Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Impact Of The COVID-19 Pandemic on Hospital Admissions and In-Hospital Lethality From Cardiovascular Diseases in Brazil: An Ecological and Time Series Study

Lucas Gomes Santos[a,*], Regicley Vieira da Silva[a], Thiago Cavalcanti Leal[b], José Emerson Xavier[c], Elaine Virgínia Martins de Souza Figueiredo[d], João Paulo Silva de Paiva[a], Leonardo Feitosa da Silva[a], Carlos Alberto de Oliveira Rocha[a], Bruno Eduardo Bastos Rolim Nunes[a], Gibson Barros de Almeida Santana[a], Tânia Rita Moreno de Oliveira Fernandes[d], Francisco de Assis Costa[a], Márcio Bezerra-Santos[c], Rodrigo Feliciano do Carmo[e], Anderson da Costa Armstrong[d], and Carlos Dornels Freire de Souza[a]

From the [a] Department of Medicine, Federal University of Alagoas, Arapiraca, Alagoas, Brazil, [b] Federal University of Alagoas, Maceió, Alagoas, Brazil, [c] Department of Morphology, Federal University of Sergipe, São Cristóvão, SE, Brazil, [d] College of Medicine, Federal University of the São Francisco Valley (UNIVASF), Petrolina, Pernambuco, Brazil and [e] College of Pharmaceutical Sciences, Federal University of the São Francisco Valley (UNIVASF), Petrolina, Pernambuco, Brazil.

Abstract: Since the onset of the coronavirus disease 2019 (COVID-19) pandemic in Brazil, several government policies have been taken. Herein, we aimed to assess the impact of the COVID-19 pandemic on hospital admissions and in-hospital lethality for cardiovascular diseases (CVD) in Brazil in 2020. An

Disclosure: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Curr Probl Cardiol 2022;00:101216
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2022.101216

ecological and time-series study on hospitalizations and deaths from CVD in Brazil was conducted from January 2018 to December 2020.The hospital admission rate for CVD reduced by 17.1%, with a significant decreasing trend between January and May 2020 (Annual Percent Change: -8,7%; *P*-value < 0.001). The in-hospital lethality rate increased from 8.2% in 2018 to 9.3% in 2020. During this period, Brazil totaled 21.8 million days of hospital stay. Indicators of hospital admissions and lethality from CVD in Brazil were impacted by the emergence of the COVID-19 pandemic in different ways in the regions and depending on the nature of the indicator. (Curr Probl Cardiol 2022;00:101216.)

Introduction

The new coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2 - SARS-CoV-2) is part of a set of viruses in the Coronaviridae family.[1] Viruses from this family have been previously observed in other smaller outbreaks, such as SARS-CoV-1 and MERS-CoV (Mediterranean Acute Respiratory Syndrome Coronavirus) reported in 2002 and 2012, in China and the Middle East, respectively. In December 2019, an outbreak of rapidly progressing pneumonia was identified in Wuhan, capital of Hubei province, China. On January 7, 2020, China attributed the outbreak to SARS-CoV-2 and the disease was named Coronavirus Disease 2019 (COVID-19).[1] The outbreak caused by the new coronavirus was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 and, since then, the disease has brought extraordinary challenges to health authorities and governments in several countries worldwide.[2]

In Brazil, the first case of COVID-19 was confirmed on February 26 and the first death on March 17.[3] The national community transmission was recognized on March 20, 2020 by the Brazilian Ministry of Health.[4] The first case was confirmed in the city of São Paulo in a patient from Italy, but the disease rapidly spread to the large metropolises of other regions until it reached smaller and more distant cities.[5–7] Despite all WHO recommendations, and the enactment of Law No. 13.979/2020 on February 7, 2020 (which provides for measures to combat COVID-19 in the country), restrictive measures for the movement of people, such as banning events with agglomeration in several states and closing all non-essential commerce were only implemented in late March.[8] As a result,

in July 2020 the first wave of the pandemic was observed in the country, with a daily average of 70 thousand new cases of COVID-19. To date, Brazil ranks second in the world in number of deaths by COVID-19.[9]

Remarkable, the COVID-19 pandemic has been causing significant impacts on public health and the global economy. Furthermore, the measures to restrict the mobility of people and the redirection of health services to fight the transmission of the virus have also affected the control of several other diseases such as cancer, dementia, and high blood pressure.[10–12] Additionally, this impact occurs directly, in patients with any comorbidity, especially chronic diseases; and indirectly, by changing the behavior of the population, such as fear of contagion and reduced demand for health services.[11,13]

Importantly, the implementation of collective measures of social distancing to contain COVID-19 resulted in changes in the routine of services. As a result, this promoted the rescheduling of elective procedures and the redistribution of hospital flow to transform face-to-face hospital care into distance care (tele-health) in several clinical situations.[14] To illustrate this impact, in an oncology center in São Paulo, there was a reduction of 45% in the number of patients treated and 57.4% in the number of patients undergoing systemic intravenous treatment.[10]

Clinically, there is an important relationship between COVID-19 and cardiovascular diseases (CVD), such as: i. the impact of CVD on the worsening of COVID-19, which is an relevant set of predictors of severity and mortality;[15] ii. the damage caused by SARS-CoV-2 in the cardiovascular system (CS) of people without underlying disease due to pathophysiological mechanisms of virus infection;[16] and iii. the worsening of CVD in individuals without COVID-19, but as a result of non-pharmacological preventive measures to reduce the circulation of the virus, such as hospital evasion of patients, delaying the care of episodes of exacerbation of these chronic conditions or making early diagnosis difficult.[11,16] Herein, we aimed to assess the impact of the COVID-19 pandemic on hospital admissions and in-hospital lethality for CVD in Brazil during the first year of the pandemic.

Methods

Study Design, Area, Population, And Period

An ecological and time-series study was conducted on hospitalizations and deaths from CVD in Brazil and its regions from January 2018 to December 2020. Data on CVD for the years 2018 and 2019 were used as

the period before the COVID-19 pandemic and were compared with data for 2020.

Study Variables and Data Collection

Herein, the following variables were assessed: i. hospital admissions rate for CVD (Chapter IX of the ICD-10) per month (from January 2018 to December 2020); ii. in-hospital lethality rate due to CVD per month (from January 2018 to December 2020); iii. total cost applied (in Brazilian reais - R$) and average cost (R$) of hospitalizations for CVD; iv. days of hospital stay and average time of stay (in days) for CVD; v. new COVID-19 cases registered per month.

To calculate the rates, the following equations were applied:

i hospital admissions rate for CVD

$$\textit{Hospital admissions rate} = \frac{\textit{Number of admissions by location and period}}{\textit{Total resident population by location and period}} x100$$

ii in-hospital lethality rate due to CVD

$$\textit{In-hospital lethality rate} = \frac{\textit{Number of in-hospital deaths by place and period}}{\textit{Total admissions by location and period}} x100$$

Data on hospitalizations and deaths due to CVD were extracted from the Hospital Information System (SIH) of the Brazilian Unified Health System (SUS) (http://www2.datasus.gov.br/DATASUS/index.php?area=0203&id=6926). The SIH is a nationwide information system, created in 1991, for the registration of medical and hospital assistance within the SUS based on Hospital Admission Authorizations (AIH) and managed by the Brazilian Ministry of Health (BRASIL, 2004). The main purpose of this system is to generate information on hospitalizations and deaths that can be used in decision-making and public management in Brazil (BRASIL, 2004; ROCHA et al., 2018). Importantly, these data were collected according to the year and month of hospitalization.

COVID-19 data were extracted from the consolidated data of the Brazilian Ministry of Health and the State Health Departments by the covid19br platform (ttps://covid19br.wcota.me/). Finally, population data

were obtained from the Brazilian Institute of Geography and Statistics (IBGE).

Statistical Treatment of Data

The statistical analysis of the data took place in 3 steps:

A) *Descriptive analysis of epidemiological indicators:* at this stage, the indicators were described in a monthly time series between January 2018 and December 2020. We also included the year 2018 in order to verify the possible existence of variations in the indicators in 2019. Random variations in 2019, for example, could compromise the assessment of the impact of the pandemic on the assessed epidemiological indicators.
B) *Percentage variation analysis:* since no random variations were observed in the indicators for the years 2018 and 2019, the percentage variation in the period was calculated, considering each month of the year 2020 in relation to the same month of 2019. Positive proportional variations indicate an increase in the indicator and negative proportional variations indicate a reduction in the value.
C) *Time series analysis:* Finally, the 2020 data were subjected to temporal trend analysis by the inflection point regression model (joinpoint regression model). This model tests whether a line with multiple segments is statistically better at describing the time evolution of a dataset than a straight line or a line with fewer segments.[17] In this sense, the model allows identifying the trend of the indicator (if stationary, increasing, or decreasing) and the points where there is a change in this trend (joins). For that, we calculated the annual percentage changes (APC), for segmented periods, and the average annual percentage changes (AAPC), for the entire period. Time trends were considered statistically significant when APC or AAPC had a P-value < 0.05 and their CI 95% did not include the zero. Importantly, a positive and significant APC or AAPC indicates an increasing trend; on the other hand, a negative and significant APC or AAPC indicates a decreasing trend; and non-significant trends are described stable, regardless of APC or AAPC values. The analyses were performed in the software *Joinpoint Regression Program* version 4.5.0.1 (*National Cancer Institute- USA*).

Ethical Aspects

This study used data from the public domain, which does not allow the identification of the subjects. For this reason, the appreciation of the Research Ethics Committee was waived.

Results

Hospital Admissions Rate For CVD

A total of 3.3 million hospitalizations for CVD were recorded in Brazil between 2018 and 2020. The average annual rate was 55.2 in 2018, 56.1 in 2019, and 46.5/10,000 inhabitants in 2020 (reduction of 17.1% compared to 2019). In March 2020, there was a decline of 4.1% in the hospitalization rate, as observed in all subsequent months, especially in July and August (both with a drop of 25.3%) (Fig 1A).

During the study period, the South region showed the highest hospitalization rates (86.1 in 2018, 87.1 in 2019 and 71/10,000 in 2020). Meanwhile, the lowest rates were observed in the North region (9.8 in 2018, 28.7 in 2019 and 22.8/10,000 in 2020). In addition, the North showed the greatest reduction in the rate between 2019 and 2020 (-20.2%) and the greatest instability among the regions of the country (Fig 1G). The highest reductions in hospital admissions occurred at different times between regions in 2020: North (-48.9% in December), Northeast (-30.9% in August), Midwest (-27.9% in August), South (-26.6% in July), and Southeast (-26.4% in May) (Fig 1B-F).

A decreasing temporal trend was observed in the hospital admissions rate for CVD in Brazil between January and May 2020 (APC: -8.7; *P*-value < 0.001). This same trend was observed in the Northeast (APC: -10.2; *P*-value < 0.001), Southeast (APC: -8.3; *P*-value < 0.001), and South regions (APC: -8.9; *P*-value < 0.001). The North (AAPC: -4.2; *P*-value < 0.001) and Central-West regions (AAPC: -2.4; *P*-value < 0.001) showed a decreasing trend throughout all the months of 2020 (Table 1).

In-Hospital Lethality Rate Due To CVD

The in-hospital lethality rate for CVD in Brazil was 8.2% in 2018, 8.3% in 2019, and 9.3% in 2020 (12.5% increase compared to 2019). Differently from what was observed in the hospitalization rate, the in-hospital lethality rate in Brazil showed an increase of 21.3% in April 2020, with a peak in May (25%) and with percentages above 12% in all other months of the year (Fig 2A).

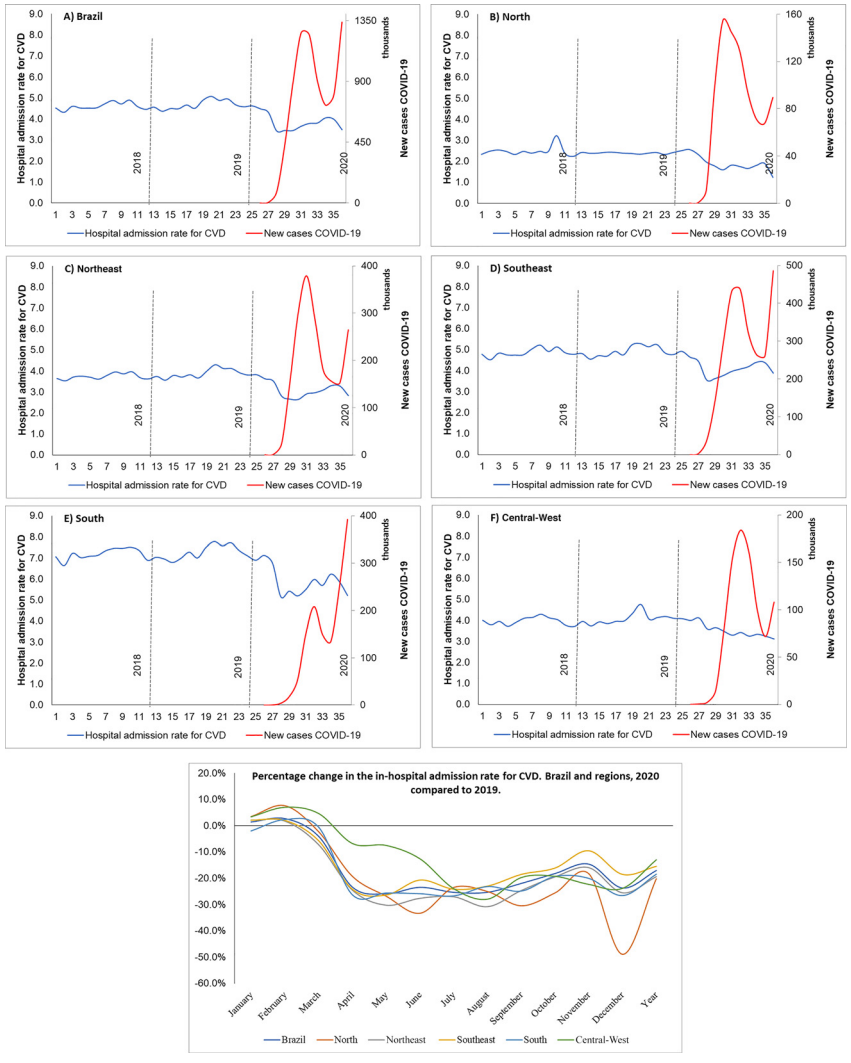
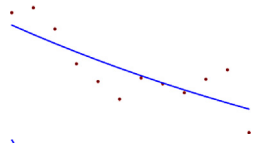
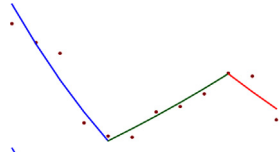
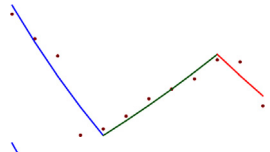
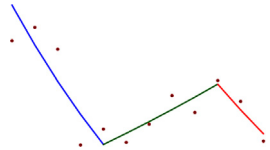
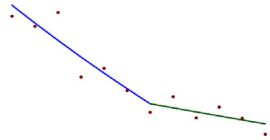
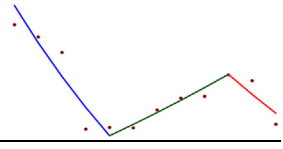


FIG 1. Temporal evolution of hospital admission rates (10 thousand inhabitants) and in-hospital mortality (100 admissions) for CVD in Brazil and regions, before and after confirmation of the COVID-19 pandemic (Color version of figure is available online.)

Among this period, the North region had the highest lethality rates in 2018 and 2019 (9.2% and 9.8%, respectively). In 2020, the highest rate was identified in the Central-west region (10.7%). On the other hand, the South region showed the lowest rates (6.4% in 2018, 6.5% in 2019, and 7.63% in 2020) (Fig 2B-F). Additionally, the North region showed the biggest increase in the lethality rate (+31.45%) between the months of

Table 1. Temporal analysis (*joinpoint regression model*) of the hospitalization rate (10 thousand inhabitants), for cardiovascular diseases in Brazil and regions between January and December 2020

Region	Period	APC/AAPC (*P*-value)	Trend	Joinpoint regression model
North	Jan/20 - Dec/20	-4.2 (<0.001) *	↓	
Northeast	Jan/20 – May/20	-10.2 (<0.001) *	↓	
	May/20 – Oct/20	4.8 (0.1)	↔	
	Oct/20 – Dec/20	-5.6 (0.5)	↔	
	Jan/20 – Dec/20	-2.8 (0.1)	↔	
Southeast	Jan/20 – Mai/20	-8.3 (<0.001) *	↓	
	May/20 – Oct/20	4.7(<0.001) *	↑	
	Oct/20 – Dec/20	-5.4 (0.5)	↔	
	Jan/20 – Dec/20	-2.0 (0.2)	↔	
South	Jan/20 – Mai/20	-8.9 (<0.001) *	↓	
	May/20 – Oct/20	3.6 (0.3)	↔	
	Oct/20 – Dec/20	-7.0 (0.6)	↔	
	Jan/20 – Dec/20	-3.0 (0.3)	↔	
Central-West	Jan/20 – Jul/20	-3.5 (<0.001) *	↓	
	Jul/20 – Dec/20	-1.0 (0.2)	↔	
	Jan/20 – Dec/20	-2.4 (<0.001) *	↓	
Brazil	Jan/20 – May/20	-8.7 (<0.001) *	↓	
	May/20 – Oct/20	3.8 (0.1)	↔	
	Oct/20 – Dec/20	-5.6 (0.6)	↔	
	Jan/20 – Dec/20	-2.6 (0.2)	↔	

Legend: APC, annual percentage change; AAPC, average annual percentage change ↔Stable; ↓Decreasing; ↑Increasing. *Statistical significance.

February and June 2020, followed by the Northeast region, with a peak of lethality in May (+11.76%) (Fig 2G).

Importantly, we observed an increasing trend in the lethality rate in Brazil between January and June 2020 (APC: 6.0; *P*-value < 0.001), with a subsequent reduction between June and December (APC: -2.9; *P*-value < 0.001). Likewise, similar trends (*P*-value < 0.001) were observed in these months (January/June and July/December) in the Northeast (APC: 7.9 and APC: -2.8), Southeast (APC: 6.3 and APC: -3.0) and Central-West regions (APC: 2.9 and APC: -6.9. Interestingly, the North (APC:

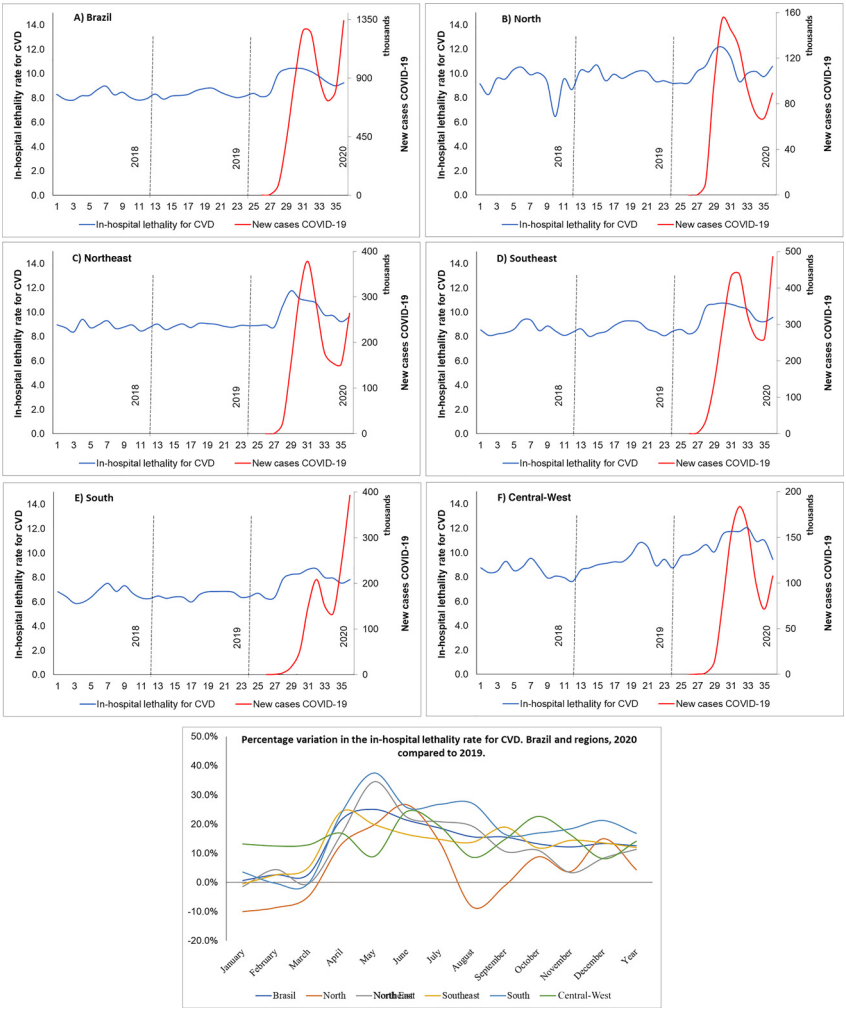


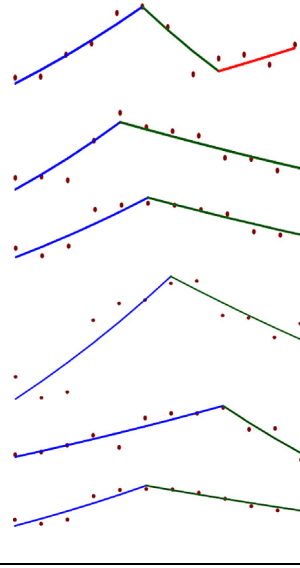
FIG 2. Temporal evolution of in-hospital lethality rate (100 admission), for CVD in Brazil and regions, before and after confirmation of the COVID-19 pandemic (Color version of figure is available online.)

6.3; *P*-value $<$ 0.001) and South regions (APC: 5.9; *P*-value $<$ 0.001) showed an increasing trend during the first half of 2020 (Table 2).

Total Cost (in Brazilian Real - R$) And Average Cost (R$) of Hospitalizations for CVD

During the study period, R$8.8 billion were spent on hospitalizations for CVD throughout Brazil, with an average cost of R$2.6 thousand per

Table 2. Time series analysis (*joinpoint regression model*) of the in-hospital lethality rate (%) due to diseases of circulatory system in Brazil and regions between January and December 2020

Region	Period	APC/AAPC (*P*-value)	Trend	Joinpoint regression model
North	Jan/20 – June/20	6.3(<0.001) *	↑	
	June/20 – Sept/20	-8.0 (0.2)	↔	
	Sept/20 – Dec/20	3.3 (0.2)	↔	
	Jan/20 – Dec/20	1.4 (0.3)	↔	
Northeast	Jan/20 – May/20	7.9 (<0.001) *	↑	
	May/20 – Dec/20	-2.8 (<0.001) *	↓	
	Jan/20 – Dez/20	0.9 (0.3)	↔	
Southeast	Jan/20 – June/20	6.3 (<0.001) *	↑	
	June/20 – Dec/20	-3.0 (<0.001) *	↓	
	Jan/20 – Dec/20	1.1 (0.2)	↔	
South	Jan/20 – Jul/20	5.9 (<0.001) *	↑	
	Jul/20 – Dec/20	-3.2 (0.1)	↔	
	Jan/20 – Dec/20	1.7 (0.1)	↔	
Central-West	Jan/20 – Sept/20	2.9 (<0.001) *	↑	
	Spet/20 – Dec/20	-6.9 (<0.001) *	↓	
	Jan/20 –Dez/20	0.2 (0.8)	↔	
Brazil	Jan/20 – June/20	6.0 (<0.001) *	↑	
	June/20 – Dec/20	-2.9 (<0.001) *	↓	
	Jan/20 – Dec/20	1.1 (0.3)	↔	

Legend**:** APC: annual percentage change; AAPC: average annual percentage change ↔Stable; ↓Decreasing; ↑Increasing. *Statistical significance.

each hospitalization. The highest cost was observed in 2019 (R$3.1 billion) and the lowest in 2020 (total cost of R$2.8 billion – a reduction of 10.3%). In addition, there was reduction in total cost from April (-15.8%) to December 2020 (Fig 3A). Conversely, the average cost of each hospitalization ranges from R$2.6 to R$2.8 thousand reais (an increase of 7.4%). Moreover, there was increase in every month of 2020, mainly in March (+5.4%), August (+11.5%), and December (+13.3%) (Fig 4A**).**

As expected, the highest hospitalization costs were identified in the Southeast region (annual average of R$1.3 billion) and the lowest in the North (annual average of R$93.9 million). The South region showed the greatest reduction in costs (-14%) (Fig 3B-F). Interestingly, all regions showed an increase in the average cost of admissions, being higher in the South (annual average of R$3.1 thousand per admission) and lower in the North (annual average of R$1.9 thousand). Furthermore, the North region was the one with the greatest instability in the average cost throughout 2020, with the lowest percentage in January (-4%) and the highest in December (24.8%) (Fig 4G).

FIG 3. Temporal evolution of total cost of hospital admission for CVD in Brazil and regions, before and after confirmation of the COVID-19 pandemic (Color version of figure is available online.)

Time trend analysis showed a stationary trend of the total cost of hospitalizations for CVD in Brazil throughout 2020 (APC: -1.0%). On the other hand, the national average cost per hospitalization showed an increasing trend (AAPC: 1.2%; *P*-value < 0.001). Among the regions, the North was the only one with a decreasing trend in 2020 (APC: -3.3; *P*-value $<$ 0.001). In the Northeast and Southeast regions, there was a reduction between January and May 2020 (APC: -8.0 and -5.9, respectively; *P*-value < 0.001), followed by an increasing from May to December (APC: 4.3 and 2.7, respectively; *P*-value < 0.001) (Table 3 and 4).

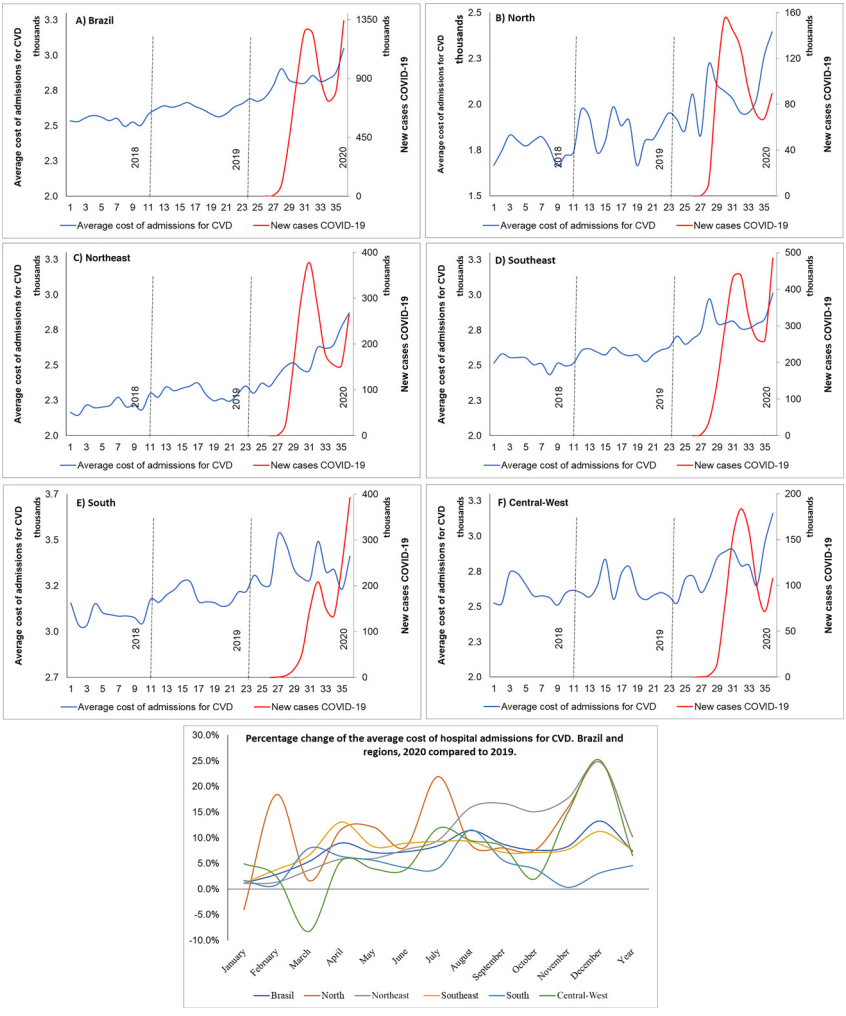


FIG. 4. Evolution temporal of the average cost of hospital admission for CVD in Brazil and regions, before and after confirmation of the COVID-19 pandemic (Color version of figure is available online.)

Length Of Stay and Average Hospital Stay (In Days) For CVD

There was a total of 21.8 million days of hospitalization for CVD in Brazil (annual average of 7.3 million) between 2018 and 2020. During this period, the average length of stay was 6.5 days. In 2020, there was a reduction of 17.1% in the total period of hospitalizations and a reduction of 1.5% in the average length of stay. With the onset of the pandemic,

Table 3. Temporal analysis (*joinpoint regression model*) of the total cost per hospital stay for cardiovascular diseases in Brazil and regions between January and December 2020.

Region	Period	APC/AAPC (*P* value)	Trend	Joinpoint regression model
North	Jan/20 – Dec/20	-3.3 (<0.001) *	↓	
Northeast	Jan/20 – May/20	-8.0 (<0.001) *	↓	
	May/20 – Dec/20	4.3 (<0.001) *	↑	
	Jan/20 – Dec/20	-0.3 (0.8)	↔	
Southeast	Jan/20 – May/20	-5.9 (<0.001) *	↓	
	May/20 – Dec/20	2.7 (<0.001) *	↑	
	Jan/20 – Dec/20	-0.6 (0.5)	↔	
South	Jan/20 – Dec/20	-1.6 (0.1)	↔	
Central-West	Jan/20 – Oct/20	-2.2 (<0.001) *	↓	
	Oct/20 – Dec/20	5.1 (0.3)	↔	
	Jan/20 – Dec/20	-0.9 (0.3)	↔	
Brazil	Jan/18 – May/20	-6.3 (<0.001) *	↓	
	May/20 – Dec/20	2.1 (0.1)	↔	
	Jan/20 – Dec/20	-1.0 (0.3)	↔	

Legend**:** APC, annual percentage change; AAPC, average annual percentage change ↔Stable; ↓Decreasing; ↑Increasing. *Statistical significance.

there was a significant reduction in the total period of hospitalizations, mainly in July (-27.2%) and August 2020 (-27.6%) (Fig 5 and 6).

In the study period, the Southeast region showed the highest number of days of hospitalization for CVD (annual average of 3.4 million days) and the North had the lowest (344.9 thousand days). As of April 2020, all regions showed a reduction in the sum of days. In addition, the North was

Table 4. Temporal analysis (*joinpoint regression model*) of the average cost per hospital stay for diseases of the circulation system in Brazil and regions between January and December 2020

Region	Period	APC/AAPC (*P* value)	Trend	Joinpoint regression model
North	Jan/20 - Dec/20	1.2 (0.1)	↔	
Northeast	Jan/20 – Dec/20	1.6 (<0.001) *	↑	
Southeast	Jan/20 – Dec/20	0.6 (0.1)	↔	
South	Jan/20 – Dec/20	-0.0 (1.0)	↔	
Central-West	Jan/20 – Mar/20	-1.9 (0.6)	↔	
	Mar/20 – June/20	3.8 (0.4)	↔	
	June/20 – Oct/20	-2.0 (0.3)	↔	
	Out/20 – Dec/20	8.6 (0.2)	↔	
	Jan/20 – Dec/20	1.4 (0.1)	↔	
Brazil	Jan/18 – Apr/20	2.4 (<0.001) *	↑	
	Apr/20 – Oct/20	-0.3 (0.4)	↔	
	Oct/20 – Dcz/20	3.9 (<0.001) *	↑	
	Jan/20 – Dec/20	1.2 (<0.001) *	↑	

Legend: APC, annual percentage change; AAPC, average annual percentage change ↔Stable; ↓Decreasing; ↑Increasing. *Statistical significance.

the region with the greatest reduction in 2020 (-20.7%) (Fig 5). The average length of stay was longer in the Northeast region (7.2 days) and shorter in the South (5.4 days) (Fig 6).

Importantly, the sum of days of hospitalization showed a decline trend in Brazil (AAPC: -2.1; *P*-value < 0.001). Similarly, there was a decreasing trend in the North (AAPC: -5.5; *P*-value < 0.001) and Central-West regions (AAPC: -2.4; *P*-value < 0.001) (Table 5). Regarding the average

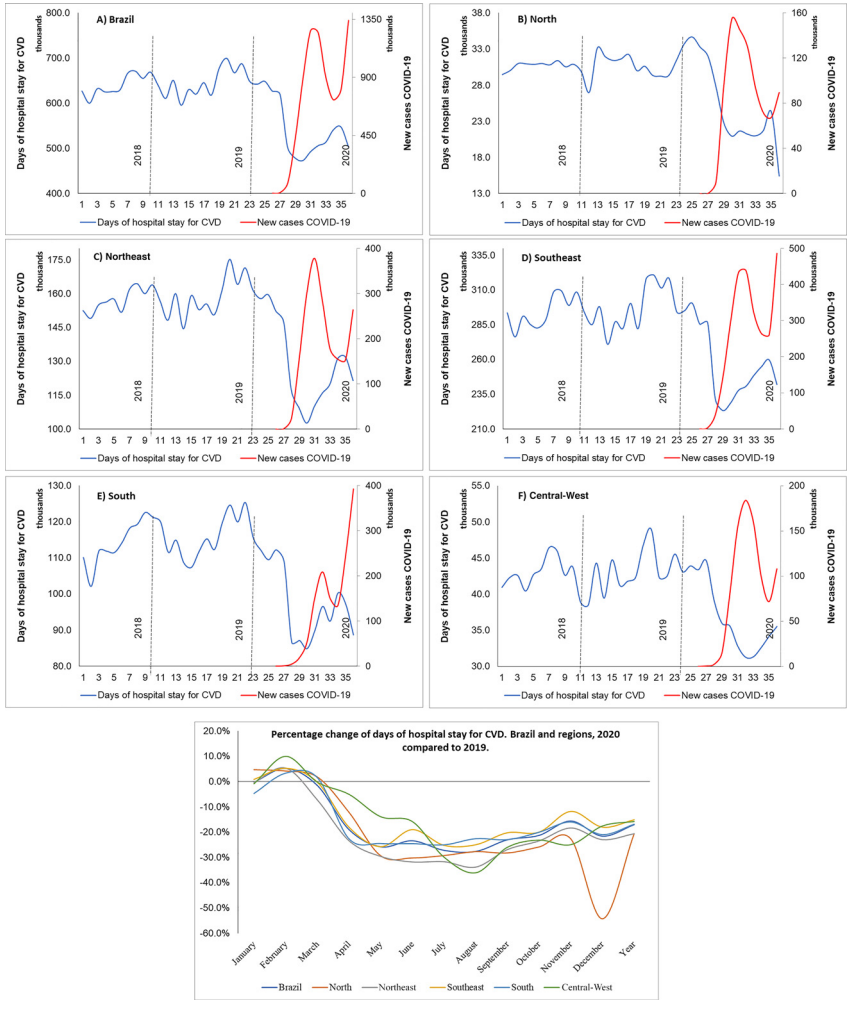


FIG 5. Temporal evolution of total of days of hospital stay for CVD in Brazil and regions, before and after confirmation of the COVID-19 pandemic (Color version of figure is available online.)

number of days of stay, there was a stationary trend in the country (AAPC: 0.0). Also, there was an increasing trend in the Northeast (AAPC: 0.2; *P*-value < 0.001) and a reduction in the North region (AAPC: -1.0; *P*-value < 0.001) (Table 6).

Discussion

Altogether, our analyses showed a reduction in hospital admissions for CVD, in the total cost of these admissions, in the absolute number and

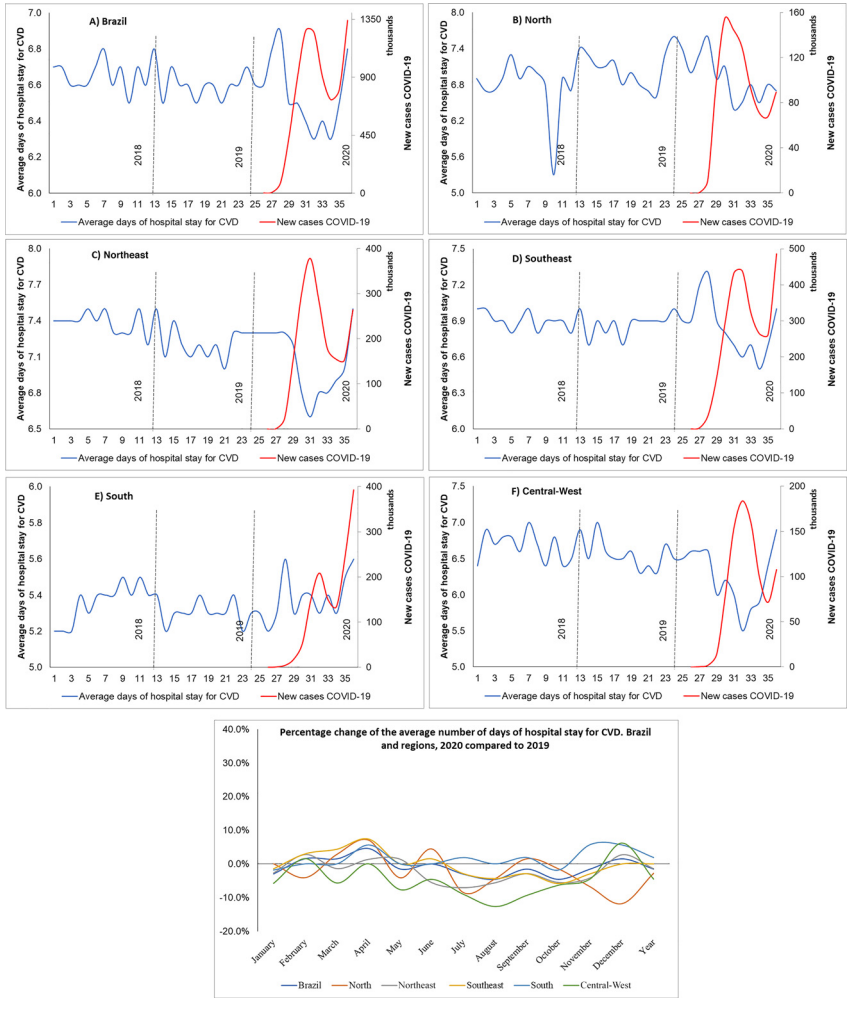
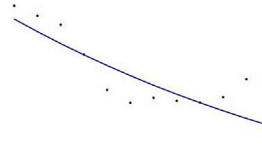
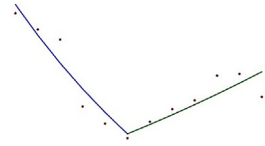
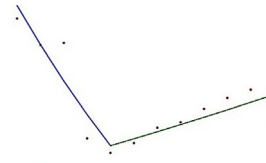
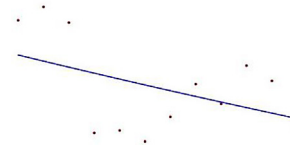
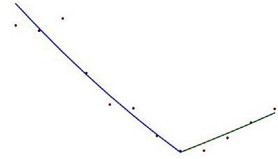
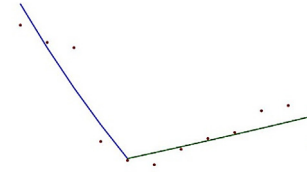


FIG 6. Temporal evolution of the average days of hospital stay for CVD in Brazil and regions, before and after confirmation of the COVID-19 pandemic (Color version of figure is available online.)

average length of hospital stay after the emergence of COVID-19 pandemic in Brazil. On the other hand, there was an increase in the in-hospital lethality rate and in the average cost of admissions. Importantly, these variations occurred unequally in time (over months) and in space (between regions), reflecting different aspects of the impact of the pandemic throughout Brazilian regions.

The reduction in hospitalizations for CDV may be the result of 2 important aspects that became present with the onset of the COVID-19 in

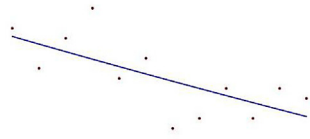
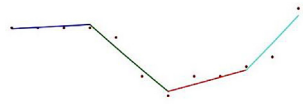
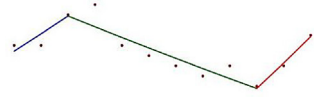
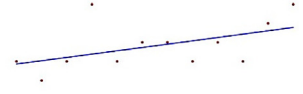
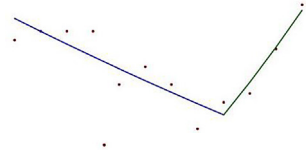
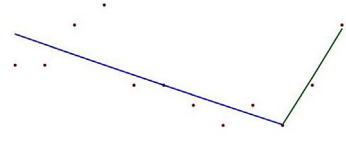
Table 5. Temporal analysis (*joinpoint regression model*) of the total days of hospital stay for cardiovascular diseases in Brazil and regions between January and December 2020

Region	Period	APC/AAPC (*P*-value)	Trend	Joinpoint regression model
North	Jan/20 – Dec/20	-5.5 (<0.001) *	↓	
Northeast	Jan/20 – June/20	-8.5(<0.001) *	↓	
	Jun/30 – Dec/20	4.1(<0.001) *	↑	
	Jan/20 – Dec/20	-1.9 (0.1)	↔	
Southeast	Jan/20 – May/20	-7.3 (<0.001) *	↓	
	May/20 – Dec/20	1.8 (0.1)	↔	
	Jan/20 – Dec/20	-1.6 (0.1)	↔	
South	Jan/20 – Dec/20	-1.2 (0.1)	↔	
Central-West	Jan/20 – Aug/20	-5.4 (<0.001) *	↓	
	Aug/20 – Dec/20	3.0 (0.1)	↔	
	Jan/20 – Dec/20	-2.4 (<0.001) *	↓	
Brazil	Jan/18 – May/20	-8.1 (<0.001) *	↓	
	May/20 – Dec/20	1.5 (0.2)	↔	
	Jan/20 – Dec/20	-2.1 (<0.001) *	↓	

Legend**:** APC, annual percentage change; AAPC, average annual percentage change ↔Stable; ↓Decreasing; ↑Increasing. *Statistical significance.

Brazil: changes in the behavior of individuals, which caused less search for and/or evasion of health services; and aspects directly related to changes in the structure and functioning of health services, such as the reduction of outpatient care and the relocation of health professionals to fight the pandemic (BORGES, 2020). Notably, these changes are consequences of the implementation of a wide range of non-pharmacological

Table 6. Temporal analysis (*joinpoint regression model*) of the average days of hospital stay for cardiovascular diseases in Brazil and regions between January and December 2020

Region	Period	APC/AAPC (*P* value)	Trend	Joinpoint regression model
North	Jan/20 – Dec/20	-1.0 (<0.001) *	↓	
Northeast	Jan/20 – Apr/20	0.2 (<0.001) *	↑	
	Apr/20 – Jul/20	-3.2 (<0.001) *	↓	
	Jul/20 – Oct/20	1.1(<0.001) *	↑	
	Oct/20 – Dec/20	4.0 (<0.001) *	↑	
	Jan/20 – Dec/20	0.2 (<0.001) *	↑	
Southeast	Jan/20 – Mar/20	2.5 (0.4)	↔	
	Mar/20 – Oct/20	-1.5 (<0.001) *	↑	
	Oct/20 – Dec/20	3.9 (0.3)	↔	
	Jan/20 – Dec/20	0.2 (0.8)	↔	
South	Jan/20 – Dec/20	0.3 (0.1)	↔	
Central-West	Jan/20 – Sept/20	-2.2 (<0.001) *	↓	
	Sept/20 – Dec/20	6.5 (<0.001) *	↑	
	Jan/20 – Dec/20	0.1 (0.9)	↔	
Brazil	Jan/18 – Oct/20	-0.8 (<0.001) *	↓	
	Oct/20 – Dec/20	3.7 (0.3)	↔	
	Jan/20 – Dec/20	0.0 (1.0)	↔	

Legend**:** APC, annual percentage change; AAPC, average annual percentage change ↔Stable; ↓Decreasing; ↑Increasing. *Statistical significance.

measures aimed at containing the spread of the SARS-CoV-2 in the Brazilian territory.[18]

Initially, the pandemic caused important changes in the behavior of the population, which may have resulted in reduced access to health services. Likewise, the need for social distancing to control the spread of the virus seems to have acted as a factor generating fear of contamination in health facilities.[19] Additionally, there was reduction of urban mobility and access to health services by the population. Taken together, these factors may have influenced the evasion of patients from different health services, whether in primary care, responsible for managing risk factors-chronic diseases, or in specialized-hospital centers.[10,11,20]

Similarly, the reduction in hospitalizations for CVD was also observed in other studies worldwide.[21,22] Corroborating our findings, a study conducted in New York (USA) observed a significant reduction in acute hospitalizations for chronic diseases in 2020, including cardiovascular diseases.[23] Importantly, the delay in patient care, observed in many countries, has resulted in serious clinical conditions rarely seen outside this context, such as cardiogenic shock and ventricular rupture due to acute myocardial infarction (AMI), which significantly increases risk of death from CVD.[24]

In Brazil, an investigation carried out with more than 45 thousand individuals showed that people with CVD had greater adherence to measures of social distancing.[25] Remarkable, this scenario can be justified by different factors, such as: i. association between the presence of CVD and increased risk of death from COVID-19[6]; ii. the fear of SARS-CoV-2 infection[27]; iii. the amount of information disseminated by the media and social networks (*infodemic*)[28,29]; and iv. the dissemination of false and unscientific information (*fake news*).[30] Taken together, they potentiated the negative effects of social isolation, causing fear, sadness, depression, anxiety, and sleep disturbances.[31]

Additionally, the same study conducted here[25] showed that patients with chronic non-communicable diseases (NCDs) had more difficulty accessing health services during the pandemic. These services included health care, appointment bookings, and medication. It should be noted that chronic diseases, due to their typically long-lasting nature, demand more control actions and the provision of health services.[32] As a result, the difficulties in accessing health services and the social isolation measures may have impacted on the reduction of hospital admissions and the increase in mortality from CVD.

Regarding changes in the structure and functioning of health care services that may have reduced the number of admissions, we highlighted: i. the reallocation of resources (financial, human and material) to assist in cases of COVID-19, which may result in the depletion of these resources for other sectors[33]; ii. the rescheduling of appointments with greater delay; iii. the preference for assistance via telemedicine[14,34]; iv. reducing the daily working hours of services, health professionals and the number of daily appointments.[35]

On the other hand, following the increase in COVID-19 cases in the country, there was an increase in in-hospital mortality due to CVD, as also observed in previous studies in Brazil[36] and in other countries.[37,38] In these studies, patients hospitalized with acute myocardial infarction,[37] coronary artery disease,[38,39] or acute cardiac injury[39] were more likely to

have fatal outcomes when co-infected with SARS-CoV-2. Furthermore, this aggravating factor and the increased demand for health professionals may also explain the increase in the average cost per hospitalization observed in our study.

More recently, COVID-19 started to be described in the scientific literature as a vascular disease, rather than respiratory disease, which increases the risk of pathophysiological interaction with CVD.[40] This interaction and the consequences of the various vascular dysfunctions caused by COVID-19 increase the risk of lethality in individuals with CVD. Different factors, such as the activation of the immune system and the cytokine storm, prothrombotic state, and dysregulation of the Renin-Angiotensin-Aldosterone system led to events such as AMI and cerebrovascular accident (CVA).[40]

Notably, regional disparities in Brazil may be associated with variations in the impact of the pandemic. The North region had the highest mortality rate, and it may be related to the precariousness of the health system in the region. The asymmetric and reduced distribution of health resources in the territory and the concentration of medical treatments in the urban centers of Manaus (Capital of the State of Amazonas) and Belém (Capital of the State of Pará) results in a migratory process in search of care. As a result, there is acceleration of COVID-19′s internalization process and rapid collapse of the health network.[41,42]

In addition, the increased severity of these patients at the time of admission significantly increases the chance of death. Hereupon, there is a reduction in the time of stay and, consequently, in the average cost of hospitalizations. This phenomenon can be exemplified by the high mortality rate due to COVID-19 observed in the state of Amazonas, which underwent a major collapse of the health system in May and December 2019, as consequence of the sharp rise in cases of COVID-19 and the inability of the health network to meet the demand.[43,44]

Otherwise, a more homogeneous distribution of health resources among municipalities in the South region, with a greater offer of ICU beds, respirators, and health professionals in the territory can directly contribute to a better compatibility between hospital supply and demand.[45] Notably, these regional disparities reflect the unequal development and concentration of wealth in the South and Southeast regions of the country and may have influenced the lower in-hospital lethality observed in this region. In fact, population with better living conditions has more access to health care services, which implies greater survival when compared to other populations without the same access facilities.

The Central-West region, which was impacted later with the arrival of COVID-19, had an average of 2.5 hospital beds/10,000 inhabitants (about 8.5% of the total number of beds in the country). Despite being the second largest Brazilian region in terms of land area, it is the second least populated, and has the second smallest GDP among the other regions.[46] In this region, about 80% of the population depends on the SUS and, during the pandemic, the Central-West had the second lowest number of ICU beds in the SUS, which contributed to a smaller variation in the rate of admissions and an increase in the in-hospital lethality rate for CVD.[47]

Furthermore, a study that assessed the population's adherence to measures to restrict physical contact and spread COVID-19 across the Brazilian regions showed that the residents of the Central-West were those with the lowest adherence to virus control measures.[48] In addition, the Central-West had the lowest percentage of total restriction of physical contact (12.3%) and the highest percentage of people who did not undergo any type of restriction (3.3%), which may have contributed to the highest CVD in-hospital lethality rate. Alternatively, the groups with the highest membership were composed of residents of the Southeast and Northeast regions.

Despite all efforts conducted by state governments to reduce hospitalization and deaths due to COVID-19 in Brazil, a second wave of the pandemic, even more severe, occurred first in the state of Amazonas (November 2020) and spread to other regions of the country in March 2021.[49] This second wave may have occurred due to multiple factors, such as: behavioral (population neglect and relaxation of post-first wave social distancing measures); delays in acquiring vaccines and low mass immunity; and iii. emergence of new variant strains of the virus (such as B.1.1.28, P.1, B.1.195, B.1.1.33 and P.2) with greater potential for transmission.[50] Unfortunately, this second wave caused chaos and collapse in health systems in all regions, which limited care for clinical complications and exacerbations in patients with CVD/COVID-19. Consequently, this may have increased the in-hospital lethality rate from CVD.

Even considering all the methodological precautions, this study has some limitations. The increase in the in-hospital lethality rate may be overestimated due to the reduction in the number of admissions (the denominator of the equation). In addition, the use of secondary data that are subject to the influence of the operative capacity of health services, which are related to the possibility of confusion as to the cause of death, both for CVD and for COVID-19.

Conclusion

Our analyzes demonstrated the impact of the COVID-19 pandemic on indicators of hospital admissions and lethality from CVD in Brazil, with variations depending on the nature of the indicator and the region of the country. Herein, we observed an increase in the hospital admission rate, in-hospital lethality, in the total cost of admissions, and in the total number of hospitalization days for CVD. Conversely, there was a reduction in the average cost per hospitalization, and in the average number of days of hospitalization due to CVD. Therefore, the study data suggest that the pandemic affected both health services and the dynamics of patients' demand for care. As a result, there has been a reduction in access to health services, diagnosis, and timely treatment of other diseases, including CVD.

REFERENCES

1. Xinhua. XINHUA. China's CDC detects a large number of new coronaviruses in the South China seafood market in Wuhan.
2. WORLD HEALTH ORGANIZATION. WORLD HEALTH ORGANIZATION. IHR procedures concerning public health emergencies of international concern (PHEIC). Published http://www.who.int/ihr/procedures/pheic/en/.
3. BRASIL. CORONAVÍRUS BRASIL: Painel de casos de doença pelo coronavírus 2019 (COVID-19). Published https://covid.saude.gov.br/.
4. BRASIL. PORTARIA Nº 454, DE 20 DE MARÇO DE 2020. 2020 https://www.in.gov.br/en/web/dou/-/portaria-n-454-de-20-de-marco-de-2020-249091587.
5. de Souza CDF, MF Machado, Do Carmo RF. Human development, social vulnerability and COVID-19 in Brazil: A study of the social determinants of health. *Infect Dis Poverty* 2020;9:4–13. https://doi.org/10.1186/s40249-020-00743-x.
6. Souza CDF de, Machado MF, Gonçalves da Silva Junior A. Bastos rolim nunes be, feliciano do carmo r. airports, highways and COVID-19: An analysis of spatial dynamics in Brazil. *J Transp Heal* 2021;21:101067. https://doi.org/10.1016/j.jth.2021.101067.
7. Carmo RF, Nunes BEBR, Machado MF, Armstrong AC, Souza CDF. Expansion of COVID-19 within Brazil: The importance of highways. *J Travel Med* 2021;27:1–3. https://doi.org/10.1093/JTM/TAAA106.
8. Aquino EML, Silveira IH, Pescarini JM, et al. Medidas de distanciamento social no controle da pandemia de COVID-19: potenciais impactos e desafios no Brasil. *Cien Saude Colet* 2020;25(suppl 1):2423–46. https://doi.org/10.1590/1413-81232020256.1.10502020.
9. JOHNS HOPKINS UNIVERSITY. JOHNS HOPKINS UNIVERSITY. COVID-19 Map. Johns Hopkins Coronavirus Resource Center; 2019. Published https://coronavirus.jhu.edu/map.html.

10. Araujo SEA, Leal A, Centrone AFY, et al. Impact of COVID-19 pandemic on care of oncological patients: experience of a cancer center in a Latin American pandemic epicenter. *Einstein (São Paulo)* 2020;19:eAO6282. https://doi.org/10.31744/einstein_journal/2021AO6282.
11. Borges KNG, Oliveira RC, Macedo DAP, Santos J do C, Pellizzer LGM. The impact of the COVID-19 pandemic on individuals with dementia. *Caring Ages*. 2021;22:2. doi:10.1016/j.carage.2020.12.001
12. Melo DO de, Ribeiro TB, Grezzana GB, Stein AT. COVID-19 e doença hipertensiva no Brasil: possibilidade de uma tempestade perfeita. *Rev Bras Epidemiol* 2020;23:1–4. https://doi.org/10.1590/1980-549720200062.
13. Bezerra ACV, Silva CEM da, Soares FRG, Silva JAM da. Fatores associados ao comportamento da população durante o isolamento social na pandemia de COVID-19. *Cien Saude Colet* 2020;25(suppl 1):2411–21. https://doi.org/10.1590/1413-81232020256.1.10792020.
14. Caetano R, Silva AB, Guedes ACCM, et al. Desafios e oportunidades para telessaúde em tempos da pandemia pela COVID-19: uma reflexão sobre os espaços e iniciativas no contexto brasileiro. *Cad Saude Publica* 2020;36:1–16. https://doi.org/10.1590/0102-311x00088920.
15. Costa BCP, Rocha Siqueira Sudré M, Gomes Musa dos Santos I, Rodrigues D, Pereira Machado J, Velludo Veiga E. Pandemia COVID-19 e sua relação com a doença cardiovascular: revisão integrativa. *Saúde Coletiva (Barueri)* 2020;10:4092–105. https://doi.org/10.36489/saudecoletiva.2020v10i59p4092-4105.
16. Nascimento JHP, Costa RL da, Simvoulidis LFN, et al. COVID-19 e Injúria Miocárdica em UTI Brasileira: Alta Incidência e Maior Risco de Mortalidade Intra-Hospitalar. *Arq Bras Cardiol* 2021;116:275–82. https://doi.org/10.36660/abc.20200671.
17. Kim H, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000;19(3):335–51. https://doi.org/10.1002/(SICI)1097-0258(20000215)19:3<335::AID-SIM336>3.3.CO;2-Q.
18. Barbosa Baptista A, Vieira Fernandes L. COVID-19, análise das estratégias de prevenção, cuidados e complicações sintomáticas. *DESAFIOS - Rev Interdiscip da Univ Fed do Tocantins* 2020;7(Especial-3):38–47. https://doi.org/10.20873/uftsuple2020-8779.
19. Schuchmann AZ, Schnorrenberger BL, Chiquetti ME, Gaiki RS, Raimann BW, Maeyama MA. Isolamento social vertical X Isolamento social horizontal: os dilemas sanitários e sociais no enfrentamento da pandemia de COVID-19. *Brazilian J Heal Rev* 2020;3:3556–76. https://doi.org/10.34119/bjhrv3n2-185.
20. Souza CDF de, Gois-Santos VT de, Correia DS, Martins-Filho PR, Santos VS. The need to strengthen primary health care in Brazil in the context of the COVID-19 pandemic. *Braz Oral Res* 2020;34:1–3. https://doi.org/10.1590/1807-3107bor-2020.vol34.0047.
21. Enache B, Claessens Y-E, Boulay F, et al. Reduction in cardiovascular emergency admissions in Monaco during the COVID-19 pandemic. *Clin Res Cardiol* 2020;109:1577–8. https://doi.org/10.1007/s00392-020-01687-w.

22. Vecchio S, Fileti L, Reggi A, Moschini C, Lorenzetti S, Rubboli A. Impatto della pandemia COVID-19 sui ricoveri per sindrome coronarica acuta: Revisione della letteratura ed esperienza monocentrica. *G Ital Cardiol* 2020;21:502–8. https://doi.org/10.1714/3386.33635.
23. Blecker S, Jones SA, Petrilli CM, et al. Hospitalizations for chronic disease and acute conditions in the time of COVID-19. *JAMA Intern Med* 2021;181:269. https://doi.org/10.1001/jamainternmed.2020.3978.
24. Yoganathan A, Sajjad MS, Harky A. Cardiovascular disease and the impact of COVID-19. *J Card Surg* 2020;35:2113. https://doi.org/10.1111/jocs.14682. -2113.
25. Malta DC, Gomes CS, Silva AG da, et al. Uso dos serviços de saúde e adesão ao distanciamento social por adultos com doenças crônicas na pandemia de COVID-19, Brasil, 2020. *Cien Saude Colet* 2021;26:2833–42. https://doi.org/10.1590/1413-81232021267.00602021.
26. Jardim B, Migowski A, Corrêa FDM, Silva GA e. Covid-19 no Brasil em 2020: impacto nas mortes por câncer e doenças cardiovasculares. 2021;20:2021-2028. doi: https://doi.org/10.1590/SciELOPreprints.2659
27. Lima SO, Silva MA da, Santos MLD, et al. Impactos no comportamento e na saúde mental de grupos vulneráveis em época de enfrentamento da infecção COVID-19: revisão narrativa. *Rev Eletrônica Acervo Saúde* 2020;46:e4006. https://doi.org/10.25248/reas.e4006.2020.
28. Garcia LP, Duarte E. Infodemia: excesso de quantidade em detrimento da qualidade das informações sobre a COVID-19. *Epidemiol e Serviços Saúde* 2020;29:e2020186. https://doi.org/10.1590/s1679-49742020000400019.
29. Teixeira PTF, Lima JDS, Guerreiro ML da S. As implicações psicológicas desencadeadas pelo excesso de informações em tempos de pandemia Covid-19 /the psychological implications triggered by the excess of information in times of pandemic Covid-19. *ID line Rev Psicol* 2021;15:676–95. https://doi.org/10.14295/idonline.v15i55.3098.
30. Pereira MD, Oliveira LC de, Costa CFT, et al. A pandemia de COVID-19, o isolamento social, consequências na saúde mental e estratégias de enfrentamento: uma revisão integrativa. *Res Soc Dev* 2020;9:e652974548. https://doi.org/10.33448/rsd-v9i7.4548.
31. Barros MB de A, Lima MG, Malta DC, et al. Relato de tristeza/depressão, nervosismo/ansiedade e problemas de sono na população adulta brasileira durante a pandemia de COVID-19. *Epidemiol e Serviços Saúde* 2020;29:e2020427. https://doi.org/10.1590/s1679-49742020000400018.
32. Malta DC, Cezário AC, Moura L de, Morais Neto OL de, Silva JB da, Junior. A construção da vigilância e prevenção das doenças crônicas não transmissíveis no contexto do Sistema Único de Saúde. *Epidemiol e Serviços Saúde* 2006;15:47–65. https://doi.org/10.5123/S1679-49742006000300006.
33. Kretzer L, Berbigier E, Lisboa R, Grumann AC, Andrade J. Recomendações Da AMIB (Associação de Medicina Intensiva Brasileira), ABRAMEDE (Associação Brasileira de Medicina de Emergência, SBGG (Sociedade Brasileira de Geriatria e

Gerontologia) e ANCP (Academia Nacional de Cuidados Paliativos) de Alocação de Recurs. 2020.

34. Sarti TD, Lazarini WS, Fontenelle LF, Almeida APSC. Qual o papel da Atenção Primária à Saúde diante da pandemia provocada pela COVID-19? *Epidemiol e Serviços Saúde* 2020;29:e2020166. https://doi.org/10.5123/S1679-49742020000200024.
35. Pereira-Neves A, Rocha-Neves J, Dias-Neto M, Cerqueira A, Fernando-Teixeira J. The impact of COVID-19 pandemic in the management of a vascular surgery department. *Rev Port Cir Cardiotorac Vasc* 2020;27:73–4 http://www.ncbi.nlm.nih.gov/pubmed/32707609.
36. Normando PG, Araujo-Filho J de A, Fonseca G de A, et al. Redução na hospitalização e aumento na mortalidade por doenças cardiovasculares durante a pandemia da COVID-19 no Brasil. *Arq Bras Cardiol* 2021;116:371–80. https://doi.org/10.36660/abc.20200821.
37. Solano-López J, Zamorano JL, Pardo Sanz A, et al. Risk factors for in-hospital mortality in patients with acute myocardial infarction during the COVID-19 outbreak. *Rev Española Cardiol (English Ed* 2020;73:985–93. https://doi.org/10.1016/j.rec.2020.07.009.
38. Nai Fovino L, Cademartiri F, Tarantini G. Subclinical coronary artery disease in COVID-19 patients. *Eur Hear J - Cardiovasc Imaging* 2020;21:1055–6. https://doi.org/10.1093/ehjci/jeaa202.
39. Li X, Guan B, Su T, et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. *Heart* 2020;106:1142–7. https://doi.org/10.1136/heartjnl-2020-317062.
40. Siddiqi HK, Libby P, Ridker PM. COVID-19 − A vascular disease. *Trends Cardiovasc Med* 2021;31:1–5. https://doi.org/10.1016/j.tcm.2020.10.005.
41. IBGE. IBGE. Deslocamentos para Busca a Serviços de Saúde. Mapa interativo. Published 2020. https://mapasinterativos.ibge.gov.br/covid/regic/
42. Garnelo L, Lima JG, Rocha ESC, Herkrath FJ. Acesso e cobertura da Atenção Primária à Saúde para populações rurais e urbanas na região norte do Brasil. *Saúde em Debate* 2018;42(spe1):81–99. https://doi.org/10.1590/0103-11042018s106.
43. BARRETO IC de HC, et al. Colapso na Saúde em Manaus : o fardo de não aderir às medidas não farmacológicas de redução da transmissão da COVID-19. *Scielo Prepr.* 2020:20. https://doi.org/10.1590/SciELOPreprints.1862. Published online.
44. Noronha KVM de S, Guedes GR, Turra CM, et al. Pandemia por COVID-19 no Brasil: análise da demanda e da oferta de leitos hospitalares e equipamentos de ventilação assistida segundo diferentes cenários. *Cad Saude Publica* 2020;36:1–17. https://doi.org/10.1590/0102-311x00115320.
45. Albuquerque MV de, Leandro Ribeiro LH. Inequality, geographic situation, and meanings of action in the COVID-19 pandemic in brazil. *Cad Saude Publica* 2020;36:1–14. https://doi.org/10.1590/0102-311X00208720.
46. Ferreira VM, Andrade LI e, Diniz RCS, et al. Avaliação epidemiológica das regiões do Brasil na pandemia de COVID-19. *Rev Eletrônica Acervo Saúde* 2021;13:e7137. https://doi.org/10.25248/reas.e7137.2021.

47. Cotrim DF, Jr, Cabral LM da S. Crescimento dos leitos de UTI no país durante a pandemia de Covid-19: desigualdades entre o público x privado e iniquidades regionais. *Physis Rev Saúde Coletiva* 2020;30:1–11. https://doi.org/10.1590/s0103-73312020300317.
48. Szwarcwald CL, Souza PRB de, Jr, Malta DC, et al. Adesão às medidas de restrição de contato físico e disseminação da COVID-19 no Brasil. *Epidemiol e Serviços Saúde* 2020;29:e2020432. https://doi.org/10.1590/s1679-49742020000500018.
49. Souza FSH de, Hojo-Souza NS, da Silva CM, Guidoni DL. Second wave of COVID-19 in Brazil: younger at higher risk. *Eur J Epidemiol* 2021;36:441–3. https://doi.org/10.1007/s10654-021-00750-8.
50. Silva SJR da, Pena L. Collapse of the public health system and the emergence of new variants during the second wave of the COVID-19 pandemic in Brazil. *One Heal.* 2021;13:100287. https://doi.org/10.1016/j.onehlt.2021.100287.