

# Risk factors for death due to COVID-19, in the state of Acre, Brazil, 2020: a retrospective cohort study

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## Abstract

**Objective:** To analyze risk factors for death in individuals with severe acute respiratory syndrome due to COVID-19.

**Methods:** This was a retrospective cohort study, comprised of adult individuals with COVID-19, from March to September 2020, notified by the Epidemiological Surveillance System in the state of Acre, Brazil. Cox regression was used. **Results:** Among 57,700 individuals analyzed, the incidence was 2,765.4/100,000 inhabitants, and mortality was, 61.8/100,000 inhabitants. The risk factors for death were: being male (HR=1.48 -95% CI 1.25;1.76), age  $\geq 60$  years (HR=10.64 -95% CI 8.84;12.81), symptom of dyspnea (HR=4.20 -95% CI 3.44;5.12) and multimorbidity (HR=2.23 -95% CI 1.77;2.81), with emphasis on heart disease and diabetes *mellitus*. 'Sore throat' and 'headache' were symptoms present in mild cases of COVID-19. **Conclusion:** Being male, elderly, having heart disease, diabetes mellitus and dyspnea were characteristics associated with death due to COVID-19.

**Keywords:** Severe Acute Respiratory Syndrome; Coronavirus infections; Longitudinal studies; Risk Factors; Mortality.

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## Introduction

Severe acute respiratory syndrome (SARS) due to COVID-19 (SARS due to COVID-19) is a viral respiratory disease caused by a newly discovered coronavirus. It was identified in Wuhan, Hubei Province, China, in December 2019.<sup>1</sup> The novel coronavirus has high transmissibility and can cause severe acute respiratory syndrome and deaths. At the end of September, 2020, more than 32.7 million COVID-19 cases and more than 1 million deaths had been confirmed worldwide. The American Continent was the hardest hit, with a number of cases exceeding 16.2 million. Brazil was the second worst affected country by COVID-19 in the Americas, with 4.8 million confirmed cases and more than 143 million deaths.<sup>2</sup>

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The pandemic has dramatically affected health services. Many studies have been conducted in the quest for practices based on scientific evidence. It is essential to contribute to epidemiological studies aimed at health promotion, disease prevention and health care planning, with the identification of individuals subjected to risk factors for mortality.<sup>3</sup>

In this scenario, some risk factors for mortality associated with SARS due to COVID-19 have been suggested, such as severe lymphopenia, high levels of C-reactive protein (correlated with severe hypoxemia), older age ( $\geq 60$  years), male gender, race/skin color (non-white), lower socioeconomic level, presence of comorbidities (e.g., diabetes *mellitus*, cardiovascular diseases, hypertension and cancer, presence of fever, dyspnea, cough and immunocompromised status), as well as obesity and unhealthy lifestyle.<sup>4</sup> However, such factors may change depending on the characteristics of the population and health services, therefore, longitudinal follow-up studies may be useful in order to understand local realities and subsidize health actions based on these realities.

The aim of this research was to analyze the epidemiological characteristics and risk factors for death in individuals with SARS due to COVID-19 in the state of Acre, Brazil, in 2020.

## Methods

This was a retrospective longitudinal cohort study. Acre is located in the northern region of the country, in the Western Brazilian Amazon, borders Peru and Bolivia, and had an estimated population of 881,935 people on July 1, 2019.<sup>5</sup> The state has 380 health facilities, including centers and hospitals, distributed among 22 municipalities.<sup>6</sup>

The study included all COVID-19 cases reported in Acre by September 1, 2020. The first COVID-19 notification, in the state, occurred on March 15, 2020, with the reported symptoms having started the day before; the last case included in the study presented the first symptoms four days before notification, on September 1, 2020. The time-zero of the cohort was defined by the date of onset of symptoms, and delta-time ( $\Delta T$ ) corresponded to the time between the date of symptom onset and outcome (cure or death) for cases with diagnostic confirmation of SARS due to COVID-19. The follow-up time was 60 days, started from the date of the first symptoms.

Every case of SARS is compulsorily notified and typed individually on the Influenza Surveillance Information System (SIVEP-Gripe), whose data were used on this notification system. On January 30, 2020, SARS due to COVID-19 was declared as a public health emergency of international concern, by WHO, therefore the Ministry of Health, through Technical Note No. 20/2020-SAPS/GAB/MS, made it compulsory to notify cases in order to enable longitudinal epidemiological investigation and formulation of health policies and strategies. This was the objective of this research.<sup>7</sup>

The diagnosis of COVID-19 was performed through laboratory tests such as, molecular test (RT-PCR) or immunological test.

SARS was defined by the concomitant presence of four criteria: (i) fever, even if self-reported, (ii) cough or sore throat, (iii) dyspnea or  $O_2$  saturation  $< 95\%$  or respiratory distress and (iv) hospitalized case or there was evolution to death, regardless of previous hospitalization.<sup>7</sup>

'Death' outcome was obtained based on a statement provided by professionals and health institutions of

the public or private sector, throughout the national territory and according to the current legislation, issued within 24 hours.

The notification form of the e-SUS Epidemiological Surveillance (e-SUS VE) contains the following information related to individuals: notification number; Federative Unit and notifying municipality; Individual Taxpayer Registration Number (CPF); whether the individual who was notified is a foreigner, health professional or public security professional; date of birth; country of origin; gender (male; female); race/skin color (white; black; Asian; brown; indigenous); passport number; postal code (ZIP Code); municipality of residence; residence address; date of notification and symptoms (fever, cough, sore throat and dyspnea, categorized dichotomically: yes; no). For other symptoms, the filling process was carried out descriptively, for which, categorical independent variables were created, in this study, such as: reduction or complete loss of the sense of smell (hyposmia/anosmia) and/or taste (hypogeusia), myalgia, diarrhea, headache and runny nose, all considered predictors of SARS due to COVID-19, according to the literature.<sup>6</sup>

The notification form also included information on the presence of comorbidities (chronic respiratory disease; chronic kidney disease; diabetes *mellitus*; chronic heart disease), chromosomal disorder, immunosuppression, and high-risk pregnancy. The 'multimorbidity' variable was defined by the presence of more than one chronic disease, among those surveyed.

In addition to these, other variables were evaluated: laboratory test ordering (requested, collected or complete); specimen collection date; types of laboratory tests (rapid antibody and/or antigen test and RT-PCR); test result (negative; positive); final classification (laboratory confirmation; clinical-epidemiological confirmation; discarded case); evolution of case (canceled; ignored; cure; death [dependent variable]; hospitalized or home treatment); date of case closure; and space for additional information.

This study is subject to information bias, resulting from the use of secondary data, with the possibility of diagnostic and registration errors, and/or the inability to control possible confounding variables. However, it is assumed that the type of information bias present is non-differential.

The measure of central tendency (minimum, mean, maximum, median and standard deviation)

was used to analyze the continuous variables; and categorical variables were described using absolute (n) and relative (%) frequency. Pearson's chi-square test and/or Fisher's exact test were used to compare independent variables with less than five occurrences.

Risk factors for death were analyzed using Cox regression to estimate hazard ratio (HR) and their respective 95% confidence intervals (95%CI). Multivariate analysis was performed using the variables that presented  $p < 0.10$  in the univariate analysis, which were analyzed together. The Wald test was used to verify the significance of the cox model coefficients. In the final model, the variables that presented  $p < 0.05$  remained by adjusting for 'sex', 'age', 'health professional', 'sore throat', 'dyspnea', 'headache', 'hyposmia/anosmia/hypogeusia', 'myalgia', 'runny nose' and 'multimorbidity' (coexistence of diseases) variables. Finally, cox-snell residual was used to estimate the model fit.

Data were transferred from the e-SUS VE/SIVEP-Gripe database, on Microsoft Excel, and then, were treated and later analyzed using the SPSS Statistics, version 22.0.

The research project followed the ethical guidelines for research involving human being of the National Health Council (CNS), Resolution No. 466, December 12, 2012, and was approved by the Research Ethics Committee of the Fundação Hospitalar Estadual do Acre (CEP/FUNDHACRE), Opinion No. 3,294,722 (Certificate of Submission for Ethical Appraisal (CAAE) No. 47577215.2.0000.5009), issued on April 30, 2019. It was not necessary to sign the Free and Informed Consent Form due to the use of secondary data.

## Results

From March 15 to September 1, 2020, 72,830 people were tested for COVID-19; of these, 10,529 did not get their test results or they were inconclusive, and 4,569 records were canceled because they showed duplicity. Of the 57,700 individuals who got their test results, 42.3% tested positive for COVID-19 (Table 1).

Of the 24,389 positive cases, the mean time from symptom onset to 'death' outcome was 33.6 days, with a standard deviation of 21.6 and a median of 23 days; the mean age was 40.8 years, the standard deviation was 14.3 and the median was 30 years. At the end of the follow-up, 18,442 (75.6%) were cured, 545 (2.2%) died, 42 (0.2%) were hospitalized and 408

**Table 1 – Characterization of the individuals who got tested for COVID-19 (N=57,700) according to test results, notified, Acre, Brazil 2020**

| Variable                     |               | Total<br>N    | Positive      |             | Negative      |             | p-value <sup>a</sup> |
|------------------------------|---------------|---------------|---------------|-------------|---------------|-------------|----------------------|
|                              |               |               | N             | %           | N             | %           |                      |
| Sex <sup>b</sup>             | Male          | 26,296        | 11,342        | 46.5        | 14,954        | 45.0        | <0.001               |
|                              | Female        | 31,342        | 13,040        | 53.5        | 18,302        | 55.0        |                      |
| Age                          | <60 years old | 50,655        | 21,048        | 86.3        | 29,607        | 88.9        | <0.001               |
|                              | ≥60 years old | 7,045         | 3,341         | 13.7        | 3,704         | 11.1        |                      |
| Race/skin color <sup>b</sup> | White         | 6,864         | 2,683         | 11.5        | 4,181         | 13.5        | <0.001               |
|                              | Brown         | 44,743        | 19,265        | 82.8        | 25,478        | 82.3        |                      |
|                              | Indigenous    | 1,406         | 806           | 3.5         | 600           | 1.9         |                      |
|                              | Black         | 1,230         | 519           | 2.2         | 711           | 2.3         |                      |
| Healthcare professionals     | Yes           | 5,440         | 1,992         | 8.2         | 3,448         | 10.4        | <0.001               |
|                              | No            | 52,260        | 22,397        | 91.8        | 29,863        | 89.6        |                      |
| Public security professional | Yes           | 1,607         | 686           | 2.8         | 921           | 2.8         | 0.730                |
|                              | No            | 56,093        | 23,703        | 97.2        | 32,390        | 97.2        |                      |
| <b>Total</b>                 |               | <b>57,700</b> | <b>24,389</b> | <b>42.3</b> | <b>33,311</b> | <b>57.7</b> |                      |

a) Pearson chi-square test; b) The differences regarding the total are due to lack of information for the variable.

**Table 2 – Distribution of COVID-19 cases (n=24,389) according to municipality of residence, signs and symptoms, and presence of multimorbidity, Acre, Brazil 2020**

| Variable                              | N                           | %      |      |
|---------------------------------------|-----------------------------|--------|------|
| Municipality of residence             | Rio Branco                  | 9,399  | 38.5 |
|                                       | Cruzeiro do Sul             | 3,178  | 13.0 |
|                                       | Tarauacá                    | 1,559  | 6.4  |
|                                       | Sena Madureira              | 1,252  | 5.1  |
|                                       | Feijó                       | 1,127  | 4.6  |
|                                       | Brasileia                   | 1,123  | 4.6  |
|                                       | Xapuri                      | 960    | 3.9  |
|                                       | Mâncio Lima                 | 757    | 3.1  |
|                                       | Others                      | 5,034  | 20.6 |
| Number of signs and symptoms reported | Asymptomatic                | 1,464  | 6.0  |
|                                       | 1 to 2                      | 10,056 | 41.2 |
|                                       | 3 to 4                      | 10,750 | 44.1 |
|                                       | 5 and more                  | 2,119  | 8.7  |
| Signs and symptoms                    | Fever                       | 17,301 | 68.3 |
|                                       | Cough                       | 15,322 | 60.5 |
|                                       | Sore Throat                 | 10,397 | 41.1 |
|                                       | Dyspnea                     | 7,576  | 29.9 |
|                                       | Headache                    | 7,735  | 30.5 |
|                                       | Hyposmia/anosmia/hypogeusia | 1,083  | 4.3  |
|                                       | Myalgia                     | 3,165  | 12.5 |
|                                       | Runny nose                  | 1,566  | 6.2  |
|                                       | Diarrhea                    | 1,779  | 7.0  |

To be continued

Continuation

**Table 2 – Distribution of COVID-19 cases (n=24,389) according to municipality of residence, signs and symptoms, and presence of multimorbidity, Acre, Brazil, 2020**

| Variable             |                             | N     | %   |
|----------------------|-----------------------------|-------|-----|
| Multimorbidity       | Yes                         | 1,492 | 5.9 |
|                      | Heart disease               | 834   | 3.3 |
| Reported Morbidities | Diabetes <i>mellitus</i>    | 443   | 1.7 |
|                      | Chronic respiratory disease | 186   | 0.7 |
|                      | Chronic kidney disease      | 103   | 0.7 |
|                      | Immunosuppression           | 173   | 0.7 |
|                      | Chromosomal disorder        | 61    | 0.2 |
|                      | High-risk pregnancy         | 63    | 0.2 |

**Table 3 – Distribution of SARS<sup>a</sup> cases due to COVID-19 (n=18,987) according to epidemiological, clinical and occurrence of death outcome due to the disease, Acre, Brazil, 2020**

| Variable                     |               | Total         | Death      |            | p-value <sup>b</sup> |
|------------------------------|---------------|---------------|------------|------------|----------------------|
|                              |               | N             | N          | %          |                      |
| Sex <sup>c</sup>             | Male          | 8,905         | 333        | 3.7        | <0.001               |
|                              | Female        | 10,075        | 212        | 2.1        |                      |
| Age                          | <60 years old | 16,424        | 173        | 1.0        | <0.001               |
|                              | ≥60 years old | 2,563         | 372        | 14.5       |                      |
| Race/skin color <sup>c</sup> | White         | 2,087         | 52         | 2.5        | 0.452                |
|                              | Brown         | 15,024        | 431        | 2.9        |                      |
|                              | Indigenous    | 505           | 14         | 2.8        |                      |
|                              | Black         | 401           | 7          | 1.7        |                      |
| Healthcare Professionals     | Yes           | 1,715         | 9          | 0.5        | <0.001               |
| Fever                        | Yes           | 13,264        | 384        | 2.9        | 0.757                |
| Cough                        | Yes           | 11,755        | 369        | 3.1        | 0.005                |
| Sore throat                  | Yes           | 7,802         | 140        | 1.8        | <0.001               |
| Dyspnea                      | Yes           | 5,971         | 357        | 6.0        | <0.001               |
| Headache                     | Yes           | 5,896         | 87         | 1.5        | <0.001               |
| Myalgia                      | Yes           | 2,623         | 39         | 1.5        | <0.001               |
| Hyposmia/anosmia/hypogeusia  | Yes           | 745           | 7          | 0.9        | 0.001                |
| Runny nose                   | Yes           | 1,248         | 18         | 1.4        | 0.002                |
| Diarrhea                     | Yes           | 1,378         | 29         | 2.1        | 0.077                |
| Multimorbidity               | Yes           | 736           | 88         | 12.0       | <0.001               |
| Heart disease                | Yes           | 616           | 32         | 5.2        | <0.001               |
| Diabetes <i>mellitus</i>     | Yes           | 358           | 25         | 7.0        | <0.001               |
| Chronic respiratory disease  | Yes           | 158           | 6          | 3.8        | 0.483                |
| Chronic Kidney disease       | Yes           | 88            | 8          | 9.1        | <0.001               |
| <b>Total</b>                 |               | <b>18,987</b> | <b>545</b> | <b>2.9</b> |                      |

a) SARS: severe acute respiratory syndrome; b) Pearson chi-square test; c) The differences regarding the total are due to lack of information for the variable.

**Table 4 – Risk factors for death due to COVID-19<sup>a</sup>, Acre, Brazil, 2020**

| Variable                            |               | Crude HR <sup>b</sup> | 95%CI <sup>c</sup> | p-value <sup>d</sup> | Adjusted HR <sup>e</sup> | 95%CI <sup>c</sup> | p-value <sup>d</sup> |
|-------------------------------------|---------------|-----------------------|--------------------|----------------------|--------------------------|--------------------|----------------------|
| Sex                                 | Male          | 1.78                  | 1.49;2.11          | <0.001               | 1.48                     | 1.25;1.76          | <0,001               |
| Age                                 | ≥60 years old | 14.83                 | 12.40;17.73        | <0.001               | 10.64                    | 8.84;12.81         | <0.001               |
| Healthcare professional             | Yes           | 0.17                  | 0.09;0.32          | <0.001               | 0.38                     | 0.20;0.74          | 0.002                |
| Cough                               | Yes           | 1.41                  | 1.18;1.69          | 0.038                | 1.13                     | 0.94;1.36          | 0.945                |
| Sore Throat                         | Yes           | 0.46                  | 0.38;0.56          | <0.001               | 0.48                     | 0.39;0.58          | <0.001               |
| Dyspnea                             | Yes           | 3.98                  | 3.34;4.75          | <0.001               | 4.20                     | 3.44;5.12          | <0.001               |
| Headache                            | Yes           | 0.46                  | 0.37;0.58          | <0.001               | 0.70                     | 0.55;0.89          | 0.002                |
| Myalgia                             | Yes           | 0.53                  | 0.38;0.74          | <0.001               | 0.79                     | 0.56;1.11          | 0.189                |
| Hyposmia/anosmia/hypogeusia         | Yes           | 0.34                  | 0.16;0.71          | 0.002                | 0.67                     | 0.31;1.42          | 0.266                |
| Runny nose                          | Yes           | 0.51                  | 0.32;0.81          | 0.005                | 0.76                     | 0.47;1.23          | 0.331                |
| Multimorbidity                      | Yes           | 4.91                  | 3.92;6.16          | <0.001               | 2.23                     | 1.77;2.81          | <0.001               |
| Heart disease <sup>f</sup>          | Yes           | 1.93                  | 1.36;2.75          | 0.004                | 1.54                     | 1.04;2.29          | 0.030                |
| Diabetes mellitus <sup>f</sup>      | Yes           | 2,69                  | 1,82;3.99          | <0.001               | 1.66                     | 1.07;2.59          | 0.029                |
| Chronic kidney disease <sup>f</sup> | Yes           | 3.15                  | 1.57;6.34          | 0.009                | 1.89                     | 0.91;3.92          | 0.111                |

a) SARS: severe acute respiratory syndrome; b) HR: hazard ratio; c) 95% CI: 95% confidence interval; d) p-value: Wald test; e) Adjusted for the following variables: 'sex', 'age', 'healthcare professional', 'sore throat', 'dyspnea', 'headache', 'hyposmia/anosmia/hypogeusia', 'myalgia', 'runny nose' and 'multimorbidity'; f) Adjusted for the variables among themselves, except for the presence and absence of multimorbidity.

(1.7%) were being treated at home. There was loss to follow-up of 4,952 individuals (20.3%).

Among the positive cases, the majority were female, aged under 60 years and with brown skin color. The percentage of infected health professionals was 8.2%; and public security professionals was 2.8% (Table 1). Regarding the health professionals, 33.2% were nursing technicians, 16.3% were nurses and 9.3% were physicians. With regard to other professions, 9.0% were community health agents, 3.7% were receptionists and 3.0% were endemic control agents, among others.

The highest percentage of positive cases was 38.5%, found in Rio Branco, the state capital of Acre. A considerable proportion of positive cases had three to four signs and symptoms (44.1%), mainly, fever (68.3%), cough (60.5%), sore throat (41.1%), headache (30.5%), dyspnea (29.9%), myalgia (12.5%), diarrhea (7.0%), runny nose (6.2%) hyposmia/anosmia/hypogeusia (4.3%) (Table 2).

Comorbidities were present in 5.9% of the cases. The main one was heart disease (3.3%), followed by diabetes mellitus (1.7%) and chronic respiratory disease (0.7%) (Table 2). Regarding other signs and symptoms, although they are not presented in the table, it is worth mentioning: weakness (3.7%), chills (2.8%), chest pain (1.4%), eye pain (1.0%),

nausea and vomiting (0.7%) and difficulty swallowing (0.6), among others (Table 2).

There was a statistically significant difference between individuals who survived, in relation to those who died, for 'sex', 'age' and 'health professional' variables, and for the following signs and symptoms: cough, sore throat, dyspnea, headache, myalgia, hyposmia/anosmia/hypogeusia and runny nose. The presence of comorbidities was also different between survivors and non-survivors ( $p < 0.05$ ) (Table 3). Among public security professionals, there were no deaths in the period.

The risk factors for death in individuals with SARS due to COVID-19, in adjusted analysis, were male (HR=1.48 -95% CI 1.25;1.76), aged 60 years or older (HR=10.64 -95% CI 8.84;12.81), presence of dyspnea (HR=4.20 -95% CI 3.44;5.12) and comorbidity, especially diabetes mellitus (HR=1.66 - 95%CI 1.07; 2.59) and heart diseases (HR=1.54 -95% CI 1.04;2.29). Symptoms of sore throat and headache, as well as being a health professional, were negatively associated with death (Table 4).

## Discussion

In this study, some conditions were identified as risk factors for death from SARS due to COVID-19, such as:

male, 60 years of age or older, dyspnea, presence of multimorbidity, especially diabetes mellitus and heart diseases; among the symptoms and signs related to better prognosis, the presence of sore throat and headache, as well as being a health professional stood out.

The pandemic began in Acre in mid-March 2020. At that moment, the emergence of COVID-19 in the state, represented an advantage for Acre by allowing more time to plan a regional Public Health response. In addition, the city of Rio Branco has a specialized infectious disease laboratory, which allowed the identification of cases at the beginning of the pandemic. Isolation measures, such as suspension of classes and restriction on non-essential activities, were also implemented early, in order to reduce the impact on the health system. However, these advantages and measures taken did not fully stop the spread of the disease, and deaths were inevitable.

In this study, the profile of infected individuals shows that those at productive age are at higher risk of infection. However, the higher mortality observed in individuals aged 60 years or older corroborates the data obtained in a study with 1,808 COVID 19 cases in the city of Rio de Janeiro, state capital of Rio de Janeiro, where, according to the researchers involved, people aged 30 to 59 years were more frequent among the cases, while individuals aged 60 to 89 years had a higher mortality rate.<sup>8</sup>

Data from SouthKorea<sup>9</sup> and Germany,<sup>10</sup> in turn, showed a high incidence in the second decade of life, an aspect to be considered equally, given that the German study suggested that this age group has played an important role in the spread of the epidemic, even after the implementation of social distancing measures. In Italy, among Intensive Care Unit (ICU) cases, a mean age of 63 years was observed, and only 13.0% were less than 51 years old.<sup>11</sup>

Elderly patients with COVID-19 are more likely to progress to severe disease,<sup>12</sup> although recent studies point out that young people are not free of this condition when they are obese. A study conducted in the United States showed that the prevalence of obesity was nearly 40%, while in China, this condition was 6.2%.<sup>13</sup> In France, a significant association was found between prevalence of obesity and SARS due to severe COVID-19, suggesting that obesity might be a risk factor for severe disease progression and, consequently, a higher risk of ICU admission.<sup>14</sup>

Severe disease involves bilateral interstitial pneumonia, which requires ventilatory support in the

ICU and may progress to acute respiratory distress syndrome (ARDS), with high mortality.<sup>4</sup> In Rio Branco, the prevalence of body mass index (BMI) above 25 kg/m<sup>2</sup> is 48.4% among individuals aged 18 to 39 years, and 62.1% in the age group 40 to 59 years,<sup>15</sup> which also puts the younger population at risk, given that adipose tissue serves as a reservoir for the virus.<sup>16</sup>

It has been shown that health professionals, especially nursing technicians, physicians and nurses are at greater risk of contracting COVID-19 because they are at the forefront of health actions in the face of the pandemic. These professionals in their daily work, risk their lives to save patients with SARS due to COVID-19, despite physical and mental exhaustion, the concern and agony of having to make difficult decisions about patient screening process in health care services, the grief of losing patients, colleagues, friends, and also, the fear of transmitting the infection to their families. The lack of personal protective equipment (PPE) is also a concern<sup>17</sup> and, despite the high infection rate, this study did not find an increased risk of mortality among health professionals. As if this were not enough, the high viral load in the most severe cases, puts the professionals responsible for their care, among the groups at higher risk of infection,<sup>4</sup> in addition to the asymptomatic and presymptomatic transmission that accounted for, respectively, 51.7%<sup>18</sup> and 44.0%<sup>19</sup> of the new infections.

Regarding symptomatic people, the main symptoms observed were: fever and cough; sore throat and dyspnea were also present among them. These findings corroborate a review of 65 articles, according to which, other symptoms such as headache, diarrhea, hemoptysis and runny nose, although less frequent, were also identified;<sup>20</sup> and the most important predictors of COVID-19 infection, loss of smell and loss of taste, were also identified in another study.<sup>21</sup>

Hyposmia is a prevalent symptom in individuals with COVID-19, being more frequent in this disease than in other respiratory tract infections. It has been described as a symptom with a high positive predictive value of coronavirus infection (88.8%) and, also, as the initial symptom in up to 35% of the cases of the disease. It has been associated with less severe cases,<sup>3</sup> as revealed in the cohort of this study.

Among the symptoms reported, regarding the presence of dyspnea, there was a statistical difference between those who died and those who

survived. Dyspnea is reported in severe cases, given that COVID-19 uses the angiotensin-converting enzyme 2 (ACE2) as a receptor, which is widely found in lung, intestinal, kidney and blood vessel tissues. Moreover, this process results in the release of cytokines and consequent damage to pulmonary, renal and cardiac tissues.<sup>21</sup>

Regarding the presence of multimorbidity, it was higher among individuals who died due to COVID-19 in Acre. In New York, United States, a study conducted with 5,700 hospitalized individuals showed that 88.0% had more than one morbidity, the most prevalent were: hypertension (56.6%), obesity (41.7%) and diabetes *mellitus* (33.8%).<sup>23</sup> In China, a study conducted with 1,590 hospitalized people showed that the most prevalent morbidities were hypertension and diabetes, the hazard ratio (95%CI) was 1.79 (1.16;2.77) among individuals with at least one morbidity, and 2.59 (1.61;4.17) among those with two or more morbidities.<sup>24</sup> According to a Brazilian study conducted in the pandemic period up to the 21<sup>st</sup> Epidemiological Week of 2020, diabetes was also more prevalent in individuals hospitalized with SARS due to COVID-19, compared to the general population of the country.<sup>25</sup> The possible explanation for severe conditions in people with diabetes *mellitus* is due to constant glucose recognition by C type lectin receptors, generating greater inflammatory response.<sup>22</sup>

In a study with 1,139 cases and 11,390 controls conducted in Madrid, Spain, researchers observed that renin-angiotensin-aldosterone system inhibitors did not increase the risk of SARS due to severe COVID-19, and the discontinuity of treatment by patients was discouraged. Furthermore, continuous monitoring of these individuals was recommended because the presence of cardiovascular diseases can aggravate pneumonia and may result in unfavorable outcomes.<sup>26</sup>

Among the limitations of this study, it is worth mentioning the use of secondary data obtained from the state epidemiological surveillance, which limited information detailing, especially about the presence or not of hypertension. It is suggested the inclusion of the following variables: 'arterial hypertension', 'anosmia/hyposmia/dysgeusia/ageusia', 'myalgia', 'sore throat', 'headache', 'runny nose' and 'diarrhea', in the e-SUS VE questionnaire, in order to better support future studies. Other possible limitations of the study are (i) information quality, dependent on the complete and correct completion of the e-SUS VE notification form, and (ii)

underreported cases. However, the use of this database allows to trace the profile of severe cases of SARS due to COVID-19, fundamental in times of pandemic.

Another point to be considered is the self-report of multimorbidity, which may result in underreporting and underestimation of the strength of association with adverse outcomes. It should be remembered that self-report of chronic diseases is widely used, and that such information was obtained by health professionals. Further studies are needed to explore the theme, using primary data sources and having a longer follow-up time. Finally, the reduced number of deaths resulted in wide confidence intervals, requiring caution in the analysis of the data.

The long-term follow-up stands out as the strong point of this study, with assessment of 'cure' and 'death' outcomes. In addition, the study was conducted in a state in the Northern region of Brazil, with a population whose laboratory diagnosis for COVID 19 and notification of the disease were performed via the e-SUS VE/SIVEP-Gripe, being followed up for case closure and identification of health outcomes. The choice of the type of study and the sample size, in times of pandemic, reinforces its importance, insofar as work subsidizes knowledge about the reality of states that are far from the large urban centers in the country, enabling the identification of regional risk factors for death due to COVID-19.

Taking these results, it can be concluded that the study analyzed the epidemiological characteristics and risk factors for death in individuals diagnosed with SARS due to COVID-19 in the state of Acre. Risk groups need special attention, especially the elderly, patients with dyspnea and those with diabetes mellitus. Some symptoms were more frequent in mild cases of COVID-19 and should be better elucidated in future studies.

### Authors' contributions

Prado PR, Gimenes FRE, Lima MVM and Soares CP collaborated with the conception and design of the manuscript, data analysis and interpretation and drafting the first version of the manuscript. Prado VB and Amaral TLM collaborated with data analysis and interpretation, and critical reviewing of the manuscript. All authors have approved the final version of the manuscript and have declared themselves to be responsible for all aspects of the work, including ensuring its accuracy and integrity.

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