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ORIGINAL ARTICLE

Covid-19 in-hospital fatality among hospitalized patient residents of the two largest and smaller cities of the Brazilian states

Mortalidade hospitalar por Covid-19 entre pacientes hospitalizados residentes nas duas maiores e menores cidades dos estados brasileiros

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KEYWORDS
Covid-19
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ABSTRACT

Objective: To estimate the relative risk of COVID-19 in-hospital mortality rates among patients according to residing in the two largest cities of each state or residing in any smaller city, and to describe different patterns across states and macro-regions of Brazil. **Method:** The sample included all hospitalizations confirmed for COVID-19 that occurred in Brazil with a recorded outcome of the hospitalization by the end of December 2021. The exposure assessed was patients residing in the two largest cities of the state or any smaller cities. The outcome was in-hospital mortality rates caused by COVID-19. Multilevel Poisson regression was used to estimate adjusted relative risks for each state and macro-region of Brazil. **Result:** The analytic sample was composed of 1,658,934 hospitalized COVID-19 cases. For the whole country, living in the two largest cities of each state was associated with a lower risk of in-hospital mortality rate. Nevertheless, in two states of the North region (Amazonas and Pará), individuals living in the largest cities presented greater in-hospital fatality rates than those living in smaller cities. **Conclusion:** At the two biggest states of the Brazilian North region, the pattern of association between living in the largest cities and in-hospital fatality was inverse, and higher proportions of deaths without access to a hospital bed were identified, indicating singular vulnerability. The findings highlight the need for a more equitable distribution of health care services and qualified professionals in the vast territory of Brazil.

PALAVRAS-CHAVE
Covid-19
Mortalidade Hospitalar
Brasil

RESUMO

Objetivo: Estimar o risco relativo de taxas de mortalidade hospitalar pela COVID-19 entre pacientes de acordo com residir nas duas maiores cidades de cada estado ou residir em qualquer cidade menor e descrever diferentes padrões entre estados e macrorregiões do Brasil. **Método:** A amostra incluiu todas as internações confirmadas por COVID-19 ocorridas no Brasil com registro da internação por COVID-19 até o final de dezembro de 2021. A exposição avaliada foi pacientes residentes nas duas maiores cidades do estado ou em cidades menores. O desfecho estudado foi as taxas de mortalidade hospitalar causadas pela COVID-19. A regressão de Poisson multinível foi utilizada para estimar os riscos relativos ajustados de cada estado e

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macrorregião do Brasil. **Resultado:** A amostra analítica foi composta por 1.658.934 casos hospitalizados por COVID-19. Para todo o país, morar nas duas maiores cidades de cada estado foi associado a um menor risco de taxa de mortalidade hospitalar. Apesar disso, em dois estados da região Norte (Amazonas e Pará), os indivíduos residentes nas maiores cidades apresentaram maiores taxas de letalidade hospitalar do que aqueles residentes nas cidades menores. **Conclusão:** Nos dois maiores estados da região Norte brasileira, o padrão de associação entre morar nas maiores cidades e mortalidade hospitalar foi inverso, e foram identificadas maiores proporções de mortes sem acesso a leito hospitalar, indicando vulnerabilidade singular. Os resultados destacam a necessidade de uma distribuição mais equitativa dos serviços de saúde e de profissionais qualificados no todo território do Brasil.

INTRODUCTION

COVID-19 can be considered as the first true global pandemic in the digital era[1]. Its global impact has been of great concern and has overloaded public health systems worldwide. Globally, as of March 21st, 2023, there have been 761,071,826 COVID-19 confirmed cases, including 6,879,677 deaths[2]. Brazil was the sixth country with more confirmed cases and the second with more deaths[2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread to Brazil via international flights[3] with the first case diagnosed on February 26th, 2020[4]. SARS-CoV-2 cases were initially concentrated in metropolitan areas and then spread from state capitals to non-capital areas[3].

During 2020 and 2021, Brazil faced two waves of the pandemic of COVID-19. Over the first wave, the number of cases and deaths increased steadily until reaching its peak by the end of July 2020 and then started to decline from September to early November 2020. The second wave began in January 2021 and reached its peak by early April and started to decline from the end of June 2021[5]. The country initiated COVID-19 vaccination on January 17th, 2021[6].

Brazil is an upper-middle-income country with a large territorial area and an estimated population of over 213 million inhabitants in 2021[7]. The country has 27 states divided into five macro-regions (North, Northeast, Central-West, Southeast, and South). The Southeast region is the most developed and populous, with approximately 92 inhabitants/km^2 and a Human Development Index (HDI) of 0.784, whereas the North region has the lowest demographic density, with 4.72 inhabitants/km^2, and the Northeast region has the lowest HDI (0.608)[8].

The Brazilian health system is divided into two sectors. The public sector is a government-funded Unified Healthcare System (*Sistema Único de Saúde – SUS*), and the private sector is mostly financed for profit and comprises different modalities of insurance and private health plans[9]. The private sector provides care for those with individual or family contracts, business and collective health plans, with the purpose of medical, hospital, and dental care to their beneficiaries[10].

Although Brazilian Unified Healthcare System that covers the entire population and is responsible for around 70% of health care services delivered[11], there are substantial health and socioeconomic differences between and within its cities[12], which is reflected in the quality of regional health services, such as the availability of hospital beds and staff[13-15].

Brizzi et al. reported that in March 2020, few days after the detection of the first COVID-19 case in Brazil, large inequities in healthcare resources were present in Brazil[16]. In addition, before the beginning of the pandemic, most of the health microregions with the lowest supply of general beds, intensive care units (ICU,) and mechanical ventilation devices were concentrated in the northern region, while health micro-regions with the highest supply are in South and Southeast[17]. Therefore, the aim of this study was to estimate the relative risk of COVID-19 in-hospital mortality among Brazilian patient residents in the two largest cities and smaller cities of each state and describe different patterns across states and macro-regions of the country.

METHODS

Data source and participants

The present study analyzed all admitted cases by COVID-19 from February 26th, 2020, to December 31st, 2021. Data on hospitalizations notified in the Influenza Epidemiological Surveillance Information System (SIVEP Gripe - Sistema de Informação de Vigilância Epidemiológica da Gripe) of the Brazilian Ministry of Health were used. The analyzed sample included cases that occurred in Brazil since the beginning of the pandemic, both from public and private health services, with a recorded outcome of the hospitalization (discharge or death) by the end of 2021, regardless of the individual's age. The patient was considered hospitalized if he/she had valid data for at least one of the following variables in the data collection form: 1)"hospitalization"; 2) "date of admission to the intensive care unit (ICU)"; 3) "date of leaving the ICU"; 4) "ICU"; 5) "mechanical ventilation"; and 6) "in-patient hospital". Additionally, from the same national database, we extracted deaths attributable to COVID-19 without hospitalization.

The primary instrument of data collection was the compulsory notification sheet of cases of SARS hospitalizations, filled out by hospital teams and recorded in the SIVEP Gripe. Cases of SARS were defined as individuals with flu-like illness (acute respiratory illness, characterized by at least two of the following signs and symptoms: fever, chills, sore throat, headache, cough, runny nose, loss of smell or taste, who presented with dyspnea/respiratory discomfort, persistent pressure in the thorax, O_2 saturation less than 95% in ambient air, or blueness in the lips or face[18]. The RT-PCR was prioritized

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for diagnosis, and available resources for theses essays were allocated to hospitals around the country since the beginning of the pandemic, aiming at strengthening the diagnostic assessment of the disease.

Exposure

The exposure assessed was the patient's type of city of residence, regardless of the hospitalization city, recorded at compulsory notifications of COVID-19 hospitalizations. This variable was dichotomized in residing in one of the two largest cities of each state (including the capital and the other largest city) or residing in any smaller cities.

Outcome

The main outcome assessed was in-hospital mortality caused by COVID-19. This variable collected in the SIVEP Gripe contained three valid categories: hospital discharge (cured)/death by COVID-19/death by other causes. Individuals who progressed to death by other causes and patients with missing data about the outcome were excluded from the analytical sample, and the outcome was dichotomized into hospital discharge(cure)/death by COVID-19.

Covariates

The demographic covariates were sex (female/male), age, and self-reported skin color (white/black/brown/asian/indigenous/not given)[19]. The comorbidities were type 2 diabetes, chronic cardiovascular diseases, asthma, obesity, hematologic diseases, chronic neurological disease, chronic renal diseases, other pneumopathy, and immunodeficiency diseases.

The notification sheet of SIVEP Gripe contained the question *"Does the patient possess any risk factors/comorbidities? If yes, which ones? (Mark x)"* followed by a list of comorbidities to be measured[18]. After filling out this form, data were typed into the online information system. As a result of the format of the question in the notification sheet (*marking of x only for the present comorbidities*), individuals with a marking on the comorbidities with the category "Yes" were deemed to have the comorbidity in question, while individuals marked with the category "No" or with the field "Blank" were considered not to have the comorbidity assessed. Individuals marked with the category "Ignored" were excluded from the analyses.

Statistical analysis

Statistical software R 4.2.1 and Stata 15.1 software were used to analyze the data (Stata Corp., College Station, Texas, USA). Bivariate unadjusted analyses (between the exposure and the covariates) were performed using a chi-squared test of heterogeneity for categorical variables and t-test for the continuous variable.

Regarding multivariable analyses, we run a multilevel Poisson regression considering the clustering of the states into regions with a random slope for each state. Unadjusted and adjusted relative risks (RR) of COVID-19 case fatality, with 95% confidence intervals (95%CI), for each state and by macro-region were estimated. Exploratory post-hoc analysis estimated the proportion of deaths by COVID-19 without hospitalization among all deaths that occurred from the beginning of the COVID-19 pandemic to December 2021, for each Brazilian macro-region and for each State of North macro-region.

Ethical considerations

The secondary data utilized from SIVEP Gripe are de-identified and publicly available on the OpenDataSUS website maintained by the Brazilian Ministry of Health. Aggregated data were used, without risk to the anonymity of the participants.

RESULTS

A total of 1,825,895 SARS hospitalizations caused by COVID-19 were registered from February 2020 to December 2021 in Brazil. After excluding cases without the outcome information or deaths by other causes, the sample analyzed was 1,658,934 hospitalized COVID-19 patients (Figure 1). In all regions, patients between 40-59 years old and males had more COVID-19-associated hospitalizations. Also, cardiovascular diseases were the most prevalent comorbidities across regions followed by type 2 diabetes (Table 1).

The largest cities in Central-West, Southeast and South regions had more reported deaths from COVID-19 in 70 years or older patients than in small cities (Table 2). However, the proportions of COVID-19 deaths in this age range in the North and Northeast regions were higher in patients residing in small cities. In all regions, the proportion of patients with diabetes who died by COVID-19 was higher in residents of the largest cities than those living in smaller ones. In addition, the proportion of deaths by COVID-19 in patients with cardiovascular disease was higher in all five macro-regions.

Overall, people living in the two largest cities of each state presented 7% less risk of in-hospital lethality than

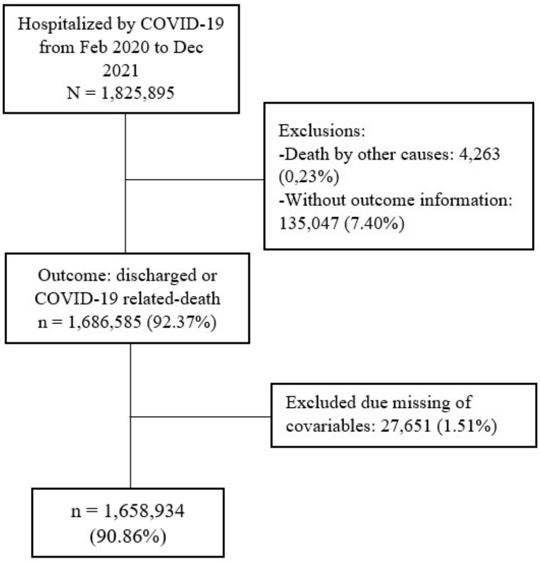

Figure 1 – Flow diagram of the selection of study participants.

Table 1 – Sample characteristics by macro-region. Brazil, 2020-2021 (n = 1,658,934).

Variables	North (n = 115,139)		Northeast (n = 260,808)		Central-West (n = 166,538)		Southeast (n = 823,535)		South (n = 292.914)	
	2 largest cities of states (n = 49,396)	Other cities of states (n = 65,743)	2 largest cities of states (n = 103,461)	Other cities of states (n = 157,347)	2 largest cities of states (n = 45,854)	Other cities of states (n = 120,684)	2 largest cities of states (n = 239,680)	Other cities of states (n = 583,855)	2 largest cities of states (n = 46,775)	Other cities of states (n = 246,139)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age. Mean (SD)	55.9 (±19.4)	55.1 (±20.2)	58.2 (±18.6)	58.4 (±19.4)	56.8 (±17.6)	55.7 (±17.4)	59.2 (±18.1)	57.8 (±17.4)	58.6 (±17.4)	57.0 (±17.2)
*p-value**	<0.001		0.014		<0.001		<0.001		<0.001	
Age										
0-17	1,555 (2.8)	2,521 (4.2)	2,530 (2.1)	3,408 (2.4)	792 (1.3)	1,400 (1.3)	4,231 (1.5)	6,645 (1.2)	667 (1.0)	2,590 (1.2)
18-39	8,996 (16.0)	10,634 (18.0)	17,222 (14.3)	20,986 (15.0)	9,908 (16.1)	18,035 (17.2)	35,674 (13.0)	78,034 (14.2)	9,172 (13.7)	34,669 (15.3)
40-59	20,345 (36.3)	19,539 (33.1)	41,504 (34.4)	46,082 (32.9)	23,296 (37.8)	41,833 (39.9)	94,682 (34.5)	206,093 (37.5)	24,059 (36.0)	86,292 (38.2)
60-69	11,398 (20.3)	10,735 (18.2)	23,828 (19.8)	24,842 (17.7)	11,818 (19.2)	19,435 (18.5)	55,923 (20.4)	111,744 (20.4)	13,763 (20.6)	45,435 (20.1)
70 and more	3,791 (24.6)	15,625 (26.5)	35,534 (29.5)	44,872 (32.0)	15,811 (25.7)	24,210 (23.1)	83,890 (30.6)	146,619 (26.7)	19,237 (28.8)	57,030 (25.2)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Sex										
Female	24,625 (43.9)	25,274 (42.8)	53,412 (44.3)	61,669 (44.0)	27,085 (43.9)	45,860 (43.7)	122,804 (44.7)	242,395 (44.1)	29,645 (44.3)	99,118 (43.8)
Male	31,460 (56.1)	33,780 (57.2)	67,206 (55.7)	78,521 (56.0)	34,540 (56.1)	59,053 (56.3)	151,596 (55.3)	306,740 (55.9)	37,253 (55.7)	126,898 (56.2)
*p-value**	<0.001		0.134		0.343		<0.001		0.036	
Skin color										
White	5,928 (10.6)	5,420 (9.2)	14,126 (11.7)	15,530 (11.1)	15,607 (25.3)	23,813 (22.7)	103,518 (37.7)	297,478 (54.2)	47,703 (71.3)	185,144 (81.9)
Black	1,259 (2.2)	1,923 (3.3)	4,229 (3.5)	5,217 (3.7)	2,020 (3.3)	3,241 (3.1)	15,167 (5.5)	29,457 (5.4)	2,483 (3.7)	5,490 (2.4)
Asian	766 (1.4)	482 (0.8)	1,309 (1.1)	1,589 (1.1)	913 (1.5)	1,147 (1.1)	3,730 (1.4)	4,578 (0.8)	610 (0.9)	965 (0.4)
Brown	42,183 (75.2)	47,249 (80.0)	59,905 (49.7)	89,361 (63.7)	25,973 (42.2)	52,713 (50.2)	84,562 (30.8)	134,367 (24.5)	3,161 (4.7)	15,858 (7.0)
Indigenous	173 (0.3)	1,196 (2.0)	121 (0.1)	259 (0.2)	183 (0.3)	533 (0.5)	182 (0.1)	286 (0.1)	22 (0.03)	357 (0.2)
Not given	5,776 (10.3)	2,784 (4.7)	40,928 (33.9)	28,234 (20.1)	16,929 (27.5)	23,466 (22.4)	64,241 (24.5)	82,969 (15.1)	12,919 (19.3)	18,202 (8.1)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Asthma	1,199 (2.1)	900 (1.5)	2,751 (2.3)	2,371 (1.7)	1,278 (2.1)	2,066 (2.0)	7,645 (2.8)	12,852 (2.3)	2,694 (4.0)	6,362 (2.8)
*p-value**	<0.001		<0.001		0.142		<0.001		<0.001	
Diabetes	11,719 (20.9)	10,450 (17.7)	30,259 (25.1)	33,948 (24.2)	12,434 (20.2)	20,759 (19.8)	64,899 (23.7)	123,264 (22.5)	16,181 (24.2)	47,163 (20.9)
*p-value**	<0.001		<0.001		0.009		<0.001		<0.001	
Cardiovascular diseases	15,226 (27.2)	12,108 (20.5)	38,848 (32.2)	41,513 (29.6)	16,120 (26.2)	25,653 (24.5)	100,289 (36.6)	175,763 (32.0)	24,741 (37.0)	69,109 (30.6)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Hematologic diseases	256 (0.5)	233 (0.4)	676 (0.6)	738 (0.5)	303 (0.5)	510 (0.5)	2,117 (0.8)	3,122 (0.6)	467 (0.7)	1,284 (0.6)
*p-value**	0.106		0.238		0.875		<0.001		<0.001	
Neurological diseases	1,094 (2.0)	629 (1.1)	3,617 (3.0)	3,177 (2.3)	1,625 (2.6)	2,170 (2.1)	10,699 (3.9)	16,311 (3.0)	3,833 (5.7)	8,221 (3.6)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Other pneumopathy	1,079 (1.9)	774 (1.3)	2,725 (2.3)	2,681 (1.9)	1,716 (2.8)	2,536 (2.4)	10,356 (3.8)	15,199 (2.8)	3,311 (5.0)	8,899 (3.9)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Immunodeficiency diseases	1,086 (1.9)	735 (1.2)	2,646 (2.2)	2,194 (1.6)	1,130 (1.8)	1,611 (1.5)	7,232 (2.6)	9,977 (1.8)	2,251 (3.4)	4,778 (2.1)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Obesity	3,531 (6.3)	2015 (3.4)	9,594 (8.0)	9,706 (6.9)	5,152 (8.4)	8,398 (8.0)	22,492 (8.2)	44,472 (8.1)	9,435 (14.1)	26,481 (11.7)
*p-value**	<0.001		<0.001		0.010		0.124		<0.00	
Chronic renal diseases	1,647 (2.9)	1244 (2.1)	4,263 (3.5)	4,277 (3.1)	1,963 (3.2)	2,884 (2.8)	10,290 (3.8)	16,540 (3.0)	2,756 (4.1)	6,370 (2.8)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Deaths	22,580 (40.3)	20,518 (34.7)	43,352 (35.9)	57,611 (41.1)	18,874 (30.6)	32,096 (30.6)	89,859 (32.8)	182,605 (33.3)	20,543 (30.7)	68,917 (30.5)
p-value	<0.001		<0.001		0.884		<0.001		0.287	

* P-value refers to the chi-square test of heterogeneity without multivariable adjustment.

Table 2 – Characteristics of death by COVID-19 by macro-region. Brazil, 2020-2021 (n= 556,955).

Variables	North (n = 43,098)		Northeast (n = 100,963)		Central-West (n = 50,970)		Southeast (n = 272,464)		South (n = 89,460)	
	2 largest cities of states (n = 22,580)	Other cities of states (n = 20,518)	2 largest cities of states (n = 43,352)	Other cities of states (n = 57,611)	2 largest cities of states (n = 18,874)	2 largest cities of states (n = 22,580)	Other cities of states (n = 20,518)	2 largest cities of states (n = 43,352)	Other cities of states (n = 57,611)	2 largest cities of states (n = 18,874)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age. Mean (SD)	64.0 (±15.9)	64.9 (±16.8)	66.4 (±16.3)	66.0 (±17.2)	65.2 (±15.9)	63.9 (±16.0)	67.9 (±15.6)	65.6 (±15.6)	67.8 (±15.2)	65.1 (±15.4)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Age										
0-17	114 (0.5)	211 (1.0)	241 (0.6)	467 (0.8)	41 (0.2)	89 (0.3)	187 (0.2)	399 (0.2)	25 (0.1)	168 (0.2)
18-39	1,541 (6.8)	1,426 (7.0)	2,501 (5.8)	4,139 (7.2)	1,230 (6.5)	2,341 (7.3)	4,280 (4.8)	10,765 (5.9)	928 (4.5)	4,106 (6.0)
40-59	6,412 (28.4)	5,172 (25.2)	10,840 (25.0)	14,089 (24.5)	5,177 (27.4)	9,728 (30.3)	20,171 (22.5)	49,070 (26.9)	4,709 (22.9)	18,999 (27.6)
60-69	5,656 (25.1)	4,739 (23.1)	9,773 (22.5)	11,601 (20.1)	4,311 (22.8)	7,362 (22.9)	20,844 (23.2)	43,851 (24.0)	4,772 (23.2)	16,606 (24.1)
70 and more	8,857 (39.2)	8,970 (43.7)	19,997 (46.1)	27,315 (47.4)	8,115 (43.0)	12,576 (39.2)	44,377 (49.4)	78,520 (43.0)	10,109 (49.2)	29,038 (42.1)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Sex										
Female	9,617 (42.6)	8,121 (39.6)	19,358 (44.6)	25,250 (43.8)	8,129 (43.1)	13,587 (42.3)	40,239 (44.8)	80,619 (44.2)	9,128 (44.4)	29,709 (43.1)
Male	12,963 (57.4)	12,397 (60.4)	23,994 (55.4)	32,361 (56.2)	10,745 (56.9)	18,509 (57.7)	49,620 (55.2)	101,986 (55.8)	11,415 (55.6)	39,208 (56.9)
*p-value**	<0.001		0.009		0.104		0.002		0.001	
Skin color										
White	2,815 (12.5)	2,037 (9.9)	6,104 (14.1)	6,895 (12.0)	4,717 (25.0)	7,534 (23.5)	37,677 (41.9)	100,564 (55.1)	14,806 (72.1)	55,969 (81.1)
Black	496 (2.2)	675 (3.3)	1,945 (4.5)	2,395 (4.2)	639 (3.4)	1,169 (3.6)	6,379 (7.1)	11,503 (6.3)	861 (4.2)	1,956 (2.8)
Asian	266 (1.2)	167 (0.8)	394 (0.9)	607 (1.1)	266 (1.4)	380 (1.2)	1,113 (1.2)	1,524 (0.8)	207 (1.0)	303 (0.4)
Brown	16,888 (74.8)	16,243 (79.2)	22,544 (52.0)	37,188 (64.6)	7,895 (41.8)	16,569 (51.6)	27,858 (31.0)	45,776 (25.1)	976 (4.8)	5,152 (7.5)
Indigenous	73 (0.3)	439 (2.1)	40 (0.1)	122 (0.2)	48 (0.3)	210 (0.7)	45 (0.1)	89 (0.1)	6 (0.03)	98 (0.1)
Not given	2,042 (9.0)	957 (4.7)	12,325 (28.4)	10,404 (18.1)	5,309 (28.1)	6,234 (19.4)	16,787 (18.7)	23,149 (12.7)	3,687 (18.0)	5,439 (7.9)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Asthma	340 (1.5)	270 (1.3)	772 (1.8)	821 (1.4)	405 (2.2)	571 (1.8)	1,991 (2.2)	3,928 (2.2)	775 (3.8)	1,874 (2.7)
*p-value**	0.096		<0.001		0.004		0.277		<0.001	
Diabetes	5,924 (26.2)	4,942 (24.1)	13,978 (32.2)	17,393 (30.2)	5,276 (28.0)	8,390 (26.1)	27,369 (30.5)	53,116 (29.1)	6,925 (33.7)	20,234 (29.4)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Cardiovascular diseases	7,837 (34.7)	5,910 (28.8)	17,591 (40.6)	20,691 (35.9)	6,878 (36.4)	10,367 (32.3)	41,386 (46.1)	74,299 (40.7)	10,240 (49.9)	29,143 (42.3)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Hematologic diseases	129 (0.6)	109 (0.5)	329 (0.8)	411 (0.7)	133 (0.7)	199 (0.6)	988 (1.1)	1,380 (0.8)	234 (1.1)	616 (0.9)
*p-value**	0.575		0.401		0.251		<0.001		0.001	
Neurological diseases	591 (2.6)	313 (1.5)	2,032 (4.7)	1,875 (3.3)	866 (4.6)	1,060 (3.3)	6,085 (6.8)	8,771 (4.8)	2,262 (11.0)	4,554 (6.6)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Other pneumopathy	662 (2.9)	465 (2.3)	1,479 (3.4)	1,606 (2.8)	998 (5.3)	1,345 (4.2)	5,380 (6.0)	7,979 (4.4)	1,764 (8.6)	4,634 (6.7)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Immunodeficiency diseases	568 (2.5)	404 (2.0)	1,254 (2.9)	1,224 (2.1)	582 (3.1)	770 (2.4)	3,408 (3.8)	4,743 (2.6)	1,199 (5.8)	2,439 (3.5)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	
Obesity	1,649 (7.3)	987 (4.8)	3,749 (8.7)	4,438 (7.7)	2,226 (11.8)	3,308 (10.3)	8,450 (9.4)	17,695 (9.7)	3,404 (16.6)	10,271 (14.9)
*p-value**	<0.001		<0.001		<0.001		0.017		0.003	
Chronic renal diseases	1,075 (4.8)	720 (3.5)	2,548 (5.9)	2,689 (4.7)	1,202 (6.4)	1,583 (4.9)	5,791 (6.4)	9,331 (5.1)	1,595 (7.8)	3,481 (5.1)
*p-value**	<0.001		<0.001		<0.001		<0.001		<0.001	

*P-value refers to the chi-square test of heterogeneity without multivariable adjustment.

individuals living in smaller cities (p=0.029). In the adjusted analyses only, the Northeast showed strong statistical evidence of the lowest risk of in-hospital fatality (RR=0.89, 95%CI 0.81 – 0.97) (Figure 2). In two of the seven states of the North macro-region (Amazonas RR=1.14, 95%CI 1.03 – 1.27 and Pará RR=1.23, 95%CI 1.11 – 1.36), individuals residing in the two largest cities of the state presented greater in-hospital fatality than those living in other cities of the same state (Figure 3). In addition, in Amapá (RR=1.06, 95%CI 0.92 – 1.23) from the same macro-region, patients living in the two largest cities displayed greater in-hospital fatality compared to those living in smaller cities, but precision was

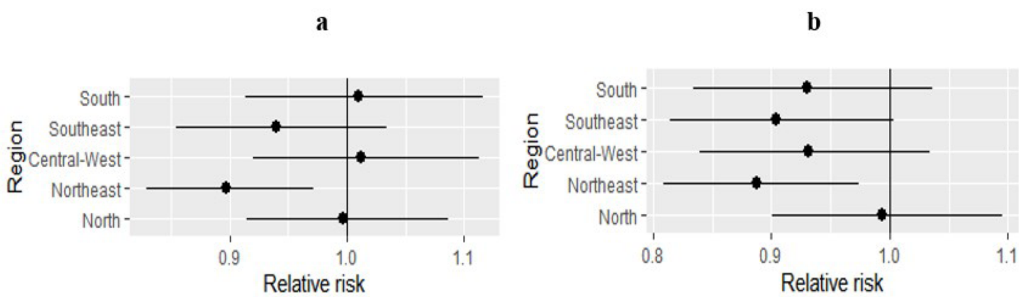

Figure 2 – Unadjusted and adjusted association between COVID-19 patients residing in the two largest cities or residing in smaller cities of each state and COVID-19 in-hospital case-fatality according to Brazilian macro-region and state. 2020-2021. (**a**) Unadjusted association; (**b**) Adjusted for sex, age and self-reported skin color, diabetes mellitus, chronic cardiovascular diseases, asthma, obesity, hematologic diseases, hepatic diseases, chronic neurological disease, chronic renal diseases, other pneumopathy, immunodeficiency diseases.

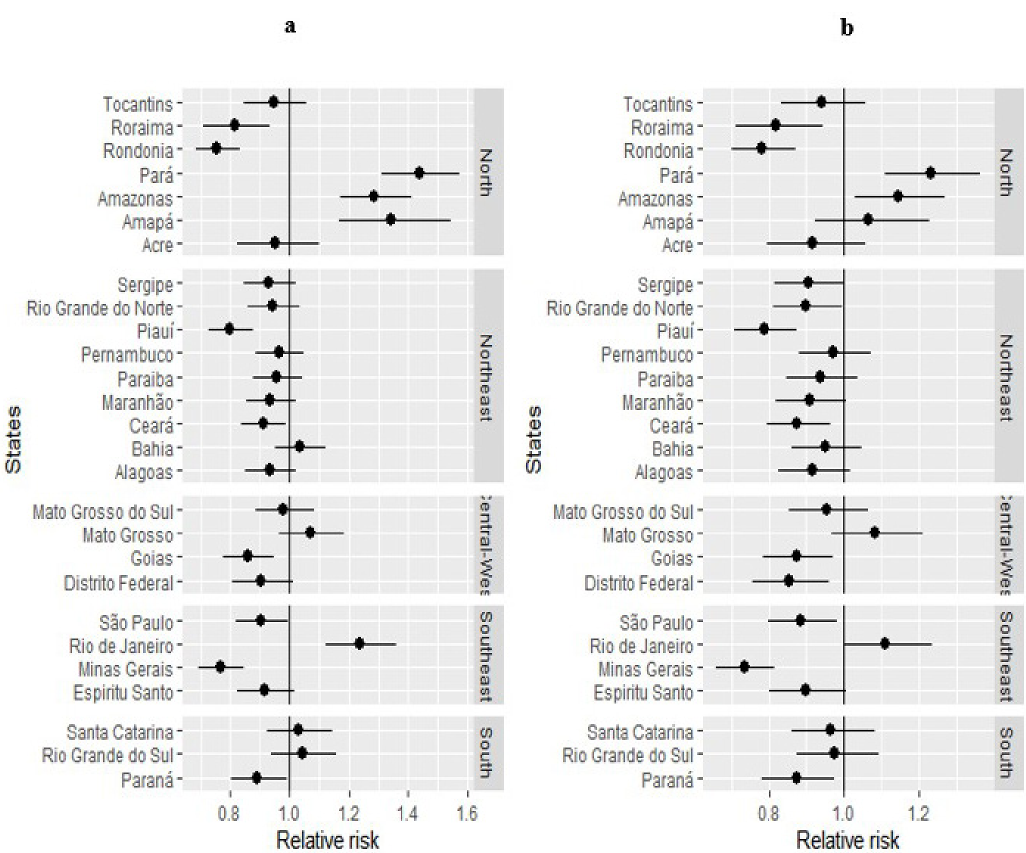

Figure 3 – Unadjusted and adjusted association between COVID-19 patients residing in the two largest cities or residing in smaller cities of each state and COVID-19 in-hospital case-fatality according to Brazilian macro-region and state. 2020-2021. (**a**) Unadjusted association; (**b**) Adjusted for sex, age and self-reported skin color, diabetes mellitus, chronic cardiovascular diseases, asthma, obesity, hematologic diseases, hepatic diseases, chronic neurological disease, chronic renal diseases, other pneumopathy, immunodeficiency diseases.

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Table 3 – Proportion of deaths by COVID-19 without hospitalization among all deaths recorded by COVID-19 in Brazil, according to macro-regions and states of the North macro-region. February 2020 to December 2021.

Regions	Death proportions	
	%	95%CI
South	1.83	1.74 – 1.92
Southeast	1.59	1.55 – 1.64
Central-West	1.50	1.40 – 1.61
Northeast	2.95	2.85 – 3.05
North*	3.85	3.68 – 4.03
Acre	0.96	0.57 – 1.61
Amazonas	5.11	4.76 – 5.49
Amapá	3.23	2.47 – 4.22
Pará	4.57	4.27 – 4.89
Rondônia	0.57	0.40 – 0.80
Roraima	1.11	0.71 – 1.74
Tocantins	3.49	2.92 – 4.16

% Proportion of deaths by COVID-19 without hospitalization. 95% CI: Confidence Interval at 95%. *Given North region presented the highest proportion among regions, the proportion for each state of that specific region was provided.

low to identify a strong association. For all other Brazilian states, except for Mato Grosso in Central-West and Rio de Janeiro in Southeast, patients residing in the two largest cities presented lower in-hospital fatality than those living in smaller cities of the same state.

Table 3 shows the proportions of deaths from COVID-19 without hospitalization among all deaths recorded by COVID-19 in Brazil according to macro-regions and states of the North macro-region. Among all regions, the North region reported the highest proportion of COVID-19 deaths without hospitalization (3.85%, 95%CI 3.68 – 4.03). The states of Amazonas (5.11%, 95%CI 4.76 – 5.49) and Pará (4.57%, 95%CI 4.27 – 4.89) showed higher proportions of deaths without access to hospital beds.

DISCUSSION

This study compared in-hospital fatality by COVID-19 of inhabitants living in the two largest cities of each state of Brazil compared with those living in any smaller city, divided by macro-region. The findings highlight that, in Brazil as a whole, living in the two largest cities was associated with a lower risk of in-hospital case-fatality ratio by COVID-19. However, two states in the North macro region presented a higher risk for those living in the largest cities; additionally, the biggest states (Amazonas and Pará), which covers a larger part of the Amazon Forest, also had the highest proportions of deaths without hospitalization, indicating a different pattern of impact of the COVID-19 pandemic.

Since the beginning of the pandemic, the Brazilian states and municipalities were allowed to make their own decisions as the implementation of measures to contain and reduce mortality from coronavirus[4]. However, there were substantial social and spatial inequalities in access to health services during the pandemic and the availability of ICU beds and equipment varied considerably between cities, and it was substantially lower among black and poor communities[20]. A considerable geographical heterogeneity had been reported in a previous study assessing spatial and temporal fluctuations in COVID-19 fatality rates in Brazilian hospitals conducted in 14 Brazilian state capitals cities[16].

Larger cities concentrate a large part of health resources and services. The dialectical and unequal condition of the metropolises shows that the concentration and diversification of resources and health services are often insufficient to meet the demands or are not accessible to everyone due to extortion processes and vulnerability[21]. In the Central-west and part of the Northeast, the areas that concentrate the necessary health services are those with consolidated urbanization, or in frank expansion and consolidation. In the South and Southeast regions (the most populated), the healthcare network is well distributed across the countryside. In addition, the largest cities of these regions concentrate on high-income, more complex, and specialized public and private health resources and services[21]. Therefore, this may be why residents from those largest cities showed fewer COVID-19 in-hospital case-fatality rates than non-capitals.

In our study, in the Southeast region, Rio de Janeiro showed a non-significant difference of in-hospital COVID-19 fatality rates between patients living in the main and small cities. The spatialization index of vulnerability to severe COVID-19 in the capital Rio de Janeiro revealed the existence of critical areas in different parts of the city's territory, reflecting its urban complexity. The areas with the greatest vulnerability were in the North and West Zones of the city and in poor neighborhoods nested within upper-income parts of the South and West Zones[22].

In our analyses, two capitals in the Northern region had a higher risk of death of patients hospitalized for COVID-19 than smaller cities, showing a contrast from other regions. The Northern region is one of the poorest in Brazil. Furthermore, the Gamma variant of concern was first detected in December 2020 in Manaus, Amazonas state, in north Brazil[23, 24] and its rapid spread in the Northern region caused huge life losses. In states of the North region, such as Amazonas, Pará and Acre, more than 20% of the population lives in areas where it takes up to four hours to travel to a high-complexity care hub city[25]. In addition, in the Northern region many patients infected by COVID-19 residing in areas with a small population went to capitals in search of healthcare, so that capital's hospitals could register an overload. In Amazonas state, in August 2020, the ICUs was concentrated only in its capital, Manaus[26]. In addition, the Gamma variant of concern contributed to a rapid increase in the COVID-19 incidence, which could lead to an overload of the medical-hospital network and an increase in lethality[27].

The COVID-19 vaccine was introduced to reduce COVID-19 severity and of COVID-19 death[28]. Brazil started vaccination in January 2021[6], about one year after the beginning of the pandemic and after the first

COVID-19 wave in Brazil[5]. Our study also included data after the beginning of vaccination against COVID-19, which may impact negatively COVID-19 case fatality in cities with lower vaccine coverage. For instance, the North region had many of the states with low first COVID-19 vaccine dose coverage[29] potentially impacting the COVID-19 case fatality in some cities of this region.

In our exploratory analysis, higher proportions of COVID-19 deaths without hospitalization were found in the two states with higher in-hospital case-fatality rates for residents in the largest cities (Pará and Amazonas states). The possible contributing factors to that singular pattern were likely the delayed presentation to the hospital, delayed ability to access services, and lack of availability of hospital beds at all at some specific time points when incidence was extremely high. This study presents some limitations. We have not explored historical aspects that can be a source of heterogeneity of risk between states. Some COVID-19-positive cases could be not notified, and all these may lead to underestimated mortality risk by COVID-19 at population level, although hospitalized cases are less prone to underreporting. Also, the supply of tests could have been heterogeneous between states, given part of it was acquired by each state with federal equitable founding, but once again we argue hospitalized cases were prioritized to get tested across all states. To control for socioeconomics position in the models only the variable skin color was used, and it presented not given category. In addition, the variable level of schooling was not included in the multivariable analysis because it presented more than fifty percent missing value. Therefore, residual confusion may exist super-estimating the lower risk associated with living in largest cities. Also, the way data on the prevalence of comorbidities were collected, given the format of the question on the notification form, induces the notifier to leave it blank if the answer is "no" for a given comorbidity. And then in the analysis we considered "blank" comorbidities as "no".

The findings could contribute to preparedness for future health emergencies by strengthening health services and disposing of health resources equitably between states and within state cities. In addition, rigorous federal policies at the national level in case of such pandemics may be important for reducing the negative impact on small city populations.

CONCLUSION

During the COVID-19 pandemic in Brazil in 2020 and 2021, residents in the largest cities of each state showed lower in-hospital lethality. However, at the two biggest states of the Amazon region (North macro-region), a higher in-hospital lethality among residents of the largest cities was found, along with higher proportions of deaths without access to a hospital bed, indicating singular vulnerability. The findings highlight the need for equitable distribution of healthcare services in situations of health emergency in the vast territory of Brazil.

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