 25 days. The authors concluded that the time of hospitalization, an increase in c-reactive protein, were predictors for ICU lethality by COVID-19 [54]. Thus, the outcomes of ICU and invasive ventilation were associated with death, as well as being influenced by other risk factors such as male gender and pre-existing illness. A cohort study in Brazil also independently associated the need for supplemental oxygen on admission and invasive ventilation with increased chances of death in hospitalized cases of COVID-19 [55].

Studies that identify predictors of death, like our study for example, allow for better clinical evaluation and prediction of disease severity. One study for example created a strategy to predict the severity and mortality of COVID-19 in hospitalized patients, a risk score, which included ge, blood urea nitrogen, number of comorbidities, C-reactive protein, SpO2/FiO2 ratio, platelet count, and heart rate. The model had high discriminatory value (AUROC 0.844, 95% CI 0.829-0.859). It is implemented in a freely available online risk calculator (https://abc2sph.com/) [56]. These tools are essential to contribute to the clinical practice of case management and treatment, which can have an impact on reducing mortality from the disease.

There is also a limitation for those vaccinated against influenza, as the form only has the options “yes” or “no”, regarding whether they had been vaccinated in the last year—after all, in Brazil, the influenza vaccination campaign is annual. Thus, there is a risk of bias, due to the analysis of retrospective secondary data. Another point to be highlighted as a limitation is the absence of continuous data such as temperature, blood saturation levels, blood pressure, because the answers were binary and the database does not have these measured values for each case. We also emphasize that we did not perform the interaction between the predictors that might or might not have similar or different results.

The treatment and management of hospitalized cases were based on oxygen therapy and other known care for critically ill patients, and that were already carried out in the surveillance and care flow for acute and severe respiratory syndromes in Brazil, which has existed since 2009. However, it is worth noting the limitation of the types of treatment of the cases, which we believe was not different between the cases because the SARS protocol already exists in Brazil.

The cases refer to those who were hospitalized, and most were confirmed by laboratory criteria; however, the results of the clinical characteristics and outcome associated with death were similar to the literature. The lethality of the hospitalized patients was higher than that of those hospitalized in Brazil overall, which may be associated with the factors of vulnerability of the region or weaknesses in epidemiological surveillance in the notification and closure of investigations, such that the surveillance predominantly focuses on investigating deaths, influenced by the high demand for service and few professionals trained in health surveillance in the region, as well as the turnover of professionals in epidemiological surveillance both at the state and municipal level. The main author is an epidemiologist in the state, and has experienced all these weaknesses first-hand.

5. CONCLUSION

The determined predictors of lethality due to COVID-19 were invasive ventilation, other pneumopathy, dyspnea, immunodeficiency, hospitalized in ICU, chronic kidney disease, diabetes mellitus, and male sex.

The lethality was higher than the other studies, while the predictors were similar. Evidencing that

COVID-19 had more impact on deaths, which may be associated with the vulnerability factors of the region.

Those vaccinated against influenza were associated with survival; namely, they showed a lower risk of death in the regression and showed longer survival in the survival analysis, when compared to those who were not vaccinated.

ETHICAL APPROVAL

According to Resolution No. 510 of April 7, 2016, Article II stands out, which addresses surveys that use publicly accessed data, according to Law No. 12.527 of November 18, 2011, Articles III (surveys that use information in the public domain) and V (surveys in databases whose information is aggregated, without the possibility of individual identification), the following shall not be registered or evaluated by the Ethics and Research Committee system (CEP/CONEP). Thus, these types of studies are not recommended to be submitted for ethical review and can be freely conducted, as the publicly available data do not include data such as the participant's names, telephone numbers, and addresses [57,58].

DATA AVAILABILITY STATEMENT

The data are available in the Brazilian Ministry of Health's platform: https://opendatasus.saude.gov.br/dataset?tags=SRAG.

DISCLAIMER

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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