doi: 10.5216/rpt.v52i1.73977

ORIGINAL ARTICLE

SPACE-TIME RISK CLUSTERS OF COVID-19 IN A TOURISM AREA IN THE NORTHEASTERN BRAZIL: AN EPIDEMIOLOGICAL OVERVIEW AFTER TWO YEARS OF PANDEMIC

Letícia Pereira Bezerra[1], Rosália Elen Santos Ramos[2], Joyce da Silva Nascimento[3], Laryssa Oliveira Silva[3], Wandklebson Silva da Paz[2], Loane Márzia Lopes Costa[3], Israel Gomes de Amorim Santos[3], Márcio Bezerra Santos[4] and Karina Conceição Gomes Machado de Araújo[4]

ABSTRACT

The world is facing a serious viral infection caused by the new Severe Acute Respiratory Syndrome Coronavirus 2. We aimed to evaluate and map the high-risk clusters of COVID-19 in the State of Alagoas, a touristic area in northeastern Brazil, after two years of pandemic by a population-based ecological study, using COVID-19 cases reported in the State of Alagoas, between March, 2020 and April, 2022. We performed a descriptive and statistical analysis of epidemiological data. We then map high-risk areas for COVID-19, using spatial analysis, considering the incidence rate by municipality. 297,972 positive cases were registered; 56.9% were female and 42.7% aged between 20 and 39 years old. Men (OR = 1.59) and older than 60 years old (OR = 29.64) had a higher risk of death, while the highest incidence rates of the disease occurred in the metropolitan region. Our data demonstrate the impact of COVID-19 in the State of Alagoas, through the two years of pandemic. Although the number of cases were greater among women and young adults, the chance of death was greater among men and older adults. High-risk clusters of the disease initially occur in metropolitan cities and tourist areas.

KEY WORDS: SARS-CoV-2; COVID-19; spatial analysis; Brazil.

1. Aggeu Magalhães Institute/FIOCRUZ. Departament of Parasitology, Recife, PE, Brazil.
2. Federal University of Pernambuco, Department of Tropical Medicine, Recife, PE, Brazil.
3. State University of Alagoas, Department of Biological Sciences, Santana do Ipanema, AL, Brazil.
4. Federal University of Sergipe, Department of Morphology, São Cristóvão, SE, Brazil.

Letícia Pereira Bezerra ORCID: https://orcid.org/0000-0001-6375-633X; Rosália Elen Santos Ramos ORCID: https://orcid.org/0000-0002-9958-9331; Joyce da Silva Nascimento ORCID: https://orcid.org/0000-0002-3941-3705; Laryssa Oliveira Silva ORCID: https://orcid.org/0000-0002-2713-1989; Wandklebson Silva da Paz ORCID: https://orcid.org/0000-0002-2898-2646; Loane Márzia Lopes Costa ORCID: https://orcid.org/0000-0001-8602-422X; Israel Gomes de Amorim Santos ORCID: https://orcid.org/0000-0002-5210-6697; Márcio Bezerra Santos ORCID: https://orcid.org/0000-0001-9962-6537; Karina Conceição Gomes Machado de Araújo ORCID: https://orcid.org/0000-0003-4433-5227

Corresponding author: Letícia Pereira Bezerra. E-mail: pleticia706@gmail.com

Received for publication: 5/9/2022. Reviewed: 22/12/2022. Accepted: 30/1/2023.

INTRODUCTION

The world is currently facing a serious viral infection caused by the new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (WHO, 2022a). The first cases of the disease, named Coronavirus Disease 2019 (COVID-19), were reported as an outbreak of pneumonia in December 2019, in the city of Wuhan, China. Since then, SARS-CoV-2 has spread rapidly throughout the entire World and COVID-19 was declared as a pandemic by the World Health Organization (WHO) in March of 2020 (WHO, 2020). Up to September of 2022, 585,950,085 cases of the disease have been reported in more than 200 countries and more than 6,425,422 deaths worldwide (WHO, 2022b).

Clinically, COVID-19 may present with nonspecific and mild symptoms, or even asymptomatic in most individuals (Brasil, 2020). The most common symptoms reported by the WHO are fever, tiredness, dry cough, headache, sore throat, dyspnea, and changes in taste and smell. Furthermore, the disease can also progress with severity, causing pneumonia, respiratory failure, thrombosis, and death, especially in more vulnerable groups such as the older adults, obese people, and those with coexisting illnesses such as cardiovascular diseases and diabetes (OPAS, 2021; Brasil, 2020).

SARS-CoV-2 has a high transmission capacity and the control of the pandemic has represented one of the greatest challenges in public health for governments and health managers worldwide (Werneck et al., 2020; Andrade et al., 2020; Gomes et al., 2020). Furthermore, the disease can be more severe in areas of greater social vulnerability. Corroborating this, prior studies have shown that the transmission of the virus and the mortality rate by COVID-19 is higher in poorer regions (Silva et al., 2021; Souza et al., 2020a).

Considering that Brazil is among the countries with the greatest social inequality in the World, strategies for controlling the pandemic are even more complex (Werneck et al., 2020). The country has continental dimensions and there are populations living in low-income conditions, with limited access to drinking water or sewage system, and in household clusters, mainly in the slums (Werneck et al., 2020). Notably, the COVID-19 pandemic has been severe in the poorest regions of the country - the North and Northeast (Kerr et al., 2020). Moreover, some States have factors that increase the risk of spreading the virus such as high urban density in metropolitan areas, high number of informal workers, presence of airports with international flow, and touristic areas (Kerr et al., 2020).

Importantly, the use of spatial and temporal analysis tools has greatly contributed to the understanding of the distribution and dynamics of various diseases in space and time (Rebolledo et al., 2018; Lima et al., 2019). Likewise, using spatial analysis tools, some studies have mapped the spatial distribution of COVID-19 in regions of Brazil and identified the areas most affected by the pandemic. Thereby, identifying these spatial clusters can assist in resources and strategies distribution for the disease control in priority areas (Rebolledo et al., 2018; Nascimento et al., 2020).

Alagoas is the State with the lowest human development index (HDI = 0.631) in Brazil (IBGE, 2021). Furthermore, the State has failures in many other socioeconomic indicators such as illiteracy rate, social vulnerability index (SVI), access to drinking water, and sewage system (IBGE, 2021). Regardless of the precarious conditions and due to the idyllic beaches, Alagoas has become one of the main touristic routes in the Northeastern Brazil, receiving visitors from Brazil and even from other countries. Considering the high influx of visitors, and the poverty still prevalent in the State, we aimed herein to assess the epidemiological characteristics, the spatial, and the spatiotemporal patterns of COVID-19 in Alagoas, Northeastern Brazil, between March, 2020 and April, 2022.

METHODS

Study design and area

We conducted an ecological and population-based study, using spatial and spatiotemporal analysis tools. All cases of COVID-19 in the State of Alagoas were included. The spatial analysis units were the 102 municipalities and the 10 health regions (HR) of the State. We excluded from the study those cases lacking the date of the diagnosis or the municipality of residence.

Alagoas is located in the Northeastern Brazil and it corresponds to 0.3% of the national territory, with 27,843 km^2 of extension. Alagoas has an estimated population of 3,351,543 inhabitants, the demographic density is 120.4 inhabitants/km^2, and it is the 17^{th} most populous State in the country. Geographically, the State is divided into 102 municipalities, which are organized into 10 health regions (HR) (Figure 1) (IBGE, 2021).

Data source

For the analysis, we considered all confirmed cases of COVID-19 in the State of Alagoas between March, 2020 and April, 2022. For that, we first collected the data from the Department of Informatics of the Unified Health System (DATASUS), from the Brazilian Ministry of Health, available on the Open-DATASUS platform (http://opendatasus.saude.gov.br/dataset/casosnacionais) and the COVID-19 panel in Brazil (covid.saude.gov.br), together with the data obtained from the COVID-19 epidemiological bulletin in Alagoas. For the spatial and spatiotemporal analysis, we extracted the cartographic mesh of the State of Alagoas, from the website of the Brazilian Institute of Geography and Statistics (IBGE). Information on population per municipality was also obtained from the IBGE website, considering the census population estimate for 2020.

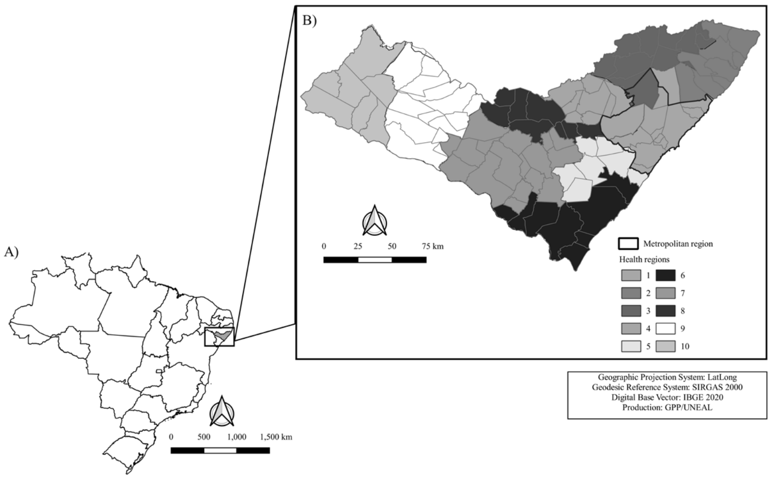

Figure 1. Study area map. A) Map of Brazil, highlighting the State of Alagoas. B) Map of the State of Alagoas, divided into the 10 health regions, and highlighting the metropolitan area.

Variables, measures, and analysis of epidemiological data

For descriptive analysis of the epidemiological characteristics of COVID-19 in the State, we considered the following variables: gender, age group, method of diagnosis, presence and type of comorbidity related to cases and deaths. As the outcome of the study, we considered the incidence rate of the disease per municipality. The incidence rate was calculated considering the number of confirmed cases, divided by the local population of each municipality and the result multiplied by 1,000 inhabitants.

Additionally, we performed association analysis between deaths from COVID-19 with the epidemiological variables: gender and age. Chi-squared test and odds ratio (OR) with 95% confidence interval (CI) were employed to analyze the associations of categorical variables. The significance level was set at 0.05.

Spatial and spatiotemporal analysis of COVID-19 data in Alagoas

First, to better understand the spatial and temporal dynamics of COVID-19 incidence in the State, we have prepared maps which represent the gross incidence rates and related to the period available. Furthermore, we use the Local Empirical Bayesian method to smooth these incidence rates. This method corrects possible random fluctuations in space, and provides greater stability to the rates (Brasil, 2007). The results were represented on choropleth maps, according to the parameters of the incidence rate: low (<3.0/1,000 inhabitants); moderate (3.0 to 8.0); high (8.1 to 13.0); and very high (>13.1).

Thereafter, we applied the Global Moran Index (I) to verify the existence of spatial autocorrelation. This technique identifies the occurrence of spatial patterns in the study area, and presents values ranging from -1 to +1: values close to +1 indicate positive spatial autocorrelation; alternatively, values close to -1 indicate negative spatial autocorrelation; values crossing the zero suggest spatial randomness (Anselin & Bao, 1997; Druck, 2004). Once the existence of positive spatial autocorrelation was identified, we also calculated the Local Indicators of Spatial Association (LISA) index, to evaluate the occurrence of local autocorrelation. This technique identifies the existence of high and low-risk spatial clusters, in addition to transition areas, also considering the values of adjacent municipalities, and presents the following results: municipalities with values similar to their neighbors, Q1 (high/high) or Q2 (low/low); and municipalities with different values from their neighbors, Q3 (high/low) or Q4 (low/high) (Anselin, 1995). For spatial statistical analysis, we used TerraView software version 4.2.2. (http://www.dpi.inpe.br/terralib5/wiki/doku.php?id=start) Results were considered significant when p-value <0.05 was obtained. Maps were prepared using the QGIS software version 3.18.2, with the cartographic projection corresponding to the SIRGAS 2000, Universal Reference System.

Finally, for spatiotemporal scan analysis, we used the retrospective analysis method, and applied the Poisson distribution method, which checks high-risk clusters of incidence rates in space and time (Kulldorff, 1997). In this analysis, the parameters used were generic aggregation time, no overlapping clusters, maximum spatial cluster size of 50% of the population at risk, and maximum of 50% for the temporal cluster in the period of the study. Additionally, the likelihood ratio (LLR) test was used to detect clusters. Results with p-value <0.05 and using 999 Monte Carlo simulations were considered significant. Analysis were performed using SatScan software version 9.7 and maps created using QGIS software version 3.18.2.

Ethical considerations

In this study, we used secondary data in the public domain and without the possibility of identifying the individuals. Therefore, the informed consent and ethics committee approval was dispensed. Regardless, we followed the national and international ethical recommendations, as well as the rules of the Helsinki Convention.

RESULTS

We identified 297,972 cases of COVID-19 in the State of Alagoas between March, 2020 and April, 2022. From this total, 56.9% (n = 169,581) were in women, 42.7% (127,298) between 20 and 39 years old, and 59.7% (177,855) were diagnosed using rapid test (Table 1). During this period, there were 6,926 COVID-19-related deaths in Alagoas (lethality rate = 2.3%). Among the deaths, 54.5% (3,772) were men, 66.4% (4,598) older adults (≥60 years old), and 78.1% (5,409) had comorbidity. The most prevalent comorbidities among the deaths were diabetes (38.4%; n = 2,659) and heart disease (21.8%;1,510).

We observed that men had a higher chance of death from COVID-19 (OR = 1.59; p-value <0.0001; Table 2). Considering the age groups, as expected, we observed higher chance of death in individuals with >60 years old (OR = 51.06; p-value <0.0001).

The maps in Figure 2 show the spatial distribution of COVID-19 cases in the municipalities of Alagoas, according to the crude (2A) and smoothed (2B) incidence rates, in the period under analysis. We observed that only five municipalities of the State, had a high incidence rate of the disease (8.1 to 13/1,000 inhabitants) (Figure 2A). Smoothing of crude incidence rates by the Bayesian method show significant difference during the study period (Figure 2B). There was an expressive decrease in those with moderate and very high incidence (only one municipality in HR 8 and one in HR 9).

Additionally, our analysis demonstrated the occurrence of spatial autocorrelation (I= 0.077; p-value = 0.056). Figure 2C shows that, over the study period, there were high-risk clusters (high-high, in red) close to the metropolitan region and in the inland of the State.

Finally, we performed spatiotemporal scan analysis and identified two high-risk clusters for COVID-19 in the State (Figure 2D). Both were statistically significant for the incidence of COVID-19 in Alagoas (Table 3). Moreover, the primary cluster had the highest number of cases (n = 48,868), distributed in 5 municipalities from the HR 1, and with an annual incidence rate (AIR) of 1,615,469.0 (RR = 16.4; p-value <0.0001). The second cluster had 30,762 cases, distributed in 63 municipalities from the HR 4, 5, 6, 7, 8 and 9 (AIR = 361456.2; RR = 3.3; p-value <0.0001).

Table 1. Epidemiological characteristics of cases and deaths by COVID-19 in the State of Alagoas, Northeastern Brazil, between March, 2020 and April, 2022.

Epidemiological Variables	Cases		Deaths	
	n	%	n	%
Gender				
Women	169,581	56.9	3,154	45.5
Men	128,391	43.1	3,772	54.5
Age group (years old)				
≤ 19	29,491	9.9	75	1.1
20-39	127,298	42.7	434	6.3
40-59	101,269	34.0	1,819	26.3
≥ 60-69	39,914	13.4	4,598	66.4
Diagnosis method				
Rapid test	177,855	59.7	-	-
RT-PCR	100,857	33.8	-	-
Immunoassay	3,506	1.2	-	-
Clinical	15,541	5.2	-	-
Uninformed	213	0.1	-	-
Comorbidities				
No comorbidities	-	-	1,517	21.9
Heart diseases	-	-	1,510	21.8
Diabetes	-	-	2,659	38.4
Respiratory diseases	-	-	481	6.9
Immunosuppression	-	-	69	1.0
Kidney disease	-	-	261	3.8
Others	-	-	429	6.2

n = number. (-) absent.

Table 2. Association of the epidemiological variables (gender and age group) with COVID-19-related deaths in the State of Alagoas, Northeastern Brazil, between March, 2020 and April, 2022.

Variables	Deaths from COVID-19		OR (CI 95%)	p-value
	Yes	No		
Gender				
Women	3,154	166,427	--	--
Men	3,772	124,619	1.59 (1.52 to 1.67)	<0.0001
Age group (years old)				
≤ 19	75	29,416	--	--
20-39	434	126,864	1.34 (1.05 to 1.71)	0.0185
40-59	1,819	99,450	7.17 (5.69 to 9.04)	<0.0001
≥ 60-69	4,598	35,316	51.06 (40.80 to 64.24)	<0.0001

OR = odds ratio; CI = confidence interval.

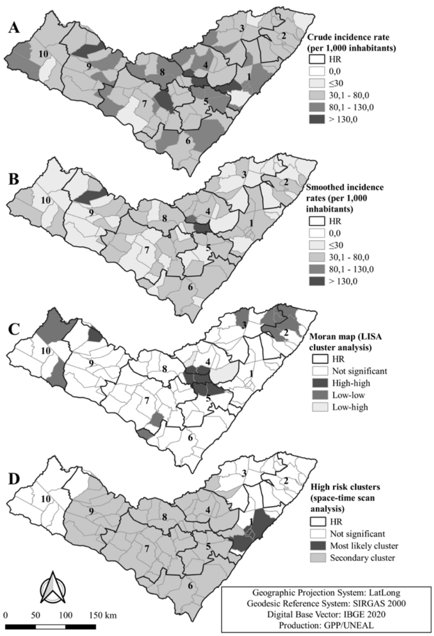

Figure 2. Spatial analysis maps according to COVID-19 incidence rates in the municipalities of Alagoas, Northeastern Brazil. (A) Gross incidence rate. (B) Smoothed incidence rate. (C) Moran maps (LISA). (D) Spatiotemporal scan maps.

Table 3. Spatiotemporal clusters of COVID-19 incidence rates per 100000 inhabitants in the municipalities of Alagoas, Northeastern Brazil, between March, 2020 and April, 2022.

Clusters	Period	Municipalities (n)	Number of cases	Expected new cases	Annual incidence rate *	RR	LLR	p-value
1	03/2021	5	48,868	3,508.6	1,615,469.0	16.4	87,048.2	<0.0001
2	04/2020 05/2020	63	30,762	9,869.9	361,456.2	3.3	14,854.3	<0.0001

RR: relative risk of the cluster compared to other municipalities in the State; LLR: likelihood ratio. *Incidence rate of COVID-19 per 100,000 inhabitants.

DISCUSSION

To date, this is the first study to assess the epidemiological characteristics and the spatial and spatiotemporal dynamics of COVID-19 cases, and the factors associated with deaths, in the State of Alagoas, in the two years of the pandemic. Regarding the cases, we observed that they occurred mostly among women, aged between 20 and 39 years old, and the rapid test was the main diagnosis method used. Otherwise, the highest odds of death were observed among men and in older adults. Finally, applying spatiotemporal analysis techniques, we identified high-risk clusters of COVID-19, in the metropolitan region and in municipalities inland State.

Our findings differ from those reported by Teich and colleagues (Teich et al., 2020). In a national study, the authors identified that most cases of COVID-19 occurred among males (56.9%). On the other hand, Kopel and colleagues point out that the dynamics of SARS-CoV-2 transmission between genders is particular in each region (Kopel et al., 2020). Although women were more affected by COVID-19 herein, men had a higher risk of death (OR = 1.59). Similar data were observed in another study carried out in Alagoas, but in a different period (March to August, 2020) (Baggio et al., 2021).

Importantly, the highest rates of severe cases and deaths observed in men may result from biological, immunological, genetic, and behavioral conditions (Souza et al., 2020b). Some authors justify that higher plasma concentrations of angiotensin-converting enzyme 2 (ACE2) in men may be a contributing factor to the severity of the infection (Hamming et al., 2004; Fathizadeh et al., 2020; Sama et al., 2020). Conversely, women's immune system to the virus is stronger, and this could be related to protection by genes expressed on the X chromosome and sex hormones such as estradiol, which play an important role in the immune response (Shepherd et al., 2021; Soares et al., 2020). Additionally, COVID-19 is more severe in individuals with comorbidities such as hypertension, diabetes and especially heart disease (Almeida-Pititto et al., 2020). In behavioral aspects, men are usually more negligent and more resistant to seeking health services for medical care in Brazil, especially in inland municipalities (Souza et al., 2020b). As a result, these comorbidities are more frequent among them, and this would justify the higher number of deaths. Nevertheless, these are just assumptions, and further studies are needed to explain why men are more likely to evolve to death from COVID-19.

Concerning age group, most cases of COVID-19 occurred among individuals between 20 and 39 years old. Similarly, Teich and colleagues (Teich et al., 2020) report that the mean age of those infected was 40 years old. This age group is represented by the most active working class, daily exposing themselves to the SARS-CoV-2 in public transport and in the work environment, and enabling greater dissemination of the virus (Walker et al., 2020). Furthermore, it was initially believed that the severity of COVID-19 was mainly among the older population. Herewith, many young people and adults, unaware of the risks of infection and severity, did not comply with social isolation measures and, as a result, were more infected by the virus.

Consistent with the previous literature, we observed that older adult patients are more likely to have a fatal outcome from SARS-CoV-2 (Nascimento et al., 2020; Soares et al., 2020). Additionally, the most reported coexisting illnesses in patients who died from COVID-19 were diabetes, cardiovascular diseases, respiratory diseases and kidney disease.

Regarding the high risk of severity and death among the older adults, there are some aspects that may justify the greater vulnerability to SARS-CoV-2 in this age group. First, the senescence of the immune system that naturally weakens with aging and makes the individual more susceptible to infections and inflammatory diseases (Ray & Yung, 2018; Pinti et al., 2016). Aging affects both the adaptive and innate immunity systems as inducing neutrophil apoptosis, inflammation, and release of more pro-inflammatory cytokines (Pinti et al., 2016). As a result, changes in innate and adaptive immunity with age contribute to decreased efficiency of responses to new infections (Ray & Yung, 2018). Additionally, older adults were usually more exposed to other viruses throughout their lives, which increases the risk of presenting an immunological mechanism called antibody-dependent enhancement (ADE) (Wang et al., 2016). ADE facilitates virus entry into cells, increases viral replication, and potentiates inflammatory responses, which can cause more severity and death in older patients. Finally, there is a higher prevalence of chronic diseases in older populations, which contributes to worsening general health (Soares et al., 2020).

Likewise, a study conducted by Soares and colleagues also showed that the risk of death is significantly higher among people older than 60 years old, and who have some type of comorbidity. In this study, cardiovascular diseases were reported as an independent risk factor for hospital admission from COVID-19, increasing odds of hospitalization by 1.3 (Soares et al., 2020). Furthermore, the authors identified that the chances of hospitalization are greater for patients with kidney disease, who also have a high risk of death. Herein, we observed 1,510 deaths in patients with heart disease and 261 with kidney disease.

Throughout these two years of the pandemic, cases of COVID-19 in all municipalities in the State of Alagoas were observed. As expected, the first year of the pandemic (2020) was the one with the highest incidence rate in the State, and consequently the period in which we detected high-risk clusters of disease. This period corresponds to the first wave of the pandemic in Brazil, with community transmission of the virus, and dissemination of cases to all municipalities in the State (Castro et al., 2021). Nevertheless, spatial analysis maps, including spatial autocorrelation, the high rates concentrated in the cities located in the metropolitan area (Barra de São Miguel, Coqueiro Seco, Maceió, Pilar, Satuba and Santa Luzia do Norte) may be related to factors such as greater urban density, population flow, and the presence of important tourist areas (Kerr et al., 2020). This corroborates that the gateway to the virus are more developed municipalities, and those with the greatest flow of visitors. The metropolitan region of Alagoas is located on the coast, where the main tourist areas and the only airport in the State are located (Souza et al., 2020a). As a result, there is a greater influx of tourists and a high risk of spreading the virus, which first reached the metropolitan cities and spread to the poorest municipalities in the State.

Correspondingly, the spatiotemporal analysis demonstrated the occurrence of high-risk clusters for COVID-19 in municipalities in the coastal region of the State. Notwithstanding, there was a heterogeneous distribution of the pandemic, with the formation of high-risk clusters in most health regions of State. Importantly, the rapid advance of the pandemic in the municipalities results from the high transmission capacity of the virus and the inefficiency and mitigation of measures to control the disease in Alagoas, as occurred in Brazil (Walker et al., 2020; Raymundo et al., 2021).

Unfortunately, until April, 2022 Brazil ranked third in the World in number of cases and second in number of deaths from COVID-19 (only behind the USA) (OPAS, 2021; WHO, 2022). Remarkable, several problems may have contributed to the worsening of the pandemic in the country such as the encouragement in using medicines without scientific evidence, the delays in acquiring vaccines, disorganization in the national immunization program, the unstable political scenario, and the mismatch among governments for implementation of social distance (Moreira et al., 2020).

This study has some limitations that should be highlighted. First, considering that we use secondary data, the information may have some bias, such as underreporting of cases or irregularities, and even delays in notifications by municipalities. In addition, it is important to highlight that the underreporting of cases in Brazil is mainly caused by the reduced availability of tests for extensive investigation of suspected cases. This may have affected the accuracy of our analysis. Lastly, the lack of information in some cases led to the exclusion of incomplete observations, which limited the use of some variables in the study.

Taken together, our data demonstrate the impact of COVID-19 in the State of Alagoas, an important touristic area in Brazil, in these two years of pandemic. We observed that, despite the number of cases being higher among women and young adults, the chance of death is significantly higher among men and older adults. Additionally, data from spatial and spatiotemporal analysis showed the occurrence of high-risk clusters of the disease, mainly in the metropolitan region (areas with the highest population density and tourism flows). Thereby, we propose that preventive strategies, as measures of social distancing, along with financial support by the government, and widespread vaccination of the population shall be implemented urgently to reduce the risk of a new wave of the pandemic and avoid the collapse on the health system in Brazil.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest to disclose.

REFERENCES

1. Almeida-Pititto B, Dualib PM, Zajdenverg L, Dantas JR, Souza FD, Rodacki M, Bertoluci MC. Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. *Diabetol Metab Syndr 12*: 1-12, 2020.
2. Andrade LA, Gomes DS, Góes MA de O, Souza MSF de, Teixeira DCP, Ribeiro CJN, Alves JAB, Araújo KCGM de, Santos AD dos. Surveillance of the first cases of COVID-19 in Sergipe using a prospective spatiotemporal analysis: the spatial dispersion and its public health implications. *Rev Soc Bras Med Trop 53*: 1-5, 2020.
3. Anselin L, Bao S. Exploratory Spatial Data Analysis Linking SpaceStat and ArcView. *In:* Fischer, M.M., Getis, A. (eds) *Recent Developments in Spatial Analysis. Advances in Spatial Science.* Springer, Berlin, Heidelberg, 1997. p.25-95.
4. Anselin L. Local Indicators of Spatial Association-LISA. *Geogr Anal 27:* 93-115, 1995.
5. Baggio JAO, Machado MF, Carmo RF do, Armstrong A da C, Santos AD dos, Souza CDF de. COVID-19 in Brazil: spatial risk, social vulnerability, human development, clinical manifestations and predictors of mortality - a retrospective study with data from 59,695 individuals. *Epidemiol Infect 23*: 149:e100, 2021.
6. Brasil. *Introdução à Estatística Espacial para Saúde Pública*. Ministério da Saúde. Secretaria de Vigilância em Saúde. Brasília; 2007.
7. Brasil. Ministério da Saúde. *Diretrizes para diagnóstico e tratamento da Covid-19 Brasil.* 2020. p. 73. Available from: https://saude.rs.gov.br/upload/arquivos/202004/14140600-2-ms-diretrizes-covid-v2-9-4.pdf. Accessed at 29.ago.2022.

8. Castro MC, Kim S, Barberia L, Ribeiro AF, Gurzenda S, Ribeiro KB, Abbott E, Blossom J, Rache B, Singer BH. Spatiotemporal pattern of COVID-19 spread in Brazil. *Science 372*: 821-826, 2021.
9. Druck S, Carvalho MS, Câmara G, Monteiro AMV. *Análise Espacial de Dados Geográficos*. Embrapa, Brasília, 2004.
10. Fathizadeh H, Maroufi P, Momen-Heravi M, Dao S, Köse Ş, Ganbarov K, Pagliano P, Esposito S, Kafil HS. Protection and disinfection policies against SARS-CoV-2 (COVID-19). *Infez Med 28*: 185-191, 2020.
11. Gomes DS, Andrade LA, Ribeiro CJN, Peixoto MVS, Lima SVMA, Duque AM, Cirilo TM, Góes MAO, Lima AGCF, Santos MB, Araújo KCGM, Santos AD. Risk clusters of COVID-19 transmission in Northeastern Brazil: prospective space-time modeling. *Epidemiol Infect 148:* 1-23, 2020.
12. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol 203:* 631-637, 2004.
13. IBGE. Instituto Brasileiro de Geografia e Estatística. *Cidades e Estados. 2021*. Available from: https://www.ibge.gov.br/cidades-e-estados/al.html. Accessed at 29.dez.2021.
14. Kerr L, Kendall C, Silva AAM da, Aquino EML, Pescarini JM, Almeida RLF de, Ichihara MY, Oliveira JF, Araújo TVB de, Santos CT, Jorge DCP, Miranda Filho D de B, Santana G, Gabrielli L, Albuquerque M de FPM de, Almeida-Filho N, Silva N de J, Souza R, Ximenes RA de A, Martelli CMT, Brandão Filho SP, Souza WV de, Barreto ML. COVID-19 no Nordeste brasileiro: sucessos e limitações nas respostas dos governos dos estados. *Cien Saude Colet 25:* 4099-4120, 2020.
15. Kopel J, Perisetti A, Roghani A, Aziz M, Gajendran M, Goyal H. Racial and Gender-Based Differences in COVID-19. *Front Public Health 8*: 418, 2020.
16. Kulldorff M. A spatial scan statistic. *Commun Stat Theory Methods 26:* 1481-1496, 1997.
17. Lima SVMA, Dos Santos AD, Duque AM, De Oliveira Goes MA, Da Silva Peixoto MV, Da Conceição Araújo D, Ribeiro CJN, Santos MB, De Araújo KCGM, Nunes MAP. Spatial and temporal analysis of tuberculosis in an area of social inequality in Northeast Brazil. *BMC Public Health 19*: 1-9, 2019.
18. Moreira WC, Sousa AR de, Nóbrega M do PS de S. Mental illness in the general population and health professionals during covid-19: a scoping review. *Texto Contexto Enf 29*: 1-17, 2020.
19. Nascimento JDS, Bezerra LP, Ramos RES. Prevalência e aspectos epidemiológicos da COVID-19 na 9ª Região de Saúde de Alagoas. *J Health Biol Sci 8*: 1, 2020.
20. Oliveira WK de, Duarte E, França GVA de, Garcia LP. Como o Brasil pode deter a COVID-19. *Epidemiol Serv Saude 29*: e2020044, 2020.
21. OPAS. Organização Pan-Americana da Saúde. *Folha informativa sobre COVID-19*. 2021. Available from: https://www.paho.org/pt/covid19#sintomas. Accessed at 29.dez.2021.
22. Pinti M, Appay V, Campisi J, Frasca D, Fülöp T, Sauce D, Larbi A, Weinberger B, Cossarizza A. Aging of the immune system - focus on inflammation and vaccination. *Eur J Immunol 46:* 2286-2301, 2016.
23. Ray D, Yung R. Immune Senescence, Epigenetics and Autoimmunity. *Clin Immunol 196:* 59-63, 2018.
24. Raymundo CE, Oliveira MC, de Araujo Eleuterio T, André SR, da Silva MG, da Silva Queiroz ER, de Andrade Medronho R. Spatial analysis of COVID-19 incidence and the sociodemographic context in Brazil. *PLoS One 16*:1-16, 2021.

25. Rebolledo EAS, Neto FC, Giatti LL. Experiencias, beneficios y desafíos del uso de geoprocesamiento para el desarrollo de la atención primaria de salud. *Rev Panam Salud Publica 42:* e153, 2018.

26. Sama IE, Ravera A, Santema BT, Van Goor H, Ter Maaten JM, Cleland JGF, Rienstra M, Friedrich AW, Samani NJ, Ng LL, Dickstein K, Lang CC, Filippatos G, Anker SD, Ponikowski P, Metra M, Van Veldhuisen DJ, Voors AA. Circulating plasma concentrations of angiotensin-converting enzyme 2 inmen and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. *Eur Heart J 41:* 1810-1817, 2020.

27. Shepherd R, Cheung AS, Pang K, Saffery R, Novakovic B. Sexual Dimorphism in Innate Immunity: The Role of Sex Hormones and Epigenetics. *Front Immunol 11*: 1-16, 2021.

28. Silva RR, Ribeiro CJN, Moura TR, Santos MB, Santos AD, Tavares DS, Santos PL. Basic sanitation: a new indicator for the spread of COVID-19? *Trans R Soc Trop Med Hyg 115*: 832-840, 2021.

29. Soares R de CM, Mattos LR, Raposo LM. Risk Factors for Hospitalization and Mortality due to COVID-19 in Espírito Santo State, Brazil. *Am J Trop Med Hyg 103*: 1184-1190, 2020.

30. Souza CDF, Machado MF, do Carmo RF. Human development, social vulnerability and COVID-19 in Brazil: a study of the social determinants of health. *Infect Dis Poverty 9*: 124, 2020a.

31. Souza LG, Randow R, Siviero PCL. Reflexões em tempos de COVID-19: diferenciais por sexo e idade. *Com Ci Saúde 31:* 75-83, 2020b.

32. Teich VD, Klajner S, Almeida FAS de, Dantas ACB, Laselva CR, Torritesi MG, Canero TR, Berwanger O, Rizzo LV, Reis EP, Cendoroglo M. Epidemiologic and clinical features of patients with COVID-19 in Brazil. *Einstein (São Paulo) 18*: 1-17, 2020.

33. Walker PGT, Whittaker C, Watson OJ, Baguelin M, Winskill P, Hamlet A, Djafaara BA, Cucunubá Z, Olivera Mesa D, Green W, Thompson H, Nayagam S, Ainslie KEC, Bhatia S, Bhatt S, Boonyasiri A, Boyd O, Brazeau NF, Cattarino L, Cuomo-Dannenburg G, Dighe A, Donnelly CA, Dorigatti I, van Elsland SL, FitzJohn R, Fu H, Gaythorpe KAM, Geidelberg L, Grassly N, Haw D, Hayes S, Hinsley W, Imai N, Jorgensen D, Knock E, Laydon D, Mishra S, Nedjati-Gilani G, Okell LC, Unwin HJ, Verity R, Vollmer M, Walters CE, Wang H, Wang Y, Xi X, Lalloo DG, Ferguson NM, Ghani AC. The impact of COVID-19 and strategies for mitigation and suppression in low- and middle-income countries. *Science 369*: 413-422, 2020.

34. Wang Q, Zhang L, Kuwahara K, Li L, Liu Z, Li T, Zhu H, Liu J, Xu Y, Xie J, Morioka H, Sakaguchi N, Qin C, Liu G. Immunodominant SARS coronavirus epitopes in humans elicited both enhancing and neutralizing effects on infection in non-human primates. *ACS Infect Dis 2*: 361-376, 2016.

35. Werneck GL, Carvalho MS. A pandemia de COVID-19 no Brasil: crônica de uma crise sanitária anunciada. *Cad Saude Publica 36*: 1-3, 2020.

36. WHO. World Health Organization. *Coronavirus disease (COVID-19)*. 2022a Available from: https://www.who.int/health-topics/coronavirus#tab=tab_1. Accessed at 29.ago.2022.

37. WHO. World Health Organization. *Archived: WHO Timeline - COVID-19. 2020*. Available from: https://www.who.int/news/item/27-04-2020-who-timeline---covid-19. Accessed at 29.ago.2022.

38. WHO. World Health Organization. *Coronavirus (COVID-19) Dashboard With Vaccination Data*. 2022b. Available from: https://covid19.who.int/. Accessed at 29.ago.2022.