



# Severe Acute Respiratory Syndrome by SARS-CoV-2 Infection or Other Etiologic Agents Among Brazilian Indigenous Population: An Observational Study from the First Year of Coronavirus Disease (COVID)-19 Pandemic

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## Summary

**Background** Indigenous peoples are vulnerable to pandemics, including to the coronavirus disease (COVID)-19, since it causes high mortality and specially, the loss of elderly Indigenous individuals.

**Methods** The epidemiological data of severe acute respiratory syndrome (SARS) by SARS-CoV-2 infection or other etiologic agents (OEA) among Brazilian Indigenous peoples during the first year of COVID-19 pandemic was obtained from a Brazilian Ministry of Health open-access database to perform an observational study. Considering only Indigenous individuals diagnosed with SARS by COVID-19, the epidemiology data were also evaluated as risk of death. The type of sample collection for virus screening, demographic profile, clinical symptoms, comorbidities, and clinical evolution were evaluated. The primary outcome was considered the death in the Brazilian Indigenous individuals and the secondary outcome, the characteristics of Brazilian Indigenous infected by SARS-CoV-2 or OEA, as the need for intensive care unit admission or the need for mechanical ventilation support. The statistical analysis was done using Logistic Regression Model. Alpha of 0.05.

**Findings** A total of 3,122 cases of Indigenous individuals with SARS in Brazil were reported during the first year of the COVID-19 pandemic. Of these, 1,994 were diagnosed with COVID-19 and 730/1,816 (40.2%) of them died. The death rate among individuals with SARS-CoV-2 was three-fold increased when compared to the group of individuals with OEA. Several symptoms (myalgia, loss of smell, and sore throat) and comorbidities (cardiopathy, systemic arterial hypertension, and diabetes mellitus) were more prevalent in the COVID-19 group when compared to Indigenous individuals with OEA. Similar profile was observed considering the risk of death among the Indigenous individuals with COVID-19 who presented several symptoms (oxygen saturation <95%, dyspnea, and respiratory distress) and comorbidities (renal disorders, cardiopathy, and diabetes mellitus). The multivariate analysis was significant in differentiating between the COVID-19-positive and non-COVID-19 patients [ $\chi^2_{(7)}=65.187$ ; P-value<0.001]. Among the patients' features, the following contributed in relation to the diagnosis of COVID-19: age  $\geq 43$  years-old [y.o.];

**Abbreviations:** %, Percentage; 95%CI, 95% Confidence Interval; COVID-19, Coronavirus Disease (2019); H1N1, H1N1 Strain of the Flu (Influenzae) virus; HRCT, High-Resolution Computed Tomography; ICU, Intensive Care Unit; MV, Mechanical Ventilation; NA, Not Applicable; OEA, Other Etiologic Agents; OR, Odds Ratio; RT-PCR, Real Time-Polymerase Chain Reaction; SAH, Systemic Arterial Hypertension; SARS, Severe Acute Respiratory Syndrome; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SUS, Sistema Único de Saúde (Brazilian Public Health System); y.o., Years Old; SIVEP-Gripe, Information System for Epidemiological Surveillance of Influenza (Sistema de Informação de Vigilância Epidemiológica da Gripe)

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OR=1.984 (95%CI=1.480-2.658)]; loss of smell [OR=2.373 (95%CI=1.461-3.854)]; presence of previous respiratory disorders [OR=0.487; 95%CI=0.287-0.824)]; and fever [OR=1.445 (95%CI=1.082-1.929)]. Also, the multivariate analysis was able to predict the risk of death [ $\chi^2_{(9)}=293.694$ ; P-value<0.001]. Among the patients' features, the following contributed in relation to the risk of death: male gender [OR=1.507 (95%CI=1.010-2.250)]; age  $\geq 60$  y.o.; OR=3.377 (95%CI=2.292-4.974)]; the need for ventilatory support [invasive mechanical ventilation; OR=24.050 (95%CI=12.584-45.962) and non-invasive mechanical ventilation; OR=2.249 (95%CI=1.378-3.671)]; dyspnea [OR=2.053 (95%CI=1.196-3.522)]; oxygen saturation <95% [OR=1.691 (95%CI=1.050-2.723)]; myalgia [OR=0.423 (95%CI=0.191-0.937)]; and the presence of kidney disorders [OR=3.135 (95%CI=1.144-8.539)].

**Interpretation** The Brazilian Indigenous peoples are in a vulnerable situation during the COVID-19 pandemic and presented an increased risk of death due to COVID-19. Several factors were associated with enhanced risk of death, as male sex, older age ( $\geq 60$  y.o.), and need for ventilatory support; also, other factors might help to differentiate SARS by COVID-19 or by OEA, as older age ( $\geq 43$  y.o.), loss of smell, and fever.

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**Keywords:** COVID-19; Ethnicity; Intensive Care Unit; Indigenous; Pandemic; Race; Respiratory Disease; Severe Acute Respiratory Syndrome; Virus

### Research in context

#### *Evidence before this study*

The Indigenous peoples are a vulnerable population with poor access to health worldwide and especially in Brazil. They are at increased risk for several contagious infectious diseases, as the Influenza and the now the coronavirus disease (COVID)-19. However, little is known about the epidemiological characteristics associated with increased risk of death in COVID-19 Indigenous Brazilian individuals.

#### *Added value of this study*

This study shed light in the clinical characteristics and outcomes of COVID-19 Indigenous Brazilian individuals. It was analyzed the differences between clinical characteristics of individuals with SARS due to COVID-19 and other etiologic agent; also, the risk of death was evaluated for several clinical characteristics as well.

#### *Implications of all the available evidence*

The evidence of this study might contribute to a better understanding of the COVID-19 pandemic in the Indigenous peoples as well as the natural history of the disease and to differentiate severe acute respiratory syndrome (SARS) by COVID-19 and other etiologic agent. In addition, the present study allowed us to identify those Indigenous individuals with enhanced risk of death due to COVID-19.

### Introduction

Severe acute respiratory syndrome (SARS) is a disease first reported in 2003 caused by, at that time, severe acute respiratory syndrome coronavirus (SARS-CoV).<sup>1</sup> However, in 2019, a new virus, named SARS-CoV-2 emerged, and it was responsible for one of the greatest pandemics of the 21<sup>st</sup> century. This virus is also responsible for symptoms associated with the lower respiratory tract, such as shortness of breath and cough, and systemic symptoms, like fever and myalgia.<sup>2</sup> Unfortunately, coronavirus disease (COVID)-19 can progress to pneumonia, severe acute respiratory distress syndrome and death,<sup>2</sup> mostly in vulnerable patients, such as Afro-Americans, Hispanics and Indigenous population.<sup>3-6</sup>

The COVID-19 pandemic in Brazil reaffirms the scenario of inequalities experienced by extreme poverty population groups. In South America, several groups as Afro-descendants, homelessness, low-incomes, food delivery riders, poor rural communities, women shelter, and Indigenous peoples, are more susceptible to develop SARS.<sup>7-11</sup> and perhaps, the most neglected and vulnerable group among them are the Indigenous peoples.<sup>5-7,12</sup>

Unfortunately, the risk factors for SARS-CoV-2 infection and deaths due to COVID-19 are also very different across ethnicities in Brazil. For example, Indigenous peoples have the largest proportion of the population vulnerable to COVID-19 (28.5%), followed by *Pardos* (23.8%), Afro-descendants (19.2%), Caucasians (12.5%), and Asians (7.5%).<sup>12</sup> The COVID-19 caused a great

impact among the Indigenous peoples, especially from the Amazonian region, and it can cause the dissemination of ethnic groups as demonstrated by the last male from Juma Brazilian tribe, who died due to COVID-19. Also, it was reported a high rate of confirmed cases of the disease in several isolated Indigenous peoples from tribes in Ecuador as the Waorani, Siona, Kichwa, Shuar, and Kofan.<sup>8,13,14</sup> Concomitantly, it was observed a high mortality rate among elderly Indigenous individuals, which had an important impact on cultural issues, since tribal knowledge is transmitted mainly by the elderly ones.<sup>15</sup> Interestingly, in order to protect the *Pikenani*, the Waorani people sued Ecuador's President and Vice President, forcing the Ecuadorian political leaders to combat the SARS-CoV-2 among Waorani individuals.<sup>14</sup>

To date, Brazil accounts for 896,917 Indigenous individuals distributed among 505 Indigenous lands, with the first confirmed case of COVID-19 in an Indigenous individual described in June 2020.<sup>5</sup> After exactly one year of the COVID-19 pandemic, 44,648 Brazilian Indigenous individuals were infected, 41,589 cases with clinical cure, and 605 cases of death were accounted for by the Brazilian Ministry of Health.<sup>8,16</sup>

The Brazilian population, especially the most vulnerable, has reaped the fruits of mismanagement in tackling the pandemic. Unfortunately, the government has relaxed laws that protect the environment and Indigenous peoples, leading to the mining, the wood exploration and the deforestation of environmental preservation, increasing the risk of Indigenous individuals be infected by SARS-CoV-2 or other infectious diseases.<sup>5,6,17,18</sup> The marginalization of the Indigenous peoples has been recurrent in the current federal government, with projects' creation for the construction of highways and hydroelectric plants in the Amazon region. In addition, invasions in Indigenous demarcation lands, put Indigenous peoples at risk for the SARS-CoV-2 spread.<sup>5,6</sup>

To date, few studies have focused on the collection of demographic and clinical characteristics of Indigenous peoples in Brazil with SARS during the COVID-19 pandemic.<sup>5–8</sup> The National Survey of Indigenous People's Health and Nutrition in Brazil was the first study conducted in 2008–2009 to obtain baseline information based on a nationwide representative sample.<sup>19</sup> However, in the best of our knowledge, there are no studies including clinical characteristics and outcomes of Indigenous individuals with SARS-CoV-2 infection in Brazil.

Thus, the primary goal of the present study was to explore the risk factors of death from COVID-19 in Brazilian Indigenous people infected with SARS-CoV-2. The secondary objective was to compare the death rates between those infected with SARS-CoV-2 and those with other etiologic agents and assess the differences in the characteristics of Brazilian Indigenous people infected by SARS-CoV-2 versus those infected by other etiologic agents.

## Methods

In the present study it was performed a cross-sectional and analytical epidemiological analysis, using epidemiologic (demographic and clinical) data available at OpenDataSUS (<https://opendatasus.saude.gov.br/>). The data were computed by Brazilian Ministry of Health according to the surveillance data of SARS and from the platform of Information System for Epidemiological Surveillance of Influenza (SIVEP-GRIPE). The primary outcome was death, and the secondary outcome was the characteristics of Brazilian Indigenous people infected by SARS-CoV-2 or those infected by other etiologic agents such as the need for intensive care unit (ICU) admission or for mechanical ventilation (MV) support.

The data were obtained for the first 57 epidemiological weeks of COVID-19 pandemic in Brazil (from January 01, 2020 to January 28, 2021) and comprised the following information: (i) viruses' profiles that cause the SARS and sample collection for viruses screening; (ii) demographic profile including sex, age, education level, and place of residence; (iii) data for place of residence with flu outbreak, presence of hospital acquired infection (nosocomial), workplace or contact with poultry or swine, and antiviral drug use to treat Influenza virus infection; (iv) presence of comorbidities [cardiopathy, diabetes mellitus, systemic arterial hypertension (SAH), respiratory disorders, obesity, and others]; (v) clinical symptoms related to SARS (fever, cough, loss of smell, loss of taste, myalgia, and others); (vi) the need for ICU and/or MV; (vii) findings for chest X-ray of the lungs; (viii) outcomes (recovered or death).

For accuracy, all epidemiological data from Indigenous individuals with SARS obtained in the dataset were revised by two authors (FALM and MNB). The definitions for symptoms and previous diseases were done by both authors (FALM and MNB). New markers were created based on the number of individuals that presented them; for example, fatigue was added to asthenia; coryza was added in the dataset.

The Indigenous individuals were grouped into two categories: positive infection by SARS-CoV-2 (COVID-19 group); negative infection by SARS-CoV-2; positive infection by other respiratory viruses or undermined results (other etiologic agents).

## Statistical analysis

The statistical analysis was performed by the Statistical Package for the Social Sciences software (IBM SPSS Statistics for Macintosh, Version 27.0.) and OpenEpi software (OpenEpi: Open-Source Epidemiologic Statistics for Public Health, Version. [www.OpenEpi.com](http://www.OpenEpi.com), 2013/04/06). It was used the chi-square or Fisher's exact statistical tests to compare the proportion of the individuals with SARS due to SARS-CoV-2 infection or SARS due to other etiologic agents, considering all patients' features evaluated in the present study. Also,

the same statistical tests were used to calculate the risk of death among individuals with positive SARS-CoV-2 infection with respect to patients' features. The odds ratio (OR) with the 95% confidence interval (95%CI) were also calculated for each analysis carried out using the chi-square or Exact Fisher statistical tests. The OR was calculated using the OpenEpi software for  $2 \times 2$  tables with the inclusion of the value for each patient characteristic. The results were summarized in tables and figures. The figures were built using the GraphPad Prism version 8.0.0 for Mac, GraphPad Software, San Diego, California USA (<http://www.graphpad.com>).

In addition, the multivariate analysis was carried out using the Logistic Regression Model with the Backward Stepwise method. The inclusion criteria as part of regression model, included the presence of significative association ( $P\text{-value} \leq 0.05$ ) at the univariate model using as outcome: (i) primary analysis: the group of individuals who died due to COVID-19 versus the group of individuals who recover from the infection; (ii) secondary analysis: the group of individuals described as infected by SARS-CoV-2 versus individuals with SARS due to other etiologic agents. A total of 17 patients' features were included in the primary analysis (independent variables: gender, age  $\geq 60$  years old (y.o.), place of residence with flu outbreak, dyspnea, the need for ICU, MV status, oxygen saturation  $< 95\%$ , respiratory distress, headache, myalgia, comorbidities, kidney disorders, cardiopathy, hepatic disorders, diabetes mellitus, smoker habit and alcoholism) and the following patients' features were included in the secondary analysis (independent variables: gender, age  $\geq 43$  y.o., vomit, loss of smell, loss of taste, cardiopathy, neurologic disorders, pneumopathy, fever, cough, oxygen saturation  $< 95\%$ , asthma, diabetes mellitus, sore throat, myalgia, headache and systemic arterial hypertension). The age was classified according to the ROC (receiver operating characteristic curve) curve, which demonstrated the cut-off for 60 y.o. (Sensitivity of 0.674 and Specificity of 0.679;  $P\text{-value} < 0.001$ ) and 43 y.o. (Sensitivity of 0.699 and Specificity of 0.540;  $P\text{-value} < 0.001$ ) and as the best cutoff points, for the primary and secondary analyses, respectively. In the Logistic Regression Model, it was presented the OR with 95%CI. The researchers used goodness-of-fit tests to choose the best model for prediction when there are fewest predictors. The data used in our study were made publicly available, not containing personal data of Indigenous individuals and being the a consent-free study, since it is not presenting risks to the participants of the research, as well as being dispensed the ethical opinion.

#### Role of the funding source

The funder did not have any role in study design, data collection, data analysis, interpretation, and writing of the report.

## Results

### Viruses profile and sample collection of Indigenous individuals with SARS

Table 1 describes virus profile in Indigenous individuals with SARS in Brazil during the first year of the COVID-19 pandemic. Of these, 1,994 were diagnosed with COVID-19, including 1,990 with SARS-CoV-2; three with SARS-CoV-2 and respiratory syncytial virus, and one with SARS-CoV-2 and rhinovirus. About 1,128 Indigenous individuals were classified with other etiologic agents. The sample collection was done mainly using swab (1,926/3,122; 66.4%) for real-time polymerase chain reaction (RT-PCR) followed by rapid test by venipuncture, blood for immunologic tests, and tissue collection.

### Characterization of the indigenous individuals with SARS

A total of 1,170,122 individuals with SARS were included encompassing the first 57 epidemiological weeks of the COVID-19 pandemic in Brazil. The individuals were distributed according to race being 443,933 (37.9%) Caucasians; 399,445 *Pardos* (34.1%); 56,654 (4.8%) Afro-descendants; 12,247 (1%) Asians; and only 3,122 (0.3%) Indigenous individuals. About 254,721 (21.7%) individuals were not race classified due to data not entered into the dataset.

The distribution of the 3,122 Brazilian Indigenous individuals with SARS due to COVID-19 and other etiologic agents during the first year of COVID-19 pandemic, according to the Brazilian States and Federal District is presented at Fig. 1 (Fig. 1A demonstrates the COVID-19 cases; Fig. 1B demonstrates the cases of SARS by other etiologic agents; Fig. 1C demonstrates the total relative number of SARS cases in the Indigenous individuals); and at Supplementary Table (ST) 1. Also, epidemiological week of filling out the notification form and epidemiological week of the first symptoms of the 3,122 Brazilian Indigenous individuals with SARS due to COVID-19 and other etiologic agents during the first year of COVID-19 pandemic are presented at Fig. 2A (ST2) and Fig. 2B (ST3), respectively.

The Indigenous individuals were originally from Brazil (3,120 patients), Venezuela (one patient), and Peru (one patient). Only four Indigenous individuals have made international trips during the fourteen days before the onset of symptoms.

### Demographic characteristics of Indigenous individuals with COVID-19 and the risk of death

In the data set, a total of 730/1,816 (40.2%) Indigenous individuals with COVID-19 died. Moreover, the deaths were associated with the male gender (64.8% vs. 52.7%;  $OR=1.654$ ; 95%CI=1.364-2.006); age ( $\geq 60$  y.o. vs.  $< 60$  y.o.;  $OR=4.365$ ; 95%CI=3.573-5.334); education level

Microorganism	Co-detection among the 1,994 COVID-19 individuals	Other etiologic agents (n=1,128)	Total (N=3,122)
Adenovirus	0 (0.0%)	1 (0.1%)	1 (0.0%)
Influenzae virus	0 (0.0%)	6 (0.5%)	6 (0.2%)
Influenzae A(H1N1) pdm09	0 (0.0%)	1 (0.1%)	1 (0.0%)
Influenzae B + Adenovirus	0 (0.0%)	1 (0.1%)	1 (0.0%)
Influenzae B (Victoria)	0 (0.0%)	1 (0.1%)	1 (0.0%)
Parainfluenza Subtype 3	0 (0.0%)	1 (0.1%)	1 (0.0%)
Rhinovirus	0 (0.0%)	4 (0.4%)	4 (0.1%)
Rhinovirus + SARS-CoV-2	1 (0.1%)	0 (0.0%)	1 (0.0%)
Respiratory syncytial virus	3 (0.2%)	0 (0.0%)	3 (0.1%)
SARS by another respiratory virus	0 (0.0%)	4 (0.4%)	4 (0.1%)
Undetermined SARS	0 (0.0%)	1,107 (98.1%)	1,107 (35.5%)
Respiratory syncytial virus	0 (0.0%)	1 (0.1%)	1 (0.0%)
Respiratory syncytial virus + Rhinovirus	0 (0.0%)	1 (0.1%)	1 (0.0%)

Sample collection	COVID-19 (n=1,994)	Other etiologic agents (n=1,128)	Total (N=3,122)
Swab for RT-PCR	1,090 (54.7%)	836 (74.1%)	1,926 (61.7%)
Rapid test by venipuncture	304 (15.2%)	45 (4.0%)	349 (11.2%)
Blood collection for immunologic tests	484 (24.3%)	127 (11.3%)	611 (19.6%)
Other (lung tissue biopsy or bronchoalveolar lavage collection for RT-PCR)	5 (0.3%)	8 (0.7%)	13 (0.4%)
Without information for sample origin	111 (5.6%)	112 (9.9%)	223 (7.1%)

**Table 1: Viruses' profile other than SARS-CoV-2 and sample collection for virus screening in Indigenous individuals with severe acute respiratory syndrome (SARS) on Brazil during the first year of coronavirus disease (COVID)-19 pandemic.**  
 H1N1, H1N1 strain of the flu (influenza) virus; RT-PCR, real time-polymerase chain reaction; % percentage; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

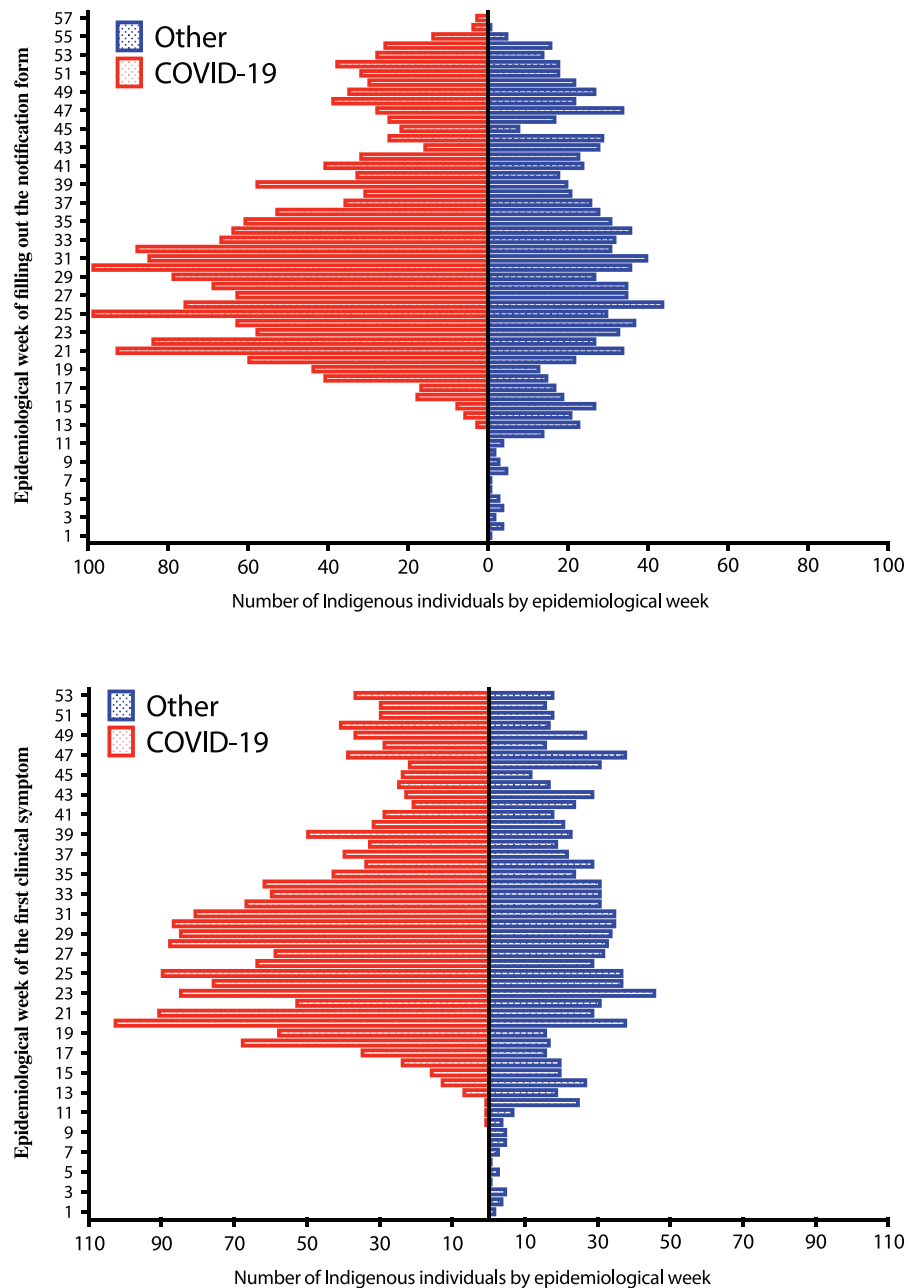
[illiterate category was associated with the higher chance of death (40.6% vs. 23.3%; OR=2.251; 95%CI=1.682-3.014)]; residence place in a region under flu outbreak (51.1% vs. 43.3%; OR=1.369; 95%CI=1.104-1.698)

(Table 2; Figure 3). Place of residence (rural, urban or peri urban), presence of hospital acquired infection (nosocomial), previous direct contact with poultry or swine by the Indigenous individual and the use of antiviral drug



**Figure 1.** The distribution of Brazilian Indigenous individuals with severe acute respiratory syndrome (SARS) due to coronavirus disease (COVID)-19 and other etiologic agents during the first year of COVID-19 pandemic, according to the Brazilian states and Federal District. **A.** Shows COVID-19 cases. **B.** Shows SARS cases by other etiologic agents. **C.** Shows the total number of SARS cases in the Indigenous peoples.

% percentage; SARS, severe acute respiratory syndrome. It was presented the ratio between the number of cases of COVID-19 and/or SARS of Indigenous individuals and the number of Indigenous inhabitants according to the Brazilian states and Federal District. The absolute number is shown in the **Supplementary Table 6.**



**Figure 2.** Epidemiological week data for severe acute respiratory syndrome (SARS) in Brazilian Indigenous individuals during the first 57 epidemiological weeks (period of January 01, 2020, to January 28, 2021) of the coronavirus disease (COVID)-19 pandemic. **A.** Epidemiological week of filling out the notification form for the Brazilian Indigenous individuals with SARS due to COVID-19 and other etiologic agents during the first year of COVID-19 pandemic. **B.** Epidemiological week of the first symptoms for the Brazilian Indigenous individuals with SARS due to COVID-19 and other etiologic agents during the first year of COVID-19 pandemic. The data described were obtained from the Brazilian Ministry of Health.

Epidemiological weeks according months: (Weeks from 1 to 5) January 2020; (Weeks from 6 to 9) February 2020; (Weeks from 10 to 14) March 2020; (Weeks from 14 to 18) April 2020; (Weeks from 14 to 18); May 2020 (Weeks 18 to 23); June 2020 (Weeks 23 to 27); July 2020 (Weeks from 27 to 31); August 2020 (Weeks from 31 to 36); September 2020 (Weeks from 36 to 40); October 2020 (Weeks from 40 to 44); November 2020 (Weeks from 45 to 49); December 2020 (Weeks from 49 to 53); and January 2021 (Weeks from 53 to 57).

Patient feature <sup>b</sup>	Data	Death (n=730)	Clinical recovery (n=1,086)	Total (N=1,816)	P-value	OR	95%CI
Sex	Male	473 (64.8%)	572 (52.7%)	1,045 (57.5%)	<0.001	1.654	1.364 to 2.006
	Female	257 (35.2%)	514 (47.3%)	771 (42.5%)		Reference	-
Age (years old)	<60 years old	238 (32.6%)	737 (67.9%)	975 (53.7%)	<0.001	Reference	-
	≥60 years old	492 (67.4%)	349 (32.1%)	841 (46.3%)		4.365	3.573 to 5.334
Pregnant <sup>*</sup>	Yes	1 (0.5%)	67 (17.1%)	68 (11.8%)	<0.001	0.026	<0.001 to 0.154
	No	185 (99.5%)	324 (82.9%)	509 (88.2%)		Reference	-
Education level <sup>**</sup>	Illiterate	152 (40.6%)	118 (23.3%)	270 (30.7%)	<0.001	2.251	1.682 to 3.014
	Elementary school (first cycle)	125 (33.4%)	186 (36.8%)	311 (35.3%)	0.341	1.651	1.226 to 2.233
	Elementary school (second cycle)	48 (12.8%)	78 (15.4%)	126 (14.3%)	0.326	0.864	0.652 to 1.144
	High school	33 (8.8%)	90 (17.8%)	123 (14.0%)	<0.001	0.447	0.293 to 0.683
	University education	16 (4.3%)	34 (6.7%)	50 (5.7%)	0.162	0.602	0.337 to 1.142
Place of residence	Urban	280 (41.5%)	441 (44.5%)	721 (43.3%)	0.246	0.885	0.726 to 1.078
	Rural	388 (57.6%)	536 (54.1%)	924 (55.5%)	0.184	1.149	0.943 to 1.400
	Peri urban	6 (0.9%)	13 (1.3%)	19 (1.1%)	0.574	0.675	0.255 to 1.785
From region with flu outbreak	Yes	296 (51.1%)	343 (43.3%)	639 (46.6%)	0.004	1.369	1.104 to 1.698
	No	283 (48.9%)	450 (56.7%)	732 (53.4%)		Reference	-
Hospital acquired infection (nosocomial)	Yes	12 (2.2%)	12 (1.6%)	24 (1.9%)	0.532	1.389	0.619 to 3.116
	No	527 (97.8%)	732 (98.4%)	1,259 (98.1%)		Reference	-
Patient worked or had direct contact with poultry or swine	Yes	20 (4.0%)	37 (5.1%)	57 (4.7%)	0.409	0.770	0.441 to 1.343
	No	481 (96.0%)	685 (94.9%)	1,166 (95.3%)		Reference	-
Antiviral drug for Influenzae virus	Yes	106 (20.5%)	160 (20.2%)	266 (20.3%)	0.888	1.021	0.776 to 1.345
	No	400 (79.5%)	632 (79.8%)	1,042 (79.7%)		Reference	-

**Table 2: Demographic profile, mother vaccination, place of residence and antiviral use for Influenzae virus in Indigenous individuals with severe acute respiratory syndrome due to SARS-CoV-2 infection on Brazil during the first year of coronavirus disease (COVID)-19 pandemic according to the outcome.<sup>a</sup>**

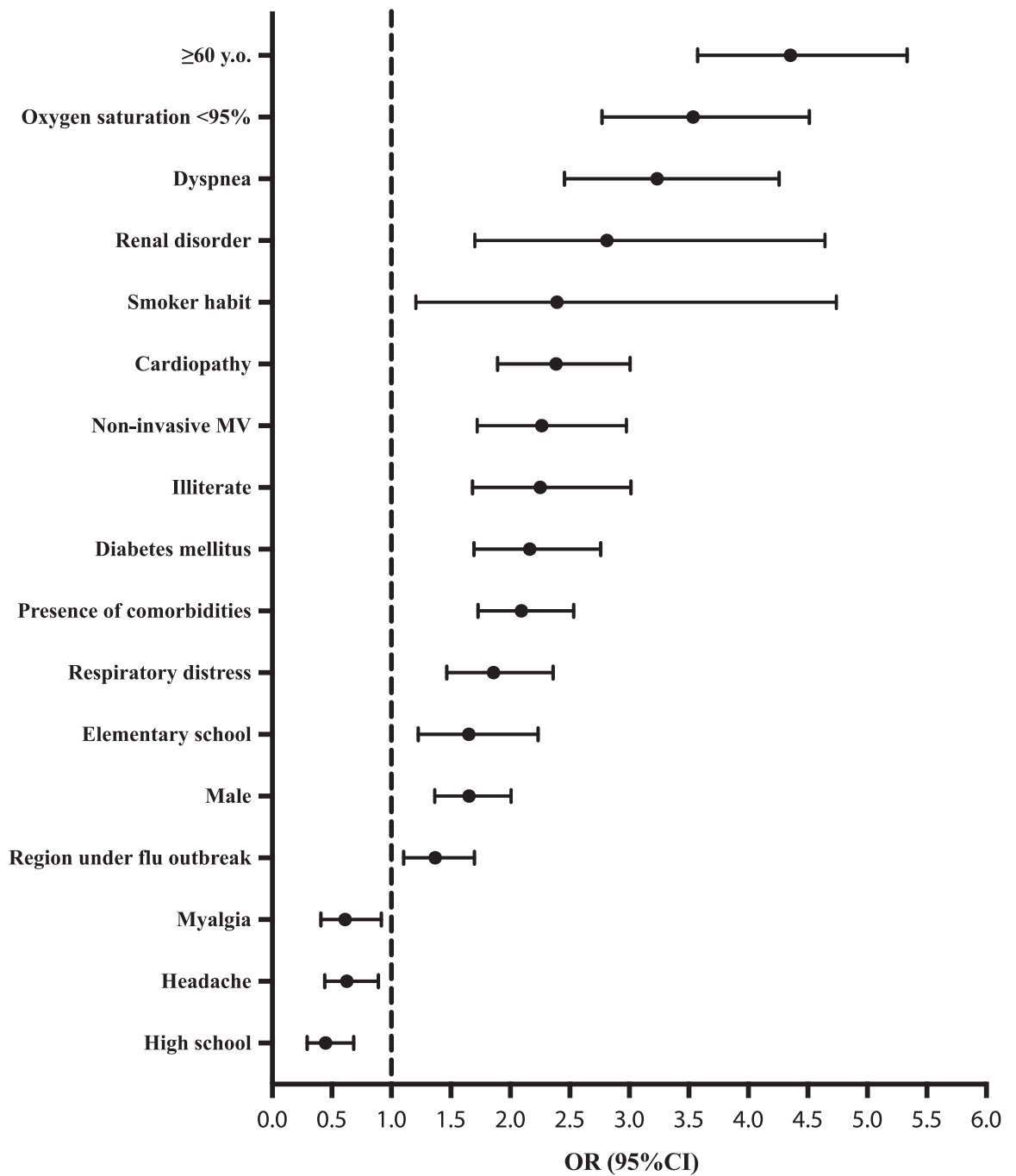
OR, odds ratio; CI, confidence interval; NA, not applicable; % percentage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>\*</sup> Only the female sex was considered.

<sup>\*\*</sup> The p-value and the OR were calculated comparing each patient category with the sum of the other categories because there is a lack of evidence at the literature to confirm the risk category for death due to COVID-19 diagnosis in Indigenous individuals regarding the education level.

<sup>a</sup> The outcome was not described for 178/1,994 (8.93%) Indigenous individuals.

<sup>b</sup> For some patients' features the data was not available for all patients.



**Figure 3.** Epidemiology data with positive association (P-value <0.05) with the risk of death by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brazilian Indigenous individuals during the first 57 epidemiologic weeks of the coronavirus disease (COVID)-19 pandemic. The data are presented as odds ratios (OR) and 95% confidence intervals (95%CI – lower and upper limits). In the figure it was not plotted the data for other findings in the chest X-ray (OR=4.619; 95%CI=2.114-10.09); interstitial infiltrate (OR=4.726; 95%CI=2.338-9.555); need for intensive care unit (OR=5.584; 95%CI=4.319-7.221); presence of consolidation (OR=13.34; 95%CI=4.904-36.29), and mixed findings in the chest X-ray (OR=6.8; 95%CI=2.953-15.06); and invasive mechanical ventilation (OR=22.23; 95%CI=14.98-33.0).

MV, mechanical ventilation; y.o.; years old; % percentage.



Clinical symptoms	Data	Death	Clinical recovery	Total	P-value	OR	95%CI
Fever	Yes	523 (79.7%)	764 (77.2%)	1,287 (78.2%)	0.223	1.163	0.914 to 1.481
	No	133 (20.3%)	226 (22.8%)	359 (21.8%)		Reference	-
Cough	Yes	558 (84.3%)	811 (82.8%)	1,369 (83.4%)	0.457	1.111	0.851 to 1.452
	No	104 (15.7%)	168 (17.2%)	272 (16.6%)		Reference	-
Sore throat	Yes	244 (41.1%)	340 (39.2%)	584 (39.9%)	0.480	1.083	0.875 to 1.339
	No	350 (58.9%)	528 (60.8%)	878 (60.1%)		Reference	-
Dyspnea	Yes	591 (88.5%)	667 (70.4%)	1,258 (77.8%)	<0.001	3.234	2.455 to 4.258
	No	77 (11.5%)	281 (29.6%)	358 (22.2%)		Reference	-
Respiratory distress	Yes	514 (79.9%)	615 (68.2%)	1,129 (73.1%)	<0.001	1.859	1.465 to 2.360
	No	129 (20.1%)	287 (31.8%)	416 (26.9%)		Reference	-
Oxygen saturation	<95%	526 (82.9%)	512 (57.3%)	1,038 (67.8%)	<0.001	3.536	2.770 to 4.512
	≥95%	111 (18.1%)	382 (42.7%)	493 (32.2%)		Reference	-
Diarrhea	Yes	107 (18.7%)	169 (20.4%)	276 (19.7%)	0.452	0.896	0.684 to 1.173
	No	465 (81.3%)	658 (79.6%)	1,123 (80.3%)		Reference	-
Vomiting	Yes	74 (13.1%)	132 (16.1%)	206 (14.9%)	0.144	0.790	0.581 to 1.074
	No	489 (86.9%)	689 (83.9%)	1,178 (85.1%)		Reference	-
Abdominal pain	Yes	44 (15.4%)	74 (15.0%)	118 (15.2%)	0.917	1.034	0.689 to 1.550
	No	241 (84.6%)	419 (85.0%)	660 (84.8%)		Reference	-
Fatigue and asthenia	Yes	128 (42.1%)	205 (38.6%)	333 (39.9%)	0.340	1.157	0.868 to 1.541
	No	176 (57.9%)	326 (61.4%)	502 (60.1%)		Reference	-
Loss of smell	Yes	58 (20.2%)	111 (21.6%)	169 (21.1%)	0.653	0.917	0.642 to 1.310
	No	229 (79.8%)	402 (78.4%)	631 (78.9%)		Reference	-
Loss of taste	Yes	50 (17.5%)	102 (20.2%)	152 (19.2%)	0.398	0.841	0.578 to 1.223
	No	235 (82.5%)	403 (79.8%)	638 (80.8%)		Reference	-
Headache	Yes	51 (9.9%)	113 (14.9%)	164 (12.9%)	0.010	0.626	0.441 to 0.891
	No	463 (90.1%)	643 (85.1%)	1,106 (87.1%)		Reference	-
Chest pain	Yes	18 (3.5%)	29 (3.8%)	47 (3.7%)	0.766	0.910	0.500 to 1.656
	No	496 (96.5%)	727 (96.2%)	1,223 (96.3%)		Reference	-
Myalgia	Yes	37 (7.2%)	85 (11.2%)	122 (9.6%)	0.020	0.612	0.409 to 0.917
	No	477 (92.8%)	671 (88.8%)	1,148 (90.4%)		Reference	-
Coryza	Yes	20 (3.9%)	26 (3.4%)	46 (3.6%)	0.760	1.137	0.628 to 2.059
	No	494 (96.1%)	730 (96.6%)	1,224 (96.4%)		Reference	-
Other clinical symptoms	Yes	56 (11.0%)	85 (11.5%)	141 (11.3%)	0.856	0.955	0.667 to 1.366
	No	452 (88.0%)	655 (88.5%)	1,107 (88.7%)		Reference	-

**Table 3: Clinical symptoms in Brazilian Indigenous individuals with severe acute respiratory syndrome due to SARS-CoV-2 during the first year of coronavirus disease (COVID)-19 pandemic according to the outcome.**

OR, odds ratio; CI, confidence interval; %, percentage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

for Influenza virus did not show any different proportions between the patients who died due to COVID-19 and the patients with clinical recovery (Table 2).

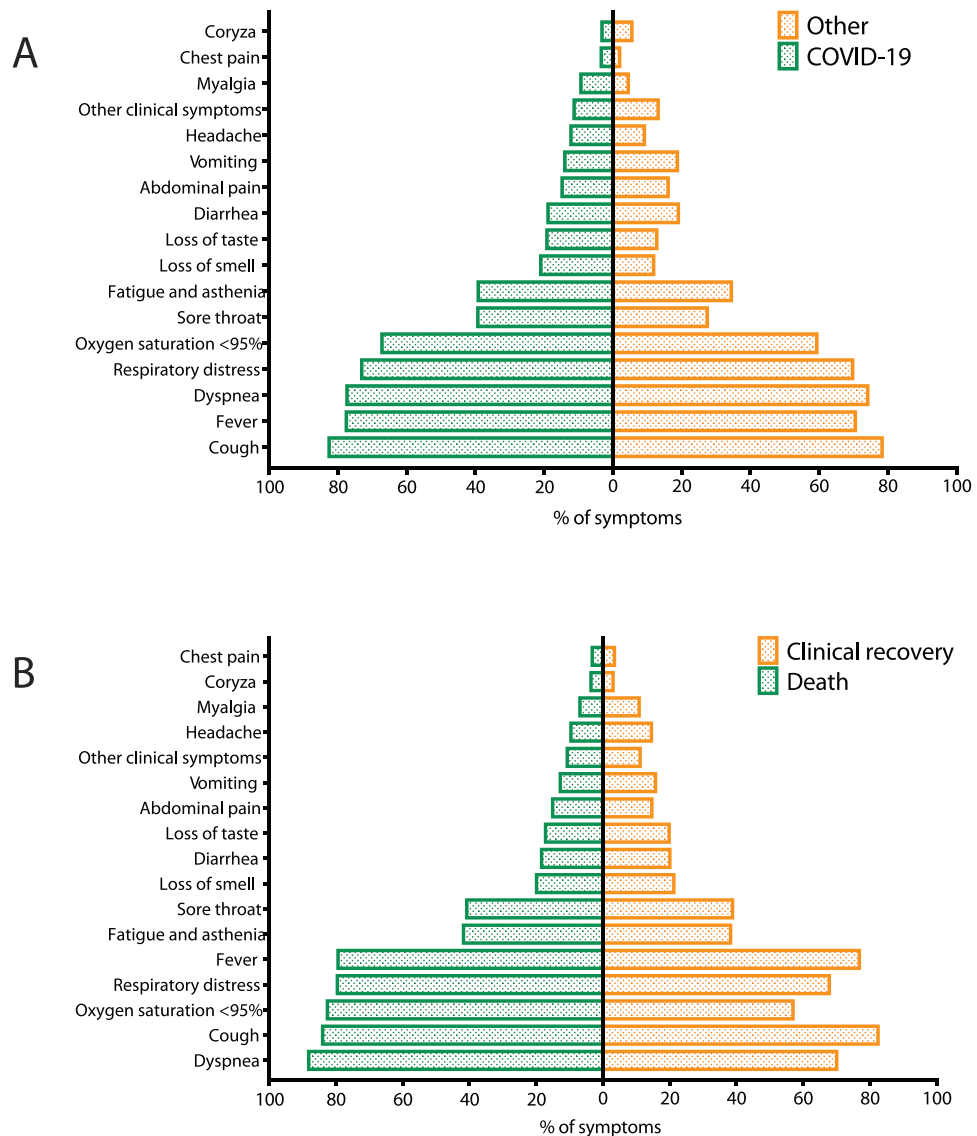
#### Association of clinical symptoms in Indigenous individuals with COVID-19 and the risk of death

Among the 17 symptoms evaluated, only three were associated with the risk of death as follow: oxygen saturation <95% (82.9% vs. 57.3%; OR=3.536; 95%CI=2.770-4.512), dyspnea (88.5% vs. 70.4%; OR=3.234; 95%CI=2.455-4.258), and respiratory distress (79.9% vs. 68.2%; OR=1.859; 95%CI=1.465-2.360) (Table 3, Figure 3). Furthermore, myalgia (7.2% vs. 11.2%; OR=0.612; 95%CI=0.409-0.917) and headache

(9.9% vs. 14.9%; OR=0.626; 95%CI=0.441-0.891) were less prevalent among the Indigenous individuals who died due to COVID-19 (Table 3; Figure 4B; Figure 3).

#### Association of comorbidities in Indigenous individuals with COVID-19 and the risk of death

Among the 17 comorbidities evaluated, only four were associated with risk of death as follow: cardiopathy (33.7% vs. 17.6%; OR=2.385; 95%CI=1.893-3.006), renal disorders (7.3% vs. 2.7%; OR=2.812; 95%CI=1.702-4.645), smoker habit (3.5% vs. 1.5%; OR=2.391; 95%CI=1.207-4.739), and diabetes mellitus (28.4% vs. 15.5%; OR=2.163; 95%CI=1.685-2.760) (Table 4; Figure 5B; Figure 3). Also, a low number of individuals



**Figure 4.** Clinical symptoms in Brazilian Indigenous individuals with severe acute respiratory syndrome (SARS) during the first year of coronavirus disease (COVID)-19 pandemic. **A.** The data demonstrated the prevalence of the clinical symptoms for both groups, SARS-CoV-2 (COVID-19 group), and Indigenous individuals with SARS due to other etiologic agents. **B.** The data shows the prevalence of the clinical symptoms for both groups, Indigenous individuals who died due to SARS-CoV-2 infection and Indigenous individuals who had clinical recovery after the SARS-CoV-2 infection. % percentage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

presented also with hepatic disorders, which were associated with increased risk of death (2% vs. 0.4%; OR=4.649; 95%CI=1.401-19.870) (Table 4).

**Clinical evolution and imaging tests findings in Indigenous individuals with COVID-19 and the risk of death**

Patients with COVID-19 who died were more likely to need invasive MV (71.6% vs. 10.2%) than non-ventilated patients (OR=22.23; 95%CI=14.98-33.00).

Similar results were observed when comparing patients with COVID-19 who died while on non-invasive MV (72.4% vs. 53.7%) versus non-ventilated patients (OR=2.264; 95%CI=1.722-2.975). The percentages for MV were calculated comparing two groups in the text; however, in the tables the percentages were calculated using the three groups for MV, such as, invasive MV, non-invasive MV and no MV. In addition, these patients were treated mainly at ICUs (44.9% vs. 12.7%; OR=5.584; 95%CI=4.319-7.221). The chest X-ray finding was more evident in

Comorbidities	Data	Death	Clinical recovery	Total	P-value	OR	95%CI
Comorbidities (Total)	Yes	431 (59.0%)	443 (40.8%)	874 (48.1%)	<0.001	2.092	1.729 to 2.532
	No	299 (41.0%)	643 (59.2%)	942 (51.9%)		Reference	-
Cardiopathy	Yes	221 (33.7%)	171 (17.6%)	392 (24.1%)	<0.001	2.385	1.893 to 3.006
	No	434 (66.3%)	801 (82.4%)	1,235 (75.9%)		Reference	-
Hematological disorders	Yes	7 (1.2%)	7 (0.8%)	14 (0.9%)	0.584	1.548	0.540 to 4.435
	No	586 (98.8%)	907 (99.2%)	1,493 (99.1%)		Reference	-
Down syndrome	Yes	4 (0.7%)	1 (0.1%)	5 (0.3%)	0.081	6.201	0.612 to 306
	No	587 (99.3%)	911 (99.9%)	1,499 (99.7%)		Reference	-
Hepatic disorders	Yes	12 (2.0%)	4 (0.4%)	16 (1.1%)	0.005	4.649	1.401 to 19.87
	No	584 (98.0%)	906 (99.6%)	1,490 (98.9%)		Reference	-
Asthma	Yes	15 (2.5%)	23 (2.5%)	38 (2.5%)	1.000	1.008	0.521 to 1.947
	No	576 (97.5%)	890 (97.5%)	1,466 (97.5%)		Reference	-
Previous respiratory disorders	Yes	45 (7.4%)	49 (5.3%)	94 (6.1%)	0.102	1.437	0.946 to 2.183
	No	560 (92.6%)	876 (94.7%)	1,436 (93.9%)		Reference	-
Diabetes mellitus	Yes	184 (28.4%)	150 (15.5%)	334 (20.6%)	<0.001	2.163	1.695 to 2.760
	No	465 (71.6%)	820 (84.5%)	1,285 (79.4%)		Reference	-
Neurologic disorders	Yes	26 (4.3%)	29 (3.1%)	55 (3.6%)	0.261	1.392	0.812 to 2.388
	No	575 (95.7%)	893 (96.9%)	1,468 (96.4%)		Reference	-
Immunological disorders	Yes	16 (2.7%)	14 (1.5%)	30 (2.0%)	0.132	1.779	0.862 to 3.672
	No	577 (97.3%)	898 (98.5%)	1,475 (98.0%)		Reference	-
Kidney disorders	Yes	44 (7.3%)	25 (2.7%)	69 (4.5%)	<0.001	2.812	1.702 to 4.645
	No	559 (92.7%)	893 (97.3%)	1,452 (95.5%)		Reference	-
Obesity	Yes	34 (5.8%)	37 (4.0%)	71 (4.7%)	0.134	1.467	0.910 to 2.365
	No	555 (94.2%)	886 (96.0%)	1,441 (95.3%)		Reference	-
Smoker habit	Yes	21 (3.5%)	14 (1.5%)	35 (2.3%)	0.013	2.391	1.207 to 4.739
	No	584 (96.5%)	931 (98.5%)	1,515 (97.7%)		Reference	-
Alcoholism	Yes	9 (1.5%)	4 (0.4%)	13 (0.8%)	0.041	3.549	0.985 to 15.84
	No	596 (98.5%)	941 (99.6%)	1,537 (99.2%)		Reference	-
Systemic arterial hypertension	Yes	85 (14.0%)	102 (10.8%)	187 (12.1%)	0.056	1.351	0.993 to 1.838
	No	520 (96.0%)	843 (89.2%)	1,363 (87.9%)		Reference	-
Other morbidities	Yes	43 (7.0%)	48 (5.0%)	91 (5.7%)	0.098	1.432	0.937 to 2.189
	No	575 (93.0%)	919 (95.0%)	1,494 (44.3%)		Reference	-

**Table 4: Comorbidities in Brazilian Indigenous individuals with severe acute respiratory syndrome due to SARS-CoV-2 during the first year of coronavirus disease (COVID)-19 pandemic according to the outcome.**

OR, odds ratio; CI, confidence interval; %, percentage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

the patients' group infected by SARS-CoV-2 and that died due to the disease, being observed interstitial infiltrate (58.3% vs. 55.6%), consolidations (8.7% vs. 2.9%), mixed findings (12.9% vs. 8.5%), and other findings (16.3% vs. 15.9%) (Table 5; Figure 3).

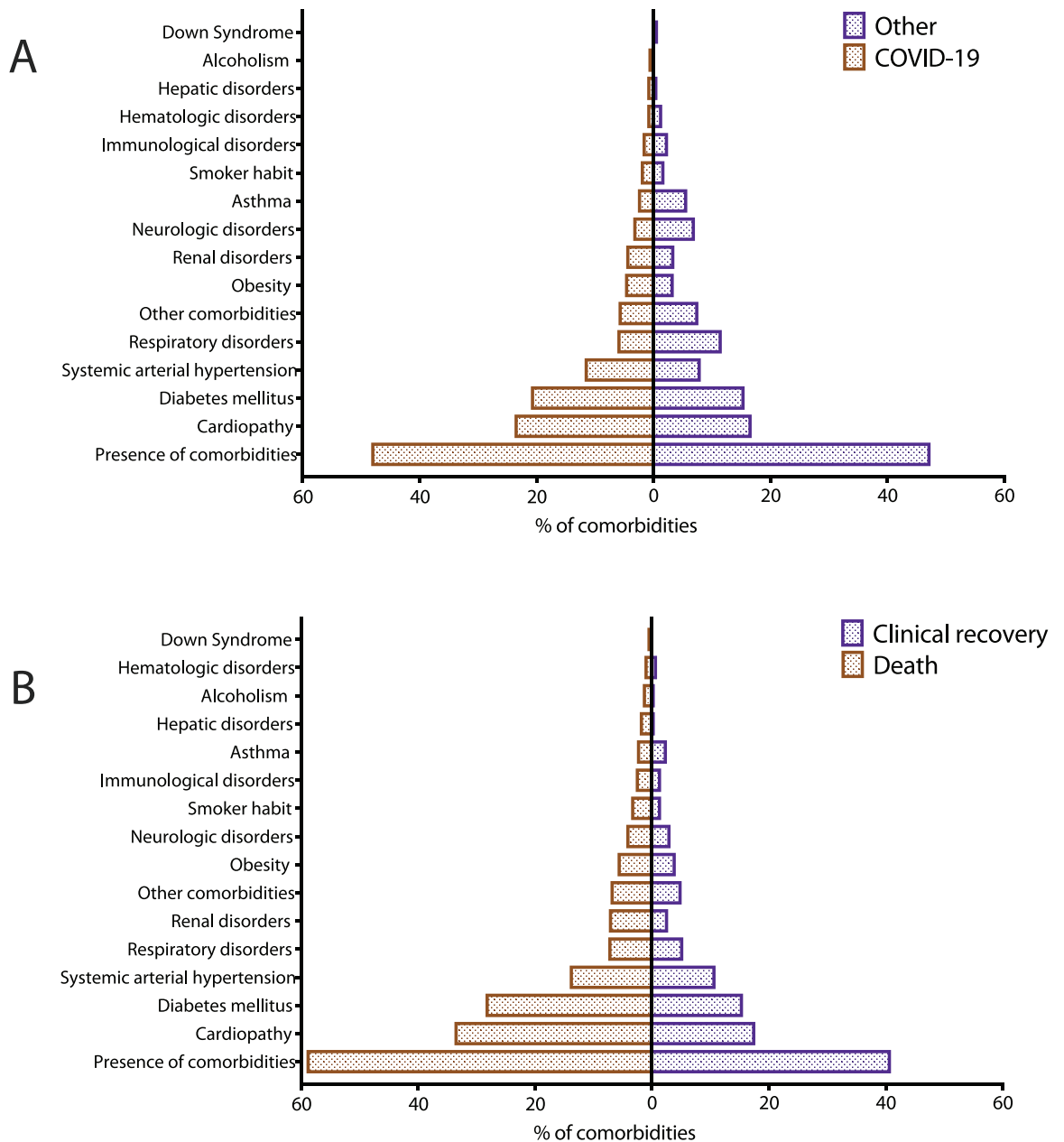
#### Multivariate analysis by Logistic Regression considering the risk of death

Binary logistic regression was performed to determine whether the patients' features were able to predict death due to COVID-19. The model containing the selected patients' features was significant in predicting the risk of death [ $X^2_{(9)}=293.694$ ; P-value < 0.001; Nagelkerke's  $R^2=0.454$ ]. Among the patients' features, the following were significant and contributed in relation to the risk of death: male gender [OR=1.507 (95%CI=1.010-2.250)];

age [ $\geq 60$  y.o.; OR=3.377 (95%CI=2.292-4.974)]; the need for ventilatory support [invasive MV; OR=24.050 (95%CI=12.584-45.962)] and non-invasive MV; OR=2.249 (95%CI=1.378-3.671)]; dyspnea [OR=2.053 (95%CI=1.196-3.522)]; oxygen saturation <95% [OR=1.691 (95%CI=1.050-2.723)]; myalgia [OR=0.423 (95%CI=0.191-0.937)]; and the presence of kidney disorders [OR=3.135 (95%CI=1.144-8.539)]; in contrast, it was not observed significance on the presence of any comorbidity in general and, this patient characteristic did not contributed to the proposed model (Table 6).

#### Demographic characteristics of Indigenous individuals with SARS

The study also accounted for 1,703/3,122 (54.5%) male Indigenous individuals presenting an OR=1.295



**Figure 5.** Comorbidities in Brazilian Indigenous individuals with severe acute respiratory syndrome (SARS) during the first year of coronavirus disease (COVID)-19 pandemic. **A.** The data shows the prevalence of the comorbidities for both groups, SARS-CoV-2 (COVID-19 group) and Indigenous individuals with SARS due to other etiologic agents. **B.** The data demonstrated the prevalence of the comorbidities for both groups, Indigenous individuals who died due to SARS-CoV-2 infection and Indigenous individuals who had clinical recovery after the SARS-CoV-2 infection. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

(95%CI=1.119-1.500) for the COVID-19 (Table 7; Figure 6).

The age of the Indigenous individuals was distributed into categories and a major part of the individuals were categorized as  $\geq 43$  y.o; also, the cut off for age was associated with a higher ORs for COVID-19 group (OR=2.647; 95%CI=2.277-3.078) (Table 7; Figure 6).

The following markers did not show any different proportions between the groups with SARS by SARS-CoV-2 or other etiologic agents as education level, place of residence (rural, urban our peri urban), presence of hospital acquired infection (nosocomial), previous direct contact with poultry or swine by the Indigenous individuals. The antiviral drug to treat Influenza virus infection

Clinical evolution <sup>b</sup>	Data	Death (n=730)	Clinical recovery (n=1,086)	Total (N=1,816)	P-value	OR	95%CI
Intensive care unit	Yes	254 (44.9%)	114 (12.7%)	368 (25.2%)	<0.001	5.584	4.319 to 7.221
	No	312 (55.1%)	782 (87.3%)	1,094 (74.8%)		Reference	-
Mechanical ventilation	Invasive	239 (41.0%)	43 (5.0%)	282 (19.5%)	<0.001	22.23	14.98 to 33.0
	Non-invasive	249 (42.7%)	440 (51.0%)	689 (47.6%)	<0.001	2.264	1.722 to 2.975
	No	95 (16.3%)	380 (44.0%)	475 (32.8%)		Reference	-
Chest X-ray finding	Interstitial infiltrate	154 (58.3%)	189 (55.6%)	343 (56.8%)	<0.001	4.726	2.338 to 9.555
	Consolidation	23 (8.7%)	10 (2.9%)	33 (5.5%)	<0.001	13.34	4.904 to 36.29
	Mixed	34 (12.9%)	29 (8.5%)	63 (10.4%)	<0.001	6.8	2.953 to 15.66
	Other	43 (16.3%)	54 (15.9%)	97 (16.1%)	<0.001	4.619	2.114 to 10.09
	Normal	10 (3.8%)	58 (17.1%)	68 (11.3%)		Reference	-

**Table 5: Clinical evolution in Indigenous individuals with severe acute respiratory syndrome due to SARS-CoV-2 infection on Brazil during the first year of coronavirus disease (COVID)-19 pandemic according to the outcome<sup>a</sup>.**

OR, odds ratio; CI, confidence interval; NA, not applicable; % percentage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup> The outcome was not described for 178/1,994 (8.93%) Indigenous individuals.

<sup>b</sup> For some patients' features the data was not available for all patients.

COVID-19 versus other etiologic agents (step 11) <sup>a</sup>	Sig.	Odds ratio	95%CI Lower limit	Upper limit
Age ≥43 years old	<0.001	1.984	1.480	2.658
Vomit (presence)	0.138	0.746	0.507	1.099
Loss of smell (presence)	<0.001	2.373	1.461	3.854
Cardiopathy (Presence)	0.057	1.492	0.988	2.252
Neurologic disorders (Presence)	0.104	0.567	0.286	1.125
Previous respiratory disorders (Presence)	0.007	0.487	0.287	0.824
Fever (Presence)	0.013	1.445	1.082	1.929
Constant	0.875	1.023		

Death due to COVID-19 versus recovery (step 10) <sup>b</sup>	Sig.	Odds ratio	95%CI Lower limit	Upper limit
Male sex	0.045	1.507	1.010	2.250
Age ≥60 years old	<0.001	3.377	2.292	4.975
No need for ventilatory support	<0.001			
On invasive mechanical ventilation	<0.001	24.050	12.584	45.962
On non-invasive mechanical ventilation	0.001	2.249	1.378	3.671
Dyspnea (presence)	0.009	2.053	1.196	3.522
Oxygen saturation <95% (presence)	0.031	1.691	1.050	2.723
Myalgia (presence)	0.034	0.423	0.191	0.937
Comorbidities (presence)	0.057	1.466	0.988	2.173
kidney disorders (presence)	0.026	3.125	1.144	8.539
Constant	<0.001	0.031		

**Table 6: Multivariate analyze using logistic regression to identify the predictors for coronavirus disease (COVID)-19 and death due to COVID-19 among Indigenous individuals with severe acute respiratory syndrome (SARS) symptoms using patients' features.**

<sup>a</sup> Patients' features included in the model (step 1): sex, age ≥43 years old, vomit, loss of smell, loss of taste, cardiopathy, neurologic disorders, pneumopathy, fever, cough, oxygen saturation <95%, asthma, diabetes mellitus, sore throat, myalgia, headache and systemic arterial hypertension.

<sup>b</sup> Patients' features included in the model (step 1): sex, age ≥60 years old, region with flu outbreak, dyspnea, need for intensive care unit, mechanical ventilation status, oxygen saturation <95%, respiratory distress, headache, myalgia, comorbidities, kidney disorders, cardiopathy, hepatic disorders, diabetes mellitus, smoker habit and alcoholism. Sig., significance (P-value); 95%CI, 95% confidence interval.

Patient feature <sup>a</sup>	Data	COVID-19 individuals (n=1,994)	Individuals with other etiologic agents (n=1,128) <sup>b</sup>	Total (N=3,122)	P-value	OR	95%CI
Sex	Male	1,134 (56.9%)	569 (50.4%)	1,703 (54.5%)	0.001	1.295	1.119 to 1.500
	Female	860 (43.1%)	559 (49.6%)	1,419 (45.5%)		Reference	-
Age (years old)	<43 years old	620 (31.1%)	614 (54.4%)	1,234 (39.5%)	<0.001	Reference	-
	≥43 years old	1,374 (68.9%)	514 (22.5%)	1,888 (60.5%)		2.647	2.277 to 3.078
Pregnant*	Yes	77 (11.9%)	28 (8.4%)	105 (10.7%)	0.102	1.472	0.934 to 2.318
	No	568 (88.1%)	304 (91.6%)	872 (89.3%)		Reference	-
Education level <sup>**</sup>	Illiterate	289 (30.6%)	156 (38.4%)	445 (32.9%)	0.001	0.706	0.554 to 0.900
	Elementary school (1 <sup>st</sup> cycle)	335 (35.4%)	128 (31.5%)	463 (34.3%)	0.189	1.193	0.931 to 1.529
	Elementary school (2 <sup>nd</sup> cycle)	133 (14.1%)	48 (11.8%)	181 (14.3%)	0.306	1.222	0.859 to 1.738
	High school	136 (14.4%)	56 (13.8%)	192 (14.2%)	0.839	1.051	0.751 to 1.470
	University education	52 (5.5%)	18 (4.4%)	70 (5.2%)	0.497	1.255	0.725 to 2.174
Place of residence	Urban	794 (43.5%)	430 (41.9%)	1,224 (42.9%)	0.477	1.068	0.915 to 1.247
	Rural	1,011 (55.4%)	581 (56.6%)	1,592 (55.8%)	0.486	0.952	0.816 to 1.111
	Peri urban	21 (1.2%)	12 (1.6%)	33 (1.3%)	0.899	0.735	0.382 to 1.415
From region with flu outbreak	Yes	694 (46.0%)	265 (31.8%)	959 (40.9%)	<0.001	1.828	1.531 to 2.183
	No	815 (54.0%)	569 (68.2%)	1,384 (59.1%)		Reference	-
Hospital acquired infection (nosocomial)	Yes	31 (2.2%)	15 (1.9%)	46 (2.1%)	0.646	1.171	0.628 to 2.182
	No	1,384 (97.8%)	784 (98.1%)	2,168 (97.9%)		Reference	-
Patient worked or had direct contact with poultry or swine	Yes	63 (4.7%)	44 (5.6%)	107 (5.0%)	0.354	0.818	0.551 to 1.214
	No	1,287 (95.3%)	755 (94.4%)	2,022 (95.0%)		Reference	-
Antiviral drug for Influenzae virus	Yes	277 (19.3%)	173 (21.3%)	450 (20.0%)	0.277	0.887	0.716 to 1.097
	No	1,156 (80.7%)	640 (78.7%)	1,796 (80.0%)		Reference	-

**Table 7: Demographic profile, mother vaccination, place of residence and antiviral use for Influenzae virus in Indigenous individuals with severe acute respiratory syndrome due to SARS-CoV-2 infection or due to another etiologic agents on Brazil during the first year of coronavirus disease (COVID)-19 pandemic.**

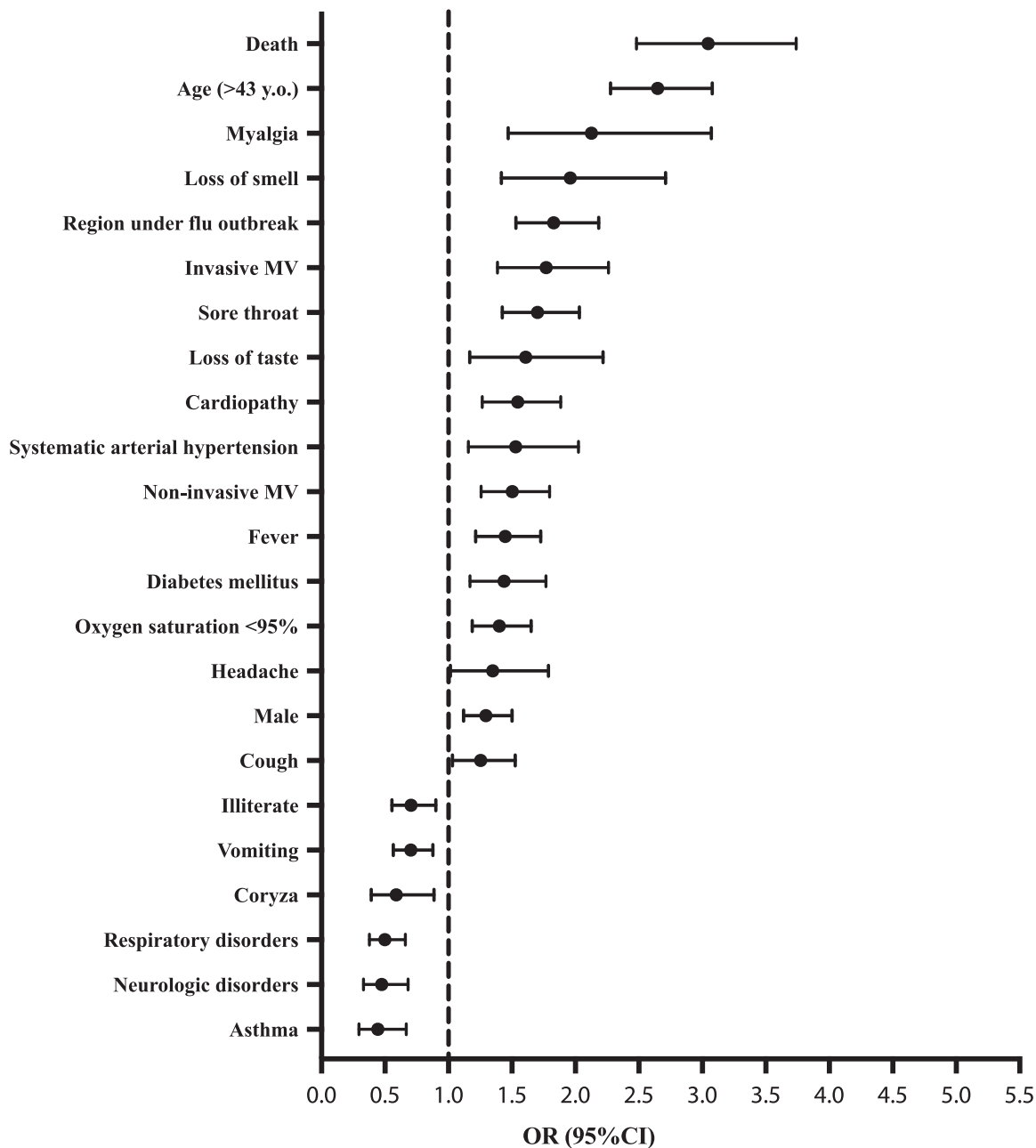
OR, odds ratio; CI, confidence interval; % percentage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

\* Only the female sex was considered.

\*\* The p-value and the OR were calculated comparing each patient category with the sum of the other categories because there is a lack of evidence at the literature to confirm the risk category for COVID-19 diagnosis in Indigenous individuals regarding the education level.

<sup>a</sup> For some patients' features the data was not available for all patients.

<sup>b</sup> Another etiologic agents were characterized as those with negative test for SARS-CoV-2 or those who were not tested for COVID-19. However, this number might be overestimated, due to several factors (i) were not a standardization of the test, which could contribute to false negative; (ii) Brazil has a lot of cases of arboviruses, especially Dengue fever, which can contribute to an enhanced number of undetermined SARS; (iii) There are a great number of underreporting of COVID-19 among Indigenous peoples; thus part of the individuals with undetermined SARS, might be COVID-19.



**Figure 6.** Epidemiology data with positive association (P-value <0.05) with the risk of severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2) infections compared with SARS by other etiologic agents in Brazilian Indigenous individuals during the first 57 epidemiologic weeks of the coronavirus disease (COVID)-19 pandemic. The data are presented as odds ratios (OR) and 95% confidence intervals (95%CI – lower and upper limits).

MV, mechanical ventilation; y.o.; years old; % percentage.

was used as therapy in 277/1,433 (19.3%) individuals with SARS-CoV-2 and in 173/813 (21.3%) individuals with SARS by other etiologic agents (P-value=0.277) (Table 7).

**Clinical symptoms in Indigenous individuals with SARS**

A total of 17 symptoms were evaluated and the most common in the Indigenous with SARS were cough (2,294/

2,818; 81.4%), dyspnea (2,139/2,796; 76.5%), fever (2,115/2,806; 75.4%), respiratory distress (1,944/2,694; 72.2%), and oxygen saturation <95% (1,703/2,635; 64.6%) (Table 8). Among the symptoms the most common features associated with the COVID-19 group were myalgia (OR=2.126; 95%CI=1.471-3.071), loss of smell (OR=1.959; 95%CI=1.416-2.710), sore throat (OR=1.701;

Clinical symptoms	Data	COVID-19	Other etiologic agents <sup>a</sup>	Total	P-value	OR	95%CI
Fever	Yes	1,402 (77.9%)	713 (70.9%)	2,115 (75.4%)	<0.001	1.448	1.214 to 1.726
	No	398 (22.1%)	293 (29.1%)	691 (24.6%)		Reference	-
Cough	Yes	1,492 (82.9%)	802 (78.7%)	2,294 (81.4%)	<0.001	1.254	1.031 to 1.526
	No	307 (17.1%)	217 (21.3%)	524 (18.6%)		Reference	-
Sore throat	Yes	630 (39.6%)	247 (27.8%)	877 (35.4%)	<0.001	1.701	1.424 to 2.032
	No	961 (60.4%)	641 (72.2%)	1,602 (64.6%)		Reference	-
Dyspnea	Yes	1,374 (77.7%)	765 (74.5%)	2,139 (76.5%)	0.058	1.191	0.996 to 1.425
	No	395 (22.3%)	262 (25.5%)	657 (23.5%)		Reference	-
Respiratory distress	Yes	1,243 (73.4%)	701 (70.1%)	1,944 (72.2%)	0.068	1.176	0.989 to 1.398
	No	451 (26.6%)	299 (29.9%)	750 (27.8%)		Reference	-
Oxygen saturation	<95%	1,130 (67.5%)	573 (59.7%)	1,703 (64.6%)	<0.001	1.400	1.188 to 1.651
	≥95%	545 (32.5%)	387 (40.3%)	932 (35.4%)		Reference	-
Diarrhea	Yes	293 (19.2%)	173 (19.4%)	466 (19.3%)	0.957	0.993	0.905 to 1.224
	No	1,230 (80.8%)	721 (80.6%)	1,951 (80.7%)		Reference	-
Vomiting	Yes	215 (14.3%)	170 (19.1%)	385 (16.1%)	0.002	0.704	0.565 to 0.878
	No	1,291 (85.7%)	719 (80.9%)	2,010 (83.9%)		Reference	-
Abdominal pain	Yes	131 (15.1%)	74 (16.4%)	205 (15.5%)	0.522	0.903	0.662 to 1.232
	No	739 (84.9%)	377 (83.6%)	1,116 (84.5%)		Reference	-
Fatigue and asthenia	Yes	367 (39.5%)	164 (34.8%)	531 (37.9%)	0.091	1.222	0.971 to 1.540
	No	562 (60.5%)	306 (65.2%)	869 (62.1%)		Reference	-
Loss of smell	Yes	190 (21.3%)	55 (12.2%)	245 (18.3%)	<0.001	1.959	1.416 to 2,710
	No	700 (78.7%)	397 (87.8%)	1,097 (81.7%)		Reference	-
Loss of taste	Yes	171 (19.5%)	59 (13.1%)	230 (17.3%)	0.004	1.609	1.168 to 2.218
	No	706 (80.5%)	392 (86.9%)	1,098 (82.7%)		Reference	-
Headache	Yes	172 (12.5%)	78 (9.5%)	250 (11.4%)	0.044	1.348	1.016 to 1.788
	No	1,209 (87.5%)	739 (90.5%)	1,948 (88.6%)		Reference	-
Chest pain	Yes	51 (3.7%)	19 (2.3%)	70 (3.2%)	0.080	1.611	0.944 to 2.747
	No	1,330 (96.3%)	798 (97.7%)	2,128 (96.8%)		Reference	-
Myalgia	Yes	133 (9.6%)	39 (4.8%)	172 (7.8%)	<0.001	2.126	1.471 to 3.071
	No	1,248 (90.4%)	778 (95.2%)	2,026 (92.2%)		Reference	-
Coryza	Yes	49 (3.5%)	48 (5.9%)	97 (4.4%)	0.013	0.589	0.392 to 0.886
	No	1,332 (96.5%)	769 (94.1%)	2,107 (95.6%)		Reference	-
Other clinical symptoms*	Yes	158 (11.6%)	107 (13.5%)	265 (12.3%)	0.221	0.846	0.650 to 1.100
	No	1,199 (88.4%)	687 (86.5%)	1,886 (87.7%)		Reference	-

**Table 8: Clinical symptoms in Brazilian Indigenous individuals with severe acute respiratory syndrome due to SARS-CoV-2 or due to other etiologic agents during the first year of coronavirus disease (COVID)-19 pandemic.**

OR, odds ratio; CI, confidence interval; %, percentage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

\* The category represents the patient without other symptoms than the previously cited in the table, such as fever, cough, sore throat, dyspnea, and respiratory distress.

<sup>a</sup> Another etiologic agents were characterized as those with negative test for SARS-CoV-2 or those who were not tested for COVID-19. However, this number might be overestimated, due to several factors (i) were not a standardization of the test, which could contribute to false negative; (ii) Brazil has a lot of cases of arboviruses, especially Dengue fever, which can contribute to an enhanced number of undetermined SARS; (iii) There are a great number of underreporting of COVID-19 among Indigenous peoples; thus part of the individuals with undetermined SARS, might be COVID-19.

95%CI=1.424-2.032), loss of taste (OR=1.609; 95%CI=1.168-2.218), and fever (OR=1.448; 95%CI=1.214-1.726) (Table 8; Figure 6 and Figure 4A). Unfortunately, data from several individuals were not available at database. The complete clinical symptoms profile is shown at ST4.

#### Comorbidities in Indigenous individuals with SARS

A total of 17 comorbidities were observed and 1,495/3,122 (47.9%) Indigenous individuals presented at least

one. The most common comorbidities were cardiopathy (591/2,787; 21.2%), diabetes mellitus (525/2,767; 19%), SAH (272/2,622 10.4%), neurologic disorders (124/2,630; 4.7%), and obesity (112/2,605; 4.3%) (Table 9; Figure 6 and Figure 5A). Among the comorbidities, the mainly ones associated with higher chance for SARS by COVID-19 were cardiopathy (OR=1.545; 95%CI=1.267-1.884), SAH (OR=1.530; 95%CI=1.157-2.025), and diabetes mellitus (OR=1.438; 95%CI=1.170-1.768). In contrast, the presence of asthma (OR=0.444; 95%CI=0.295-0.668), previously respiratory disorders



Comorbidities	Data	COVID-19	Other etiologic agents <sup>a</sup>	Total	P-value	OR	95%CI
Comorbidities (Total)	Yes	962 (48.2%)	533 (47.3%)	1,495 (47.9%)	0.602	1.041	0.899 to 1.204
	No	1,032 (51.8%)	595 (52.7%)	1,627 (52.1%)		Reference	-
Cardiopathy	Yes	423 (23.7%)	168 (16.7%)	591 (21.2%)	<0.001	1.545	1.267 to 1.884
	No	1,361 (76.3%)	835 (83.3%)	2,196 (78.8%)		Reference	-
Hematological disorders	Yes	16 (1.0%)	13 (1.4%)	29 (1.1%)	0.438	0.699	0.334 to 1.458
	No	1,632 (99.0%)	926 (98.6%)	2,558 (98.9%)		Reference	-
Down syndrome	Yes	5 (0.3%)	7 (0.7%)	12 (0.5%)	0.135	0.405	0.128 to 1.28
	No	1,641 (99.7%)	931 (99.3%)	2,572 (99.5%)		Reference	-
Hepatic disorders	Yes	16 (1.0%)	6 (0.6%)	22 (0.9%)	0.505	1.519	0.592 to 3.895
	No	1,631 (99.0%)	929 (99.4%)	2,560 (99.1%)		Reference	-
Asthma	Yes	43 (2.6%)	54 (5.7%)	97 (3.7%)	<0.001	0.444	0.295 to 0.668
	No	1,605 (97.4%)	894 (94.3%)	2,499 (96.3%)		Reference	-
Previous respiratory disorders	Yes	103 (6.1%)	113 (11.6%)	216 (8.1%)	<0.001	0.499	0.377 to 0.660
	No	1,574 (93.5%)	862 (88.4%)	2,436 (91.9%)		Reference	-
Diabetes mellitus	Yes	371 (20.9%)	154 (15.5%)	525 (19.0%)	0.001	1.438	1.170 to 1.768
	No	1,404 (79.1%)	768 (84.5%)	2,242 (81.0%)		Reference	-
Neurologic disorders	Yes	57 (3.4%)	67 (7.0%)	124 (4.7%)	<0.001	0.474	0.330 to 0.682
	No	1,609 (96.6%)	897 (93.0%)	2,504 (95.3%)		Reference	-
Immunological disorders	Yes	30 (1.8%)	22 (2.4%)	52 (2.0%)	0.382	0.768	0.441 to 1.340
	No	1,617 (98.2%)	911 (97.6%)	2,528 (98.0%)		Reference	-
Kidney disorders	Yes	76 (4.6%)	33 (3.5%)	109 (4.2%)	0.222	1.321	0.871 to 2.004
	No	1,588 (95.4%)	911 (96.5%)	2,499 (95.8%)		Reference	-
Obesity	Yes	80 (4.8%)	32 (3.4%)	112 (4.3%)	0.088	1.450	0.954 to 2.202
	No	1,578 (95.2%)	915 (96.6%)	2,493 (95.7%)		Reference	-
Smoker habit	Yes	35 (2.1%)	17 (1.8%)	52 (2.0%)	0.770	1.132	0.631 to 2.033
	No	1,658 (97.9%)	912 (98.2%)	2,570 (98.0%)		Reference	-
Alcoholism	Yes	13 (0.8%)	3 (0.3%)	16 (0.6%)	0.197	2.388	0.679 to 8.402
	No	1,680 (99.2%)	926 (99.7%)	2,606 (99.4%)		Reference	-
Systemic arterial hypertension	Yes	198 (11.7%)	74 (8.0%)	272 (10.4%)	0.003	1.530	1.157 to 2.025
	No	1,495 (88.3%)	855 (92.0%)	2,350 (89.6%)		Reference	-
Other morbidities	Yes	102 (5.9%)	73 (7.6%)	175 (6.5%)	0.103	0.763	0.559 to 1.042
	No	1,631 (94.1%)	891 (92.4%)	2,522 (93.5%)		Reference	-

**Table 9: Comorbidities in Brazilian Indigenous individuals with severe acute respiratory syndrome due to SARS-CoV-2 or due to other etiologic agents during the first year of coronavirus disease (COVID)-19 pandemic.**

OR, odds ratio; CI, confidence interval; %, percentage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup> Another etiologic agents were characterized as those with negative test for SARS-CoV-2 or those who were not tested for COVID-19. However, this number might be overestimated, due to several factors (i) were not a standardization of the test, which could contribute to false negative; (ii) Brazil has a lot of cases of arboviruses, especially Dengue fever, which can contribute to an enhanced number of undetermined SARS; (iii) There are a great number of underreporting of COVID-19 among Indigenous peoples; thus part of the individuals with undetermined SARS, might be COVID-19.

(OR=0.499; 95%CI=0.377-0.660), and neurologic disorders (OR=0.474; 95%CI=0.330-0.682) were less common in Indigenous individuals with COVID-19 compared with the Indigenous individuals with other etiologic agents (Table 9; Figure 6 and Figure 5A). The complete comorbidities profile is shown at ST5.

#### Clinical evolution and imaging tests in Indigenous individuals with SARS

Among the Indigenous individuals with SARS, 619/2,545 (22.9%), 427/2,501 (17.1%) needed the ICU on invasive MV and 1,146/2,501 (45.8%) needed the ICU

on non-invasive MV. The data from several individuals were not included in the database, mainly for the need of ICU and type for ventilation support (Table 10). Furthermore, the Indigenous individuals with COVID-19 diagnosis were more likely to be on both, invasive (OR=1.770; 95%CI=1.396-2.260) and non-invasive (OR=1.503; 95%CI=1.257-1.797) MV protocol (Table 10; Figure 6). Among the chest-ray, the most frequent finding was lung interstitial infiltrate (614/1,108; 55.4%). The SARS-COV-2 infection was associated with three times more deaths than the SARS caused by other etiologic agents (40.2% vs. 18.1%; OR=3.046; 95%CI=2.482-3.740) (Table 10; Figure 6).

Clinical evolution <sup>a</sup>	Data	COVID-19 individuals (n=1,994)	Individuals with other etiologic agents (n=1,128) <sup>b</sup>	Total (N=3,122)	P-value	OR	95%CI
Intensive care unit	Yes	404 (25.2%)	215 (22.9%)	619 (24.3%)	0.213	1.132	0.937 to 1.368
	No	1,202 (74.8%)	724 (77.1%)	1,926 (75.7%)		Reference	-
Mechanical ventilation	Invasive	299 (18.8%)	128 (14.0%)	427 (17.1%)	<0.001	1.770	1.386 to 2.260
	Non-invasive	762 (48.0%)	384 (42.1%)	1,146 (45.8%)	<0.001	1.503	1.257 to 1.797
	No	528 (33.2%)	400 (43.9%)	928 (37.1%)		Reference	-
Chest X-ray finding	Interstitial infiltrate	376 (56.6%)	238 (53.6%)	614 (55.4%)	0.106	1.354	0.939 to 1.954
	Consolidation	35 (5.27%)	29 (6.5%)	64 (5.8%)	0.991	1.034	0.572 to 1.870
	Mixed	70 (10.5%)	44 (9.9%)	114 (10.3%)	0.250	1.364	0.827 to 2.249
	Other	106 (16.0%)	67 (15.1%)	173 (15.6%)	0.199	1.356	0.866 to 2.215
	Normal	77 (11.6%)	66 (14.9%)	143 (12.9%)		Reference	-
Outcome	Death	730 (40.2%)	141 (18.1%)	871 (33.6%)	<0.001	3.046	2.482 to 3.740
	Clinical recovery	1,086 (59.8%)	639 (81.9%)	1,725 (66.4%)		Reference	-

**Table 10: Clinical evolution of Indigenous individuals with severe acute respiratory syndrome due to SARS-CoV-2 infection or due to another etiologic agents on Brazil during the first year of coronavirus disease (COVID)-19 pandemic.**

OR, odds ratio; CI, confidence interval; NA, not applicable; %, percentage; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

<sup>a</sup> For some patients' features the data was not available for all patients

<sup>b</sup> Another etiologic agents were characterized as those with negative test for SARS-CoV-2 or those who were not tested for COVID-19. However, this number might be overestimated, due to several factors (i) were not a standardization of the test, which could contribute to false negative; (ii) Brazil has a lot of cases of arboviruses, especially Dengue fever, which can contribute to an enhanced number of undetermined SARS; (iii) There are a great number of underreporting of COVID-19 among Indigenous peoples; thus part of the individuals with undetermined SARS, might be COVID-19.

### Multivariate analysis by Logistic Regression to predict the diagnosis of COVID-19 among Indigenous individuals with SARS symptoms

To build the data implementation model, the backward stepwise (conditional) method was used. Binary logistic regression was performed to determine whether the considered patients' features were able to predict the diagnosis of COVID-19 among Indigenous individuals with SARS symptoms. The model containing the selected markers was significant in differentiating the SARS patients with COVID-19 infection from non-COVID-19 infections [ $X^2_{(7)}=65.187$ ; P-value <0.001; Nagelkerke's  $R^2=0.091$ ]. Among the patients' features, the following were significant and contributed in relation to COVID-19 diagnosis: age [ $\geq 43$  y.o.; OR=1.984 (95%CI=1.480-2.658)]; loss of smell [OR=2.373 (95%CI=1.461-3.854)]; previous respiratory disorders [OR=0.487; 95%CI=0.287-0.824)]; and fever [OR=1.445 (95%CI=1.082-1.929)]; in contrast, cardiopathy and neurological disorders were not significant and did not contribute to the proposed model (Table 6).

### Discussion

The health crisis caused by COVID-19 pandemic is a concern to the Indigenous people tribes of Brazil, besides the elderly and, people with comorbidities, the native population has suffered from pathogens throughout history.<sup>15,20,21</sup> Furthermore, this might be one of the reasons that Indigenous peoples were included as priority for COVID-19 vaccination in Brazil.<sup>6</sup> Outbreaks of

respiratory diseases, such as the influenza A virus subtype H1N1 (A/H1N1) flu, in 2009, reinforce the fragility of this portion of the population and suggest that Indigenous peoples are more susceptible to diseases of the respiratory tract compared mainly by Brazilian Caucasians.<sup>7,22</sup> In the present study, out of a total of 3,122 Indigenous individuals with SARS, 1,994 were due to COVID-19. Even though some individuals presented infection by influenza, adenovirus, and rhinovirus, and most etiologic agents responsible by the SARS were undetermined. In addition, most of the Indigenous individuals with SARS included in the present study were male with 43 y.o., with elementary school level or illiterate.

To control the COVID-19 pandemic, the literature guides safe practices, such as hand hygiene, wearing masks in public spaces, and social distance/physical isolation.<sup>23-25</sup> Interestingly, the effectiveness of some practices to prevent the COVID-19 in Indigenous peoples are not totally clear, as observed in the recent experience of the Waorani people with self-isolation, which did not prevent any further infection, and by the lack of adherence to use facial masks by these communities,<sup>13,26,27</sup> especially in those places with a flu outbreak. However, it was very difficult to implement some of these practices for Indigenous peoples since they have typical cultural behaviors as community housing and diverse hygienic practices, that corroborate with the vulnerability of these populations. It is noteworthy how the rural Indigenous communities were more affected than urban or peri urban ones maybe due the fact

Indigenous individuals living in rural area are less willing to wear masks in public places, sanitize their homes, change travel plans and to work from home, which can contribute to a high infection rate.<sup>28</sup> Also, traveling to urban and peri urban regions might be troublesome, since the Indigenous individuals might be infected in these regions, and even delay the diagnosis, due to low access to health care,<sup>5,6,8</sup> something similar to what happened to the Waorani people, which caused a great contagion in their community.<sup>13</sup>

Moreover, miners, loggers and invaders continue to explore Indigenous territories illegally, increasing the risk of SARS-CoV-2 infection. In fact, a production chain is being implemented in Indigenous land, mostly in the Amazon region, to produce monoculture, which can lead to massive deforestation of the Amazon rainforest, ultimately enhancing the risk of the Indigenous peoples to be at higher risk of other potential pandemic, since the Amazon is one of the greatest reservoirs of other coronavirus and the fact the deforestation might facilitate zoonoses to spread to humans.<sup>6–8,15,18,29–34</sup> In addition, the lack of a federal government protection policy for Indigenous peoples; the limited access to health care, especially those of high complexity to treat the severe COVID-19 cases; the lack of an adequate drinking water supply system, poor hygiene conditions and difficult access to soap and alcohol gel; and, finally, the exposure in urban centers during searches for emergency financial assistance offered by the federal government were features that increased the risk of SARS-CoV-2 infection among the Indigenous peoples.<sup>6–8,15,18</sup>

In the literature, besides being scarce, previously studies have also demonstrated a higher impact of the pandemic in vulnerable groups, including the Indigenous peoples.<sup>6–8,35,36</sup> According to Millet et al. (2020), nearly 20% of the U.S. counties are disproportionately Afro-Americans and are also responsible for 52% of the COVID-19 diagnosis and 58% of death.<sup>35</sup> Yancy (2020), on the same way, observed that in the Chicago state, more than 50% of COVID-19 cases and 70% of deaths are related to Afro-American's people, even though they represent only 30% of the Chicago State population, this reaffirms that social condition and structural racism are important risk factors for COVID-19 and the disease progression/outcome.<sup>35,36</sup> Furthermore, in the Indigenous individuals from Australia, it was described an increased risk of COVID-19, due to the several inequities if compared to non-Indigenous Australian, such as low access to health service, inadequate house living, and poor access to water,<sup>37</sup> similarly to Brazil. Also, Baqui et al. (2020) performed a cross sectional study in the Brazilian population, which was observed an increased mortality in *Pardo*, Afro-descendants, and individuals from the North region, making the ethnic and regional factor extremely related to the COVID-19 death risk. Unfortunately, only eight (three survivors) Indigenous individuals were enrolled in the study done

by Baqui et al. (2020) and the conclusion for the impact of COVID-19 pandemic in this population was irrelevant based on the low number of individuals enrolled.<sup>7</sup> However, our study data are in accordance with the current literature: since the Brazilian Indigenous peoples are also a minority in our country, several factors contributed to a higher impact of the pandemic in this group, such as those aforementioned.

Nevertheless, other Indigenous peoples from South America were also extremely affected by the COVID-19 pandemic, being mostly from the Amazonian region. Only three out of five self-isolated Waorani communities, located in the Ecuadorian Amazon region, were SARS-CoV-2 free until June 2020, whereas infection in other communities reached 90% of the individuals.<sup>13</sup> Several other communities were also affected, with nearly half of the individuals who were tested with a positive test for SARS-CoV-2, such as the *Sionas*, *Kichwas*, *Kofans*, and the people with the highest infection rate, the *Shuars*.<sup>14</sup> Finally, a high prevalence of antibodies against SARS-CoV-2 was observed in the *Xikrin of Bacajá (Kayapó)* people affecting nearly 70% of the Indigenous peoples from this tribe.<sup>38</sup> This outbreak of COVID-19 in Amazonian Indigenous peoples are worrisome, since the tribes might have contact with each other, and are able to spread the virus even to tribes more isolated than others, in addition to low access to health care, which can difficult the tracking and diagnosis of new cases.<sup>6,8,14</sup>

Unfortunately, most of the individuals infected with other etiologic agents (98.1%) did not have the pathogen identified, being characterized as undetermined SARS. Several factors might have contributed to this result, for instance, the limitations of the RT-PCR, which can only identify 58.9% of the individuals with COVID-19 with only one test, making 41.1% of the individuals a false negative,<sup>39</sup> and the limitations of the serological test, which can only identify COVID-19 in 72% of symptomatic individuals and in 58% of the asymptomatic individuals.<sup>40</sup> Furthermore, the type of sample (nasopharyngeal or oropharyngeal) was not specified in the dataset, which could also contribute to false negative results, since the oropharyngeal has less accuracy than nasopharyngeal.<sup>41,42</sup> Reports demonstrated COVID-19 cases are underreported and underdiagnosis in several countries, as France, Italy, United Kingdom and especially Brazil,<sup>43–45</sup> being that a higher underreporting was observed in Indigenous individuals from Brazil than in the general Brazilian population,<sup>46</sup> which could also lead to an enhanced number of undetermined SARS.

Interestingly, the arboviruses, especially Dengue fever, have similar clinical manifestation to COVID-19 as fever.<sup>47</sup> In fact, two reports even showed that the diagnosis of COVID-19 can be mistaken for dengue, due to similar clinical features.<sup>48,49</sup> Until the 57<sup>th</sup> COVID-19 epidemiologic week from 2020 (December 2019 to January 2021), Brazil accounted for 1,076,979

notified cases of arboviruses, being those 987,173 (91.6%) suspected cases of dengue fever, 82,419 (7.6%) suspected cases of Chikungunya and, until de 51<sup>st</sup> epidemiologic week 7,387 (0.8%) suspected cases of Zika have been notified. Curiously, in our data, almost 20% of the SARS cases were categorized as other etiologic agents in Mato Grosso do Sul State, which could be explained by the high incidence of arboviruses diagnosed as undetermined SARS, especially Dengue fever, which has the highest incidence among the arboviruses.<sup>50</sup> The difficulty in differentiating Dengue fever from COVID-19, especially in dengue's endemic areas, might have contributed to an increased spread of SARS-CoV-2, once individuals wrongly diagnosed with dengue are rarely isolated.<sup>51</sup>

Interestingly, in our multivariate analysis, several factors were associated to the diagnosis of COVID-19, such as fever, age  $\geq 43$  y.o. and loss of smell, and others were related to increased risk of death, as male individuals and the need for MV. Even though the Indigenous peoples are ethnic different from most of the Brazilian population, since they have a complete different genetic background,<sup>52,53</sup> most of the factors associated with death have already been described in other populations, as the older age and the male sex.<sup>7,54</sup> It is noteworthy how the Indigenous peoples are at increased risk of COVID-19, including high mortality rates and ICU risk,<sup>4,55</sup> as addressed earlier in this study. Nonetheless, several public health policies might be implemented in order to identify those under increased risk of death and a proper healthcare should be offered in order to prevent even more deaths among the Indigenous individuals. However, only a few papers addressed the epidemiologic characteristics of Indigenous peoples during the COVID-19 pandemic.<sup>7,37,56,57</sup> The lack of information regarding the epidemiologic profile of Indigenous peoples is worrisome, since this is imperative to prevent more deaths among these peoples.

Our study also described a higher proportion of deaths by COVID-19 in elderly Indigenous individuals, in accordance with previous studies.<sup>54,58</sup> Unfortunately, for Indigenous peoples this means an even worse loss since their culture and knowledge are passed on by the elderly ones.<sup>6,15,18</sup> Curiously, we also observed a higher proportion of deaths in younger Indigenous individuals, perhaps due to the low access to the Brazilian Public Health System (SUS; in Portuguese Sistema Único de Saúde), making it difficult to treat severe cases that need more complex support as MV and ICUs.<sup>4,59,60</sup> The present study also shows that several common comorbidities in Brazilian population, as cardiopathy, SAH, and diabetes mellitus, were associated with SARS by COVID-19 in the Indigenous peoples; however, due to the lack of proper health assistance, the treatment of these chronic conditions might be difficult, leading to believe these comorbidities may have a more central role in SARS by COVID-19. Curiously, nearly 50% of

the Indigenous individuals have at least one comorbidity, being the most common cardiopathy, perhaps due to Chagas disease, since most of the Indigenous individuals are from Brazilian endemic areas as North and Northeast,<sup>61,62</sup> followed by diabetes mellitus and SAH. These last two comorbidities can be associated, for example, with the high consumption of ultra-processed food,<sup>63,64</sup> which unfortunately might be the new dietary pattern of these individuals, since 42.9% of them are living in urban areas and that type of food is cheaper. Curiously, we also observed a higher proportion of deaths in younger Indigenous individuals, perhaps due to low access to the SUS, making it difficult to treat severe cases that need more complex support as MV and ICUs.<sup>4,59,60</sup> As exposed, Indigenous people's behavior changed with their approach to Caucasian individuals. Evolutionarily, the adaptive changes of the Indigenous peoples were quickly, and the phenotypic responses to environmental changes (including social aspects) were possibly slower than the adaptation of the genotype, which may have caused the high rate of comorbidities in this population.

In brief, the most common clinical symptoms in the SARS Indigenous individuals enrolled in our study were fever, cough, dyspnea, respiratory distress, fatigue and asthenia and low oxygen saturation ( $<95\%$ ). However, it was observed a higher prevalence of several symptoms in Indigenous individuals with COVID-19 if compared to other etiologic agents, such as fever, cough, sore throat, low oxygen saturation ( $<95\%$ ), loss of smell, loss of taste, headache, and coryza. Both comorbidities and clinical symptoms more prevalent in the COVID-19 patients' group, as well as image findings, might be used to implement a machine learning tool to identify confirmed cases of COVID-19 and those with greater risk of death. In our analysis, several patients' characteristics might contribute to the differentiate the COVID-19 patients from patients with other etiologic agents, as fever and age, and to identify those with increased risk of death, as dyspnea, myalgia and age, since these clinical characteristics were independent factors associated with diagnosis and death, respectively. A recent study has evaluated the ability of an artificial intelligence (AI) to diagnose COVID-19 using high-resolution computed tomography (HRCT) images and clinical characteristics. Curiously, the models that combined image test and clinical features were more sensitive and specific compared to models that used only image test or clinical characteristics.<sup>65</sup> Thus, the machine learning tool could be able to enhance the efficacy of diagnosis tracking and treatment before the results of RT-PCR came out. The AI, using only clinical characteristics, could be used in places where RT-PCR and HRCT are not widely available, as in the Brazilian Amazonian area. Also, the AI could be an inexpensive and easier technique for diagnostics as a mobile device model. In brief, screening by RT-PCR, clinical symptoms, comorbidities profile, and,

when it is possible, chest X-ray and HRCT findings are important to differentiate risk populations, as Indigenous peoples, for SARS-CoV-2 infection.<sup>65–68</sup>

Special attention should be given to the medical care of Indigenous peoples as the adequation of treatments and prevention measures. It would be crucial not only medical and epidemiologic improvements, but also cultural and social knowledge. All of these measures would enhance the adhesion to treatments, prevention policies, and avoid the refusal to go to the hospital.<sup>6</sup> The refusal to go to the hospital is a cultural issue for Indigenous peoples, mainly for the elderly ones, as demonstrated by Mendes et al. (2021).<sup>6</sup> The hospitalization of Indigenous individuals who need it, as in the cases with SARS, is extremely important. However, the need for ICU care increased by more than five times the chance of death, revealing that the gap between the onset of symptoms and clinical intervention and health care assistance are crucial to the best outcome in the context of new coronavirus disease (COVID-19).

Despite advances in Indigenous health care in Brazil, there are still many challenges. The North is the region with the highest proportion of the population under vulnerability and serious risk to COVID-19 and also concentrates 22.7% of the Brazilian Indigenous peoples.<sup>45</sup> For this population, it is still difficult to access health services, primary care facilities or family medicine in villages, as well as complex specialized services, as patients with SARS require (hospitalization with ICUs beds and MV). Nevertheless, only access to proper health would not be considered enough to attenuate the impact of COVID-19 in the Indigenous group once it was observed a higher hospital mortality rate of Indigenous peoples compared to overall Brazilian individuals.<sup>56</sup> Several clinical symptoms presented a similar proportion between recovery and death groups. However, considering only dead individuals, the rate of dyspnea, respiratory distress and oxygen saturation <95% were higher compared to the clinical recovery individuals.

Regarding the findings for lung chest X-ray findings, both groups presented several alterations, and it was not possible to differentiate between both groups based on these findings. Unfortunately, the low number of imaging tests results were included in the dataset, causing a low statistical power. The HCRT could be used to enhance the diagnosis accuracy of COVID-19.<sup>69</sup> In several studies, structural changes found in the lung HRCT preceded RT-PCR positivity tests as well as clinical symptomatology.<sup>70,71</sup> Besides, architectural distortion implies worst outcomes as highlighted in chest X-ray findings such as consolidations and interstitial infiltrate, with statistical significance. Even though the HRCT has been considered the gold-standard in the lung disease and anatomical impairment context,<sup>72–74</sup> it is an expensive and high technology tool which is not available for the majority of the population, mainly to the poorest and most vulnerable ones. Forthcoming

radiological alternatives are needed in order to screen, evaluate, and follow-up COVID-19 lung damage. The lung ultrasound arises as a cheaper, radiation-free, good reproducibility, easy-handling and bedside alternative to the anatomical and structural appraisal.<sup>75,76</sup> The potential wider application of this tool, principally in more vulnerable population, could allow a better clinical assistance, with more often anatomical lung evaluations, without the requirement of large geographical migration to tertiary hospital or cutting-edge technologies facilities.<sup>77</sup> In brief, the Indigenous individuals who died presented the worst clinical scenario for the lung disease; in this case, the clinical symptoms from the lungs deserves special attention to be managed to control the COVID-19 disease evolution and, to reduce the number of deaths.

Our study is the first one to evaluate epidemiological data of SARS by SARS-CoV-2 infection or other etiologic agents among Brazilian Indigenous peoples. The results might highlight the importance of understanding minorities needs and stopping their disproportionate deaths. Specifically, in Brazil, Indigenous peoples do not have access to medical posts, doctors, and basic medicines, as well as the ventilators very necessary during an outbreak of COVID-19.

As main limitations, the study was based on a public dataset and the authors did not have access to the original data. Some epidemiologic data were not imputed to the dataset for all individuals, reducing the study power for some statistical analyses. Some important markers were not included in the dataset correctly were as the medicines that were used to treat the Indigenous individuals during the follow-up. The COVID-19 evolution presented a different outcome among the Brazilians regions due to the different impact for the health system in each region; however, we were not able to perform a distinctive analysis due to the low number of Indigenous individuals analyzed in each Brazilian state and Federal District. In addition, both univariate and multivariate analyses demonstrated some disparities regarding the ORs and its 95%CI presented in terms of amplitude for the same patients' features, maybe due to the exclusion of individuals in the multivariate analysis. Importantly, our data have a high number of deaths among Indigenous individuals than the presented by the Brazilian Ministry of Health as observed by Sardinha et al., which have demonstrated 470 Indigenous people's deaths by COVID-19 while the Ministry of Health have reported only 380 in the same period (from Jan 2020 to Ago 2020).<sup>78</sup>

In conclusion, our study demonstrated that Indigenous peoples are vulnerable to SARS by SARS-CoV-2 being more severe than SARS by other etiologic agents. Several factors were associated with enhanced risk of death, as male sex, older age ( $\geq 60$  y.o.), and need for ventilatory support; also, other factors might help to differentiate SARS by COVID-19 or by other etiologic agents, as older age ( $\geq 43$  y.o.), loss of smell and fever.

Thus, the understanding of the epidemiologic profile of Indigenous peoples is imperative in order to understand the natural history of the disease, which can lead to more public health policies to prevent deaths and to optimize the diagnosis.

#### Declaration of interests

None.

#### Contributors

(MNB, FALM) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and (NMSS, MNB, MMO, IAR, AOP, RTM, FALM) drafting the work or revising it critically for important intellectual content; and (NMSS, MNB, MMO, IAR, AOP, RTM, FALM) final approval of the version to be published; and (NMSS, MNB, MMO, IAR, AOP, RTM, FALM) agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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#### Data sharing statement

The data can be obtained directly with the author or at <https://opendatasus.saude.gov.br>.

#### Editorial Note

The *Lancet* Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

#### Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2021.100177.

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