Covid-19 among the Brazilian Amazon indigenous people: factors associated with death

Covid-19 entre indígenas na Amazônia brasileira: fatores associados ao óbito[1]

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Abstract

This case-control study paired by gender and age analyzes factors associated with the death of indigenous people from COVID-19 in the state of Amapá, Brazil. Data were collected from a public secondary database produced by the Amapá State Department of Health. Cases (n=29) were deaths of indigenous people from COVID-19 and controls were cures of the disease (n=87), recorded between April 2020 and January 2021. Data from individuals with active disease were excluded. Univariate analysis followed by multiple logistic regression were performed to study the independent variables associated with death. Most cases of death were women (51.7%), without comorbidities (62.1%), residing in cities of the Metropolitan Region of Macapá (RMM) (65.5%) and in urban areas (89.7%). Median age of the death group was 72 years (interquartile range=21.5). The final multiple model showed that indigenous individuals with cardiovascular comorbidity had a 4.01 times greater chance (95% confidence interval - 95% CI=1.05-15.36) of death by COVID-19 when compared with indigenous people without comorbidities. And that indigenous people residing in the RMM had a 2.90 times greater chance (95%CI = 1.10-7.67) of death when compared with indigenous residing in the countryside.

Keywords: Health of Indigenous Peoples; Ethnicity and Health; Coronavirus Infections; Comorbidity; Case-Control Studies.

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Resumo

Este estudo objetiva analisar fatores associados ao óbito de indígenas pela covid-19 no estado do Amapá, Brasil. Trata-se de um estudo caso-controle emparelhado por sexo e idade, que utilizou um banco de dados secundários público, produzido pela Secretaria de Estado da Saúde do Amapá. Os casos (n=29) foram óbitos de indígenas pela covid-19 e os controles foram curas da doença (n=87), registrados entre abril de 2020 e janeiro de 2021. Dados de indivíduos com doença ativa foram excluídos da análise. Foram realizadas análises univariadas seguidas por regressão logística múltipla para estudo das variáveis independentes associadas ao desfecho de óbito. A maioria dos casos de óbito era do sexo feminino (51,7%), sem comorbidades (62,1%), residentes em municípios da Região Metropolitana de Macapá (RMM) (65,5%) e em área urbana (89,7%). A mediana das idades do grupo de óbitos foi de 72 anos (intervalo interquartil= 21,5). O modelo múltiplo final demonstrou que indígenas com comorbidade cardiovascular apresentaram chance 4,01 vezes (intervalo de confiança de 95% - IC 95%= 1,05-15,36) maior de óbito pela covid-19 quando comparados a indígenas sem comorbidades. E que indígenas residentes na RMM apresentaram chance 2,90 vezes (IC 95%= 1,10-7,67) maior de óbito quando comparados aos indígenas residentes no interior do estado Amapá.
Palavras-chave: Saúde de Populações Indígenas; Origem Étnica e Saúde; Infecções por Coronavírus; Comorbidade; Estudos de Casos e Controles.

Introduction

The pandemic of COVID-19, a disease caused by the new coronavirus (SARS-CoV-2), is a major threat to the Brazilian indigenous population, especially people and communities with less contact with urban society that are mainly located in rural and isolated areas in the Amazon region (Ferrante et al., 2020; Hallal et al., 2020; Rodrigues; Albertoni; Mendonça, 2020). In Brazil, indigenous people suffer from historical socioeconomic vulnerability and political attacks against their rights. In the context of COVID-19, indigenous people may be further exposed due to socioeconomic and/or sociodemographic aspects, which may represent potentially higher level of infection in this population (Ferrante et al., 2020; Hallal et al., 2020; Rodrigues; Albertoni; Mendonça, 2020).

Indigenous vulnerability to SARS-CoV-2 is indicated by the high prevalence of antibodies against SARS-CoV-2. In Brazil, indigenous people presented a prevalence of antibodies 4.5 times higher than white individuals (Hallal et al., 2020). In the United States, a similar relationship was identified: American Indians and Alaska Natives were 3.5 times more likely to be diagnosed with COVID-19 than non-Hispanic whites (Burki, 2021). In addition, high rates of COVID-19 infection and mortality were found among indigenous groups when compared to general populations (Burki, 2021; Hallal et al., 2020; Santos et al., 2020b). In Brazil, this difference is partially related to the historical challenges in the access to health services by indigenous people, leading to higher rates of general mortality and mortality in children/adolescents belonging to this population when compared to non-indigenous people (Campos et al., 2017; Santos et al., 2020a).

In Brazil, most indigenous people are located in Brazil's Legal Amazon, the largest part living in rural areas, villages and indigenous communities (IBGE, 2021a). This region is one of the most affected by SARS-CoV-2 in the country (Baqui et al., 2020; Hallal et al., 2020; Santos et al., 2020b), especially the most vulnerable populations living along the Amazon River (Hallal et al., 2020).

COVID-19 incidence and mortality rates among Brazilian indigenous people were 60.0% and 42.0%, respectively, higher in the Amazon region when compared to national indigenous rates, in period from February 26, 2020 to August 28, 2020 (Santos et al., 2020b).

In the State of Amapá, by March 2021, 5.9% of all confirmed cases of COVID-19 were among indigenous people (SESA, 2021), although this population represents only 1.1% of the total population of Amapá (IBGE, 2021a). This high level of infection, which in some cases results in the death of indigenous leaders and elders, can jeopardize the existence of secular traditional cultures (Palamim; Ortega; Marson, 2020; Ferrante et al., 2020). This scenario of priceless sociocultural losses was also seen among American Indians and Alaska Natives (in the United States) (Burki, 2021), highlighting the importance of epidemiological studies assessing these populations and factors associated with the outcomes of this disease.

According to the current literature about COVID-19 in the world, some individual and environmental factors have already been strongly related to the outcome of COVID-19 in the general population, such as advanced age, male patients, presence of comorbidities, and living in neighborhoods of low social development (Cobre et al., 2020; Li et al., 2021; Starke et al., 2020). However, so far, no published study has assessed potential factors associated with the outcome of death by COVID-19 in the Brazilian indigenous population.

Although ecological studies have investigated the mortality and lethality of COVID-19 among indigenous people by region of Brazil (Santos et al., 2020b), the low frequency of deaths in this population, when compared to the general population, made it difficult to include indigenous people in individual studies assessing the general population (Baqui et al., 2020). For example, in the study conducted by Escobar, Rodriguez, and Monteiro (2020), who investigated characteristics related to death in the general population of the State of Rondônia, only 12 of 1,020 deaths caused by COVID-19 were of indigenous people (Escobar; Rodriguez; Monteiro, 2020), while in the study by Baqui et al. (2020), who analyzed variations in COVID-19 mortality according to race/ethnicity and other factors in Brazil, indigenous people were excluded from the analysis due to the small number of deaths (5 of 3,328 deaths) (Baqui et al., 2020).

Considering the above, this study aimed to analyze factors associated with death of indigenous people by COVID-19 in the State of Amapá.

Methods

Study site

The State of Amapá, located on the left margin of the Amazon River, is part of Brazil's Legal Amazon. In 2020, it had around 860,000 inhabitants, a population density of 6.0 inhabitants per square kilometer (km^2) and 16 municipalities. It has a metropolitan region, which covers the municipalities Macapá (capital), Santana, and Mazagão (Metropolitan Region of Macapá – RMM), and has a population density of approximately 31.0 inhabitants per km^2 (IBGE, 2021b).

Most municipalities in the countryside of the state present low socioeconomic and health indicators and show relevant development contrasts with the RMM, especially in terms of per capita income (Cunha et al., 2021). Although the RMM concentrates about 76.4% of the total population of Amapá and presents better indicators when compared to the countryside, the capital has significant deficiencies in the medical-hospital structure, a low technical-scientific density, and a relevant context of socio-spatial segregation (Barbosa, 2013; Cunha et al., 2021; IBGE, 2021b). It is also one of the urban areas most affected by SARS-CoV-2 in Brazil (Hallal et al., 2020).

Amapá has nine indigenous ethnic groups (Karipuna, Palikur, Galibi Marworno, Galibi Kalinã, Apalay, Waiana, Tiriyó, Kaxuyana, and Waiãpi), which constitute a population of around 10,000 individuals, according to the most recent survey conducted by the Amapá State Government (Amapá, c2015). In the latest national census, about 80.0% of the indigenous population in Amapá lived in indigenous lands or rural/isolated areas (IBGE, 2021a). By the 13th epidemiological week of 2021, Tiriyó and Karipuna were the most affected groups in terms of absolute number of COVID-19 cases reported among the indigenous ethnic groups in Amapá, with 206 and 195 cases, respectively. These combined numbers represented around 45% of the total number of indigenous cases reported in the state (SESA, 2021).

Study design and source of data/variables

This observational case-control study, paired by gender and age, analyzed secondary public data from the COVID-19 Portal database of the State of Amapá, produced by the Amapá State Health Department (SESA) (SESA, 2021). This database was created by SESA with the beginning of the SARS-CoV-2 pandemic in the state and is periodically updated with the following information: (1) new confirmed COVID-19 cases in the state; (2) update on the evolution (clinical outcome) of previously confirmed cases. COVID-19 data analyzed in this study were reported between April 2020 (14th epidemiological week of 2020) and January 2021 (3rd epidemiological week of 2021) in the State of Amapá. Cases and controls were confirmed for COVID-19 through rapid antigen testing, rapid antibody testing, or real-time polymerase chain reaction (SESA, 2021).

In case-control studies, pairing by gender and age is used to control the potential for confounding/interaction of variables related to the outcome in previous studies/analyses (Hosmer; Lemeshow; Sturdivant, 2013). This study design (paired case-control) is not necessarily conditioned to the development/follow-up of a cohort, and can be developed using a secondary database (Kainoh et al., 2021). In our study, in order to apply a pairing method, we took into account the preliminary analysis of the database from which cases and controls were extracted (Supplementary Tables 1, 2, 3, and 4), the rarity of the event of interest (indigenous deaths by COVID-19 in the State of Amapá) (Supplementary Table 1), and the relationship of events of interest by degree of freedom (DoF) in a multiple logistic regression model, in addition to the robust literature about the potential for statistical confounding or interaction of these variables (gender and age) with the outcome of COVID-19 and the prevalence of comorbidities (Borges; Crespo, 2020; Huang; Lim; Pranata, 2020; Starke et al., 2020).

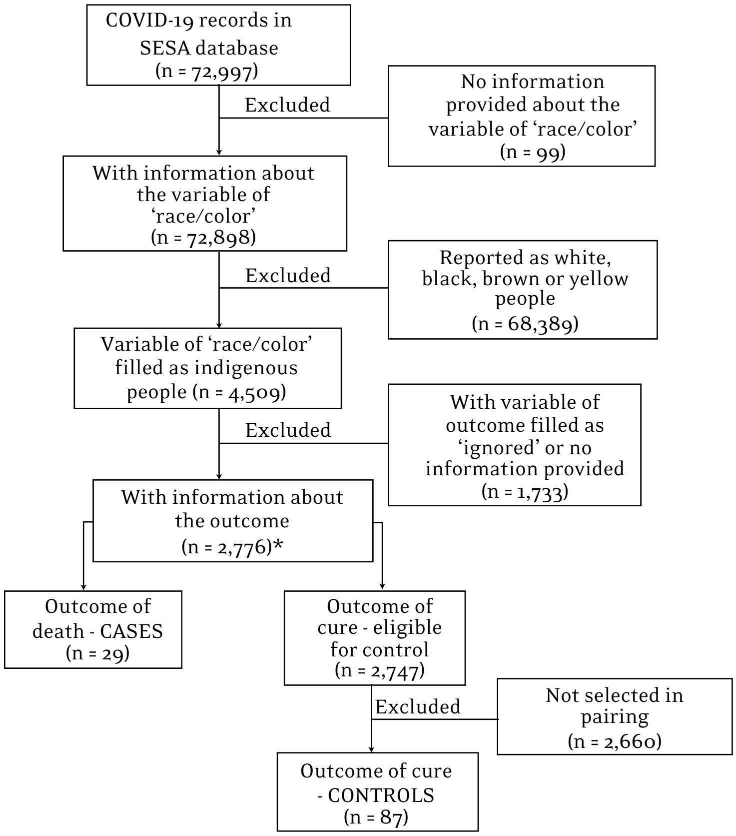
This way, data were selected from individuals with COVID-19 according to their 'race/color,' exclusively for indigenous people. Then, COVID-19 cases were screened according to the clinical outcome (dependent variable), dividing into a group of deaths (cases/events of interest) and a group of cures (controls). Then, all possible exposure variables (independent variables) existing in the database were observed and pairing of cases and controls was performed.

Inclusion and exclusion criteria

Of total 72,997 records of patients with COVID-19 in the database, 72,898 had information about the variable 'race/color.' Of these, 4,509 were indigenous. Of total 4,509 records of indigenous patients with COVID-19, 1,733 had the variable 'clinical outcome' as 'ignored' or not filled in, so they were excluded from the analysis. Then, a control was made due to a bias of undersized relative frequency of the event of interest (death), since possible active cases of the disease, which could progress to death, were not included in the analysis. Then, data from 2,776 indigenous people (residents in Amapá) with a defined COVID-19 outcome were selected, who were eligible for this analysis. Of these, 29 were included because they had an outcome of death from COVID-19 (event of interest) and 2,747, who had an outcome of cure, were eligible for the control group (Figure 1).

Considering that a higher number of controls per case can reduce the errors of the logistic regression coefficients, the largest possible number of paired controls were included for each case. Due to the low amount of data about elderly individuals among all 2,747 individuals eligible for the control group, this proportion was limited to 3 controls for each case. Of note, (1) the selection of controls, when not limited by the number of eligible individuals, was randomly performed by means of an electronic picker; (2) all 87 controls were different individuals (Figure 1).

Figure 1 – Flowchart of data selection of cases (deaths) and controls (cures). State of Amapá, Brazilian Amazon, April 2020 to January 2021.



*Supplementary analyses of data of these individuals are presented in Supplementary Tables 1, 3, and 4; SESA: Amapá State Health Department.

Variables and statistical analysis

The dependent variable of 'clinical outcome' was adapted from the original form of the database; it was dichotomized, excluding active cases of the disease from the analysis and transforming it into a binary outcome (death or cure). The independent variables of 'individual's region of residence' (Metropolitan Region of Macapá – RMM; municipalities in the countryside), 'place of residence' (indigenous village; urban area/others), and 'comorbidity' (cardiovascular comorbidity only, including arterial hypertension; other comorbidities; no comorbidity) were also adapted and categorized.

Categorical variables were submitted to the chi-square test of independence (χ^2), or Fisher's exact test in cases when the expected frequency of at least one of the cells was below five. Variables presenting p-value ≤ 0.20 were selected for the regression analysis. First, univariate logistic regression was performed for each selected variable. After univariate regression, the potential for confounding/interaction of independent variables was analyzed in two different ways: (1) Mantel-Haenszel chi-square test and Cochran-Mantel-Haenszel stratified analysis; (2) analysis of all possible combinations of multiple models to check for relevant changes in the estimators.

Then, a multiple logistic model was built. The independent variables were ordered in ascending order, according to the p-value in the univariate regression. To define the best multiple model, the backward method (Wald) was used, as well as the potential for confounding of the variables, the Omnibus Tests of Model Coefficients (OTMC), the Hosmer-Lemeshow test, the agreement analysis (C-statistic – area under the ROC curve), and an adequate relationship between the number of events of interest and the DoF. Multicollinearity analyses were performed by assessing the variance inflation factor (VIF) (Hosmer; Lemeshow; Sturdivant, 2013).

Then, odds ratio (OR) values and their respective 95% confidence intervals (95% CI) were obtained, considering a significance level of p-value ≤ 0.05 in the Wald test. The analyses were performed with the Statistical Package for the Social Sciences® 20.0.

The variables of gender (male and female) and age (in years) were used in the case-control pairing, and this analysis was performed to demonstrate a non-association with the outcome after pairing. Gender was analyzed by χ^2, and the continuous variable of age was assessed by the Wilcoxon-Mann-Whitney test, which was preceded by the Kolmogorov-Smirnov test for normal distribution and the Levene test for homogeneity of variances.

Ethical aspects

This study exclusively used aggregated secondary data of open access extracted from the COVID-19 Portal of the State of Amapá, a public platform developed by the Amapá State Health Department[2].

These data do not allow the patient identification. Then, no authorization was required from the institution to use the data due to its public and open nature. Also, following the recommendations in art. 1, Resolution #510 of 2016 issued by the Brazilian National Council of Ethics in Research (CNPb) and in accordance with Resolution #466 of 2012 of the CNPb, this study did not have to be submitted to a Research Ethics Committee for approval.

Results

In total, 29 events of death from COVID-19 and 87 controls (cure from COVID-19) were analyzed, as indicated in Figure 1. Most deaths (cases) were female (51.7%), living in the RMM (65.5%), in urban areas (89.7%), and without comorbidity (62.1%) (Table 1). Table 2 shows the descriptive statistics of ages (in years) of cases and controls.

Table 1 — Distribution according to the outcome of COVID-19 (death or cure) among indigenous people, based on sociodemographic characteristics and comorbidities. State of Amapá, Brazilian Amazon, April 2020 to January 2021 (n=116).[2]

Variable (n)	Outcome		Total (%)	p-value
	Death (%)	Cure (%)		
Total (n=116)	29 (100)	87 (100)	116 (100)	– – –
Gender (n=116)				
Male	14 (48.3)	42 (48.3)	56 (48.3)	0.999[a]
Female	15 (51.7)	45 (51.7)	60 (51.7)	
Region of residence (n=116)				
Macapá Metropolitan Region	19 (65.5)	28 (32.2)	47 (40.5)	0.002[a]
Countryside	10 (34.5)	59 (67.8)	69 (59.5)	
Place of residence (n=115)*				
Urban area/other	26 (89.7)	64 (74.4)	90 (78.3)	0.118[a]
Indigenous village	3 (10.3)	22 (25.6)	25 (21.7)	
Comorbidity (n=116)				
Cardiovascular[¶]	6 (20.7)	5 (5.7)	11 (9.5)	0.006[b]
Other comorbidities	5 (17.2)	5 (5.7)	10 (8.6)	
None	18 (62.1)	77 (88.5)	95 (81.9)	

[a]: Chi-square test; [b]: Fisher's Exact Test; *: Variable with no information in the database for one individual; [¶]: Including arterial hypertension.

2 The database used in this study can be accessed here: <http://painel.corona.ap.gov.br/>.

Table 2 — Descriptive statistics of ages (in years) of indigenous people, according to clinical outcome (death or cure) of COVID-19. State of Amapá, Brazilian Amazon, April 2020 to January (n=116).

Total n = 116				Cases (deaths) n = 29				Controls (cures) n = 87				p-value[ǀ]
Percentile			IQR	Percentile			IQR	Percentile			IQR	
25%	50%[£]	75%		25%	50%[£]	75%		25%	50%[£]	75%		
59.0	72.0	79.0	20.0	58.0	72.0	79.5	21.5	59.0	72.0	79.0	20.0	0.913

[ǀ]: Wilcoxon-Mann-Whitney test (cases vs controls); [£]: 50% percentile corresponds to median; IQR: interquartile range.

The variables of 'comorbidity,' 'region of residence,' and 'place of residence' were submitted to univariate logistic regression. In the multiple analysis, 'comorbidity' and 'region of residence' remained in the final model, showing statistical significance in at least one category. 'Place of residence' did not show statistical significance in the univariate analysis and, when included in the multiple model, it did not act as a confounding variable and did not improve the C-statistic (Table 3). The OTMC and the backward method (Wald) showed the model with the variables of 'region of residence' and 'comorbidity' was superior to the model with the three independent variables.

Table 3 — Logistic regression analysis to study the factors associated with the death by COVID-19 of indigenous people. State of Amapá, Brazilian Amazon, April 2020 to January 2021 (n=116)

Variable (n)	DoF	Univariate regression			Multiple regression[ǀ]		
		OR	95% CI	p-valor	OR	95% CI	p-valor
Region of residence (n=116)							
RMM	1	4.00	1.65 — 9.73	0.002	2.90	1.10 — 7.67	0.031
Countryside		1.00	–––	–––	1.00	–––	–––
Place of residence (n=115)*							
Urban area/other	1	2.98	0.82 — 10.81	0.097			
Indigenous village		1.00	–––	–––			
Comorbidity (n=116)							
Cardiovascular[¶]	2	5.13	1.41 — 18.70	0.013	4.01	1.05 — 15.36	0.042
Other comorbidities		4.28	1.12 — 16.36	0.034	2.82	0.63 — 12.71	0.177
None		1.00	–––	–––	1.00	–––	–––

[ǀ]: C statistic = 0.71; RMM: Macapá Metropolitan Region; *: Variable with no information in the database for one individual; DoF: Degree of freedom; OR: Odds ratio; 95% CI: 95% confidence interval; [¶]: Including arterial hypertension.

In the multiple model, indigenous people who had cardiovascular disease were 4.01 times more likely (95% CI=1.05-15.36) to die from COVID-19, when compared to indigenous people who had no comorbidity. In addition, indigenous people living in the RMM were 2.90 times more likely (95% CI=1.10-7.67) to die when compared to indigenous people living in the countryside of the state (Table 3). Regarding the model, the results of the multicollinearity analysis were satisfactory (variable with the highest VIF = 1.1), the ratio of events of interest by DoF was 9.67, C-statistic (area under the ROC curve) was 0.71, and the p-value in the Hosmer-Lemeshow test was 0.849.

Discussion

In this study, 29 deaths by COVID-19 among indigenous people (cases - events of interest) were identified in the State of Amapá between April 2020 and January 2021. Most of them were of old age. In addition, indigenous people with cardiovascular comorbidity had a greater chance of death from COVID-19, as well as indigenous residents in the RMM.

The situation of Brazilian indigenous people in the COVID-19 pandemic is a reason for concern in the perspective of collective health due to socioeconomic and/or environmental vulnerability, which synergistically cannot subject these individuals to SARS-CoV-2 (Ferrante et al., 2020; Horta et al., 2020; Hallal et al., 2020; Rodrigues; Albertoni; Mendonça, 2020). Historically, in Brazil, the indigenous population has worse epidemiological indicators of general and infant mortality when compared to the non-indigenous population (Campos et al., 2017; Santos et al., 2020a). During the pandemic in the state of Amapá, a discrepancy was also observed in mortality from COVID-19 between indigenous and non-indigenous people. Based on data from SESA, by January 2021, the cumulative mortality from COVID-19 among indigenous people was about 2.9 deaths/1,000 indigenous people, while among non-indigenous people it was about 1.1 deaths/1,000 non-indigenous people (IBGE, 2021b; SESA, 2021).

Among the possible explanations for this context is the progressive process of dissolution of indigenous culture. This process, caused by several factors, is marked by the transition from rural or isolated to urban areas, which can lead to a rupture of ties between an indigenous person and his/her traditions and beliefs, since, for the indigenous people, their territory represents much more than a geographic space. The result of this process may often be a greater exposure to the context of peripheralization, poverty, violence, racism, and reduced access to health services and general sanitation, in large/midsize cities, which are marked by exclusionary urbanization, as is the case of Macapá (Barbosa, 2013; Everaldo; Coimbra; Santos, 2000; Paula, 2014; Palmquist, 2018). In the COVID-19 pandemic, this scenario of peripheralization in metropolitan regions may be related to delayed diagnosis, especially in capitals in the North region of Brazil, and a greater chance of death from the COVID-19 (Cobre et al., 2020; Lima et al., 2021).

In Brazil, especially in large/midsize urban centers in the Amazon, the seroprevalence of SARS-CoV-2 is higher in indigenous people when compared to non-indigenous people (Hallal et al., 2020). In this scenario, the RMM, which presents an excluding urbanization process, insufficient and poorly distributed medical-hospital structure (Barbosa, 2013; Cunha et al., 2021), and the highest density of people per household among the metropolitan regions of the country (IBGE, 2019), had one of the highest seroprevalences of SARS-CoV-2 in Brazil in a study conducted by Hallal et al. (2020).

In addition, by the 13th epidemiological week of 2021, the RMM had a cumulative mortality of COVID-19 in the general population (1.62 deaths/1,000 inhabitants) about 60% higher than the countryside (1.01 deaths/1,000 inhabitants) (IBGE, 2021b; SESA, 2021). This scenario is consistent with the result of our study. The chance of death by COVID-19 among indigenous people living in the RMM is higher than that of those living in the countryside. Also, socioeconomic factors may be involved, as is the case with American Indians and Alaska Natives (Burki, 2021). In addition, the study by Gershengorn et al. (2021), conducted in the United States, showed that greater chances of hospitalization due to COVID-19 of ethnic minorities are possibly mediated by local population density, income, and family size (Gershengorn et al., 2021).

In this sense, the study by Cobre et al. (2020) conducted in the City of Rio de Janeiro, found that individuals from the general population living in neighborhoods with low social development were more likely to have a delayed diagnosis. In addition, they found that individuals with a time interval between the first signs/symptoms and diagnosis longer than 8 days had a greater chance of death (Cobre et al., 2020). Then, better social conditions favor the access to health services and diagnosis of COVID-19, which can reduce the time interval until diagnosis and, therefore, speed up the start of supportive care, which could reduce the chance of death (Gershengorn et al., 2021; Cobre et al., 2020).

This situation highlights the importance of the Indigenous Health Care Subsystem (SasiSUS). One of the main tasks of this subsystem is to promote and protect the health of indigenous people in their lands and territories, with a focus on sanitation and primary health care measures, in addition to observing and respecting sociocultural, demographic and epidemiological specificities inherent to the people served (Brasil, 2002).

The Indigenous Health Special District of Amapá and Northern Pará (DSEI-ANP) is responsible for the indigenous people in the State of Amapá. The structure of the DSEI-ANP has Base Centers and basic health units located in indigenous lands, in addition to two Casas de Saúde do Índio (CASAIs) in the urban areas of the municipalities of Macapá and Oiapoque (Brasil, 2002; IEPÉ, 2021). Among the main tasks of the CASAIs are the reception, support and health care for indigenous people referred from basic indigenous health units/Base Centers located in indigenous lands, for more complex health services in municipalities of reference from the Brazilian National Health System (SUS) (Brasil, 2002).

Then, the integration of SasiSUS in its context of action in indigenous lands and urban areas is clearly seen, in addition to its connection with the SUS network. The actions of the DSEI-ANP, with the support of other institutions, proved to be essential for controlling outbreaks of COVID-19 among indigenous people. Examples of actions and measures are sanitary barriers in indigenous lands and surrounding areas, provision of personal protective equipment (PPE), support for safe return of indigenous people from urban areas to their villages, early diagnosis (rapid tests), among other sanitary measures of mitigation (IEPÉ, 2021).

In addition, during the pandemic, many primary health care facilities located in indigenous lands received help and improvements, including training of multidisciplinary indigenous health teams to handle cases of COVID-19, increased inventory of supplies and expansion of infrastructure to improve the isolation of patients, and provision of care to moderate cases of COVID-19 (IEPÉ, 2021).

This scenario of care and protection can sometimes be different from that experienced by indigenous people living in the RMM. The public health services of the RMM were overloaded during the study period. For instance, CASAI in Macapá, despite the improvements to provide care for COVID-19, has a history of challenges to meet high demands (Brasil, 2014; IEPÉ, 2021; SESA, 2021). Then, it may be one of the facts justifying a higher chance of death of indigenous living in the RMM.

In addition to the differences in health care and social support received by indigenous people living in the countryside when compared to those in the RMM (IEPÉ, 2021; IEPÉ, 2020), it is necessary to highlight some spatial and demographic aspects of Amapá. About 76% of the total population of the state live in the RMM (IBGE, 2021), where the only airport with commercial flights in the state is located. In addition, Amapá has no land (road) connection with the rest of Brazil. These aspects, combined with the actions of the DSEI-ANP, may have been important to reduce the flow of people and, consequently, the infection by SARS-CoV-2, particularly in some more distant municipalities from the RMM and indigenous villages of difficult access (IEPÉ, 2021).

In this context, of all 13 municipalities in the state that are not part of the RMM, Oiapoque is about 600 kilometers from the RMM, located on the border between Brazil and French Guiana (IBGE, 2021b). Oiapoque has one of the largest indigenous population among Brazilian municipalities and part of its territory is located in the Montanhas do Tumucumaque National Park (IBGE, 2021a; IBGE, 2021b).

Since the beginning of the pandemic, Oiapoque has been an area of great epidemiological concern due to its large indigenous population, the presence of illegal gold mining, the international border, and the difficult access to the capital, Macapá (IBGE, 2021b; IEPÉ, 2021, 2020). However, despite the high number of COVID-19 cases among indigenous people in Oiapoque, mortality and lethality were not as high as in the RMM from April 2020 to January 2021 (IEPÉ, 2020; IBGE, 2021a; SESA, 2021). Among the possible reasons are improvements in health services in indigenous lands and health actions and measures adopted by the DSEI-ANP and partner institutions (IEPÉ, 2021, 2020).

Although Oiapoque was not directly included in the results of our study, this municipality has one of the highest numbers of COVID-19 cases among indigenous people in Amapá (SESA, 2021), showing the importance of active protection and continuous epidemiological monitoring in the Oiapoque region.

The present study showed, after pairing by gender and age and adjustment for region of residence, that indigenous people with cardiovascular comorbidity have a higher chance of death due to COVID-19 when compared to indigenous people without comorbidities. Several studies assessing the general population corroborate this finding (Li et al, 2021). Among the pathophysiological reasons are direct and indirect damage processes of COVID-19 in the cardiovascular system (CVS) (Adu-Amankwaah et al., 2021). Direct damage results from reduced regulation of angiotensin-converting enzyme 2 (ACE-2) in the CVS, as it is internalized after binding to the Spike protein of SARS-CoV-2. It reduces the protective effects of ACE-2 for the CVS. Indirect damage is related to respiratory failure, which affects the CVS function by inducing hypoxemia, oxidative stress, acidosis, and other effects. Together, direct and indirect damage caused by SARS-CoV-2 and the chronic damage inherent to cardiovascular comorbidity enable and enhance CVS disease (Adu-Amankwaah et al., 2021).

Cardiovascular comorbidities and arterial hypertension are highly prevalent in Amapá and Brazil (Borges; Crespo, 2020). In our study, CVS comorbidities (including hypertension) were more frequent among indigenous people who had a death outcome. A consistent result was observed in a previous study with the general population of Amapá (Silva et al., 2020). In a study by Silva et al. (2020) that assessed the general population of the state, the lethality of COVID-19 in individuals with cardiovascular comorbidity (including hypertension) was 15.2%, about 6.5 times higher than the general lethality of the study (Silva et al., 2020).

The meta-analysis conducted by Li et al. (2021) showed important differences in OR found by studies, with statistical significance in the analysis of association between the presence of cardiovascular comorbidity (including arterial hypertension) and death from COVID-19 in the general population. ORs described for this variable were between 3.75 (95% CI = 1.48-9.49) in a study with 904 individuals, and 1.28 (95% CI = 1.03-1.59) in a study with 90 individuals (Li et al., 2021), lower than the OR values found in our study. Also, our study had a relevant OR adjustment of the variable 'comorbidity' in the multiple analysis for the variable 'region of residence,' and one of the categories of the variable 'comorbidity' lost statistical significance in relation to the univariate analysis. One explanation is the higher prevalence of comorbidities among indigenous people living in the RMM in relation to those living in municipalities in the countryside of Amapá.

A relevant aspect regarding the descriptive results of our study was the old age (median=72 years; IQR=21.5) of the indigenous people with a death outcome. Based on their age, many can be considered elders, i.e., individuals who are possibly guardians of languages, stories and other sociocultural aspects of traditional indigenous cultures that are often transmitted orally by these individuals (Palamim; Ortega; Marson, 2020; Ferrante et al., 2020). A similar situation is experienced by American Indians and Alaska Natives who, with the expansion of the pandemic, have already lost many elders (Burki, 2021).

In our study, pairing of cases and controls by gender and age minimized the influence of these variables in the analysis, without having to include them in the model, either by association with outcome or for adjustment (Hosmer; Lemeshow; Sturdivant, 2013). Some studies had reported challenges in measuring the actual influence of these factors on the outcome of COVID-19 in the general population (Huang; Lim; Pranata, 2020; Starke et al., 2020). It can be even more difficult when analyzing only cases among the indigenous population living in a Brazilian state, due to the low absolute frequency of events.

Meta-analysis and meta-regression studies have observed this challenge may be related to statistical confounding/interaction between the variables 'comorbidity' and 'age' for the outcome (death or cure) of COVID-19 (Huang; Lim; Pranata, 2020; Starke et al., 2020), besides the possible confounding/

interaction between the variables 'gender' and 'age' for the outcome of 'comorbidity' (having it or not) (Borges; Crespo, 2020). In the previous analysis of data from the population of our study (n=2,776), a considerable potential for confounding/interaction was also found (Supplementary Tables 2 and 3), which reinforced the use of pairing, since including an 'interaction variable' in the modeling performed in our study would greatly reduce the ratio of events of interest in relation to DoF. Then, in this study, pairing by gender and age was the best way to control these variables.

In this sense, in our study, this ratio was 9.66 events in relation to DoF in the final multiple model, which is considered adequate. C-statistic of the model was 0.71, which indicates a satisfactory agreement between the estimated chance of the model and the observed data and, together with the *p*-value from the Hosmer-Lemeshow test, it demonstrates good model calibration, especially when considering the inclusion of only two independent variables.

Of note, the logistic modeling method of inserting all or almost all clinically or intuitively relevant variables in the model, regardless of the *p*-value, is widely used in epidemiology. However, besides subjectivity, one of the main problems of this type of approach is overfitting, which was controlled in our study by conservative modeling in terms of number of events per DoF. After all, more independent variables and, therefore, more DoF in the model lead to more standard errors of the model estimators (Hosmer; Lemeshow; Sturdivant, 2013).

This study analyzed data related to the State of Amapá before the COVID-19 vaccination campaign in the state, using an official COVID-19 database. In this sense, although this study does not have variables that are susceptible to recall bias and measures have been adopted to minimize other biases, it is necessary to consider the possibility of errors in notification/database completion. In addition, the data did not allow a stratified analysis of the disease severity, and it was also not possible to categorize the types of cardiovascular diseases or the ethnicity of the individuals or the SARS-CoV-2 variant that caused the infection.

Also, due to the pairing by gender and age, these variables were not included in the multiple analysis of this study, but they were analyzed and presented only to demonstrate the effectiveness of pairing. However, the analysis of these variables (gender and age) was performed in a univariate and/or stratified manner based on all indigenous people with available binary outcome (n=2,776), which is indicated in Supplementary Tables 1, 3, and 4.

Final considerations

This study identified that most deaths of indigenous people due to COVID-19 in Amapá were of elderly individuals, which may be an inestimable sociocultural loss considering the importance of the elders in the context of indigenous cultures in the Amazon. Also, after pairing by gender and age, living in a metropolitan region and presence of cardiovascular comorbidity showed, in the multiple analysis, an association with the outcome of death by COVID-19 among indigenous people in the State of Amapá.

In the context of the COVID-19 pandemic in the Brazilian Amazon, it is important to ensure isolation of indigenous villages, a better monitoring of the situation of indigenous people living in metropolitan regions, maintenance of pharmacological therapy for individuals with comorbidities, attention to the elders, and mainly broad vaccination of the indigenous population, whether in villages or not. Also, although only data from indigenous people living in Amapá were analyzed in our study, this is one of the first individual studies to investigate factors associated with the death of indigenous people in Brazil. In addition, some of the results found, such as the difference in 'metropolitan region versus countryside,' are also observed in studies focused on other states of the Brazilian Amazon.

Thus, further studies could assess different regions of the Amazon, with a higher number of events of interest and independent variables. Also, the development of spatial analyses to study the distribution dynamics of SARS-CoV-2 in Amapá will be relevant, especially in municipalities with large indigenous populations.

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Contribution of authors

Cunha contributed to the conception and design of the article, data analysis and interpretation, and wrote the first version of the manuscript. Nazima and Castilho-Martins contributed to data analysis and interpretation and critically reviewed the manuscript. All authors approved the final version to be published and are responsible for all aspects of the study, also ensuring its precision and integrity.

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Annex 1

Supplementary Table 1 — Distribution of indigenous data according to clinical outcome (death or cure) of COVID-19, sociodemographic characteristics and comorbidity. State of Amapá, Brazilian Amazon, April 2020 to January 2021 (n=2,776)

Variable (n)	Outcome		Total	Gross odds ratio[1]
	Death	Cure		
Total (n=2,776)	29	2,747	2,776	___
Gender (n=2,776)				
Male	14 (a)	1,303 (b)	1,317	1.05
Female	15 (c)	1,444 (d)	1,459	
Age group (n=2,776)				
Up to 64 years	11 (c)	2,572 (d)	2,583	24.05
65 years and older	18 (a)	175 (b)	193	
Region of residence (n=2,776)				
Macapá Metropolitan Region	19 (a)	1,172 (b)	1,191	2.55
Countryside	10 (c)	1,575 (d)	1,585	
Place of residence (n=2,713)*				
Urban area/other	26 (a)	2,218 (b)	2,244	1.82
Indigenous village	3 (c)	466 (d)	469	
Comorbidity (n=2,776)				
Cardiovascular[¶]	6	44	50	___
Other comorbidities	5	86	91	___
None	18	2,617	2,635	___

[1]: (a ÷ c) ÷ (b ÷ d), applicable to 2 × 2 contingency comparisons only; *: Variable with no information in the database for 63 individuals; [¶]: Individuals with cardiovascular comorbidity only (including arterial hypertension).

Annex 2

Supplementary Table 2 — *p*-values from Mantel-Haenszel chi-square test for univariate analysis of independent variables associated with each other and with the outcome (dependent variable). State of Amapá, Brazilian Amazon, April 2020 to January 2021 (n=2,776)

Variable*	Outcome (n=2,776)	Gender (n=2,776)	Age group (n=2,776)	Region of residence (n=2,776)	Place of residence (n=2,713)	Comorbidity (n=2,776)
Outcome (n=2,776)	___	0.928	< 0.001	0.013	0.348	< 0.001
Gender (n=2,776)	0.928	___	0.550	0.565	0.222	0.130
Age group (n=2,776)	< 0.001	0.550	___	0.821	0.543	< 0.001
Region of residence (n=2,776)	0.013	0.565	0.821	___	< 0.001	0.008
Place of residence (n=2,713)	0.348	0.222	0.543	< 0.001	___	0.937
Comorbidity (n=2,776)	< 0.001	0.130	< 0.001	0.008	0.937	___

*: Supplementary Table 1 shows the categorization of variables.

Annex 3

Supplementary Table 3 — Cochran-Mantel-Haenszel stratified analysis, with Mantel-Haenszel conditional independence test, for analysis of statistical interaction between the variables 'age group' and 'comorbidity,' according to the outcome of cure or death by COVID-19 of indigenous people. State of Amapá, Brazilian Amazon, April 2020 to January 2021 (n=2,776)

Comorbidity (n=2,776)			Age group (n=2,776)		Gross OR for stratum[1]	Common OR of M-H	M-H conditional independence test*
			65 years or older	Up to 64 years			
Cardiovascular¶	Outcome (n=50)	Death	4 (a)	2 (b)	3.50	11.58	Chi-square = 58.9 DoF = 1 *p*-value < 0.001
		Cure	16 (c)	28 (d)			
Other comorbidities	Outcome (n=91)	Death	3 (a)	2 (b)	9.25		
		Cure	12 (c)	74 (d)			
None	Outcome (n=2,635)	Death	11 (a)	7 (b)	26.40		
		Cure	147 (c)	2,470 (d)			

OR: Odds ratio; M-H: Mantel-Haenszel; [1] (a ÷ c) ÷ (b ÷ d); *: In this test, *p*-value ≤ 0.05 indicates the Odds ratios are significantly different in strata; ¶: Including arterial hypertension; DoF: degree of freedom.

Annex 4

Supplementary Table 4 — Cochran-Mantel-Haenszel stratified analysis, with Mantel-Haenszel conditional independence test, for analysis of statistical interaction between the variables 'region of residence' and 'comorbidity,' according to the outcome of cure or death by COVID-19 of indigenous people. State of Amapá, Brazilian Amazon, April 2020 to January 2021 (n=2,776)

Comorbidity (n=2,776)			Region of residence (n=2,776)		Gross OR for stratum[1]	Common OR of M-H	M-H conditional independence test*
			RMM	Countryside			
Cardiovascular¶	Outcome (n=50)	Death	5 (a)	1 (b)	5.00	2.28	Chi-square = 3.5 DoF = 1 p-value = 0.062
		Cure	22 (c)	22 (d)			
Other comorbidities	Outcome (n=91)	Death	5	0	–––		
		Cure	45	41			
None	Outcome (n=2,635)	Death	9 (a)	9 (b)	1.37		
		Cure	1,105 (c)	1,512 (d)			

OR: Odds ratio; M-H: Mantel-Haenszel; [1]: (a ÷ c) ÷ (b ÷ d); RMM: Macapá Metropolitan Region; *: In this test, *p*-value ≤ 0.05 indicates the Odds ratios are significantly different in strata; ¶: Including arterial hypertension; DoF: degree of freedom.