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Characteristics, outcomes and risk factors for mortality of 522,167 patients hospitalized with COVID-19 in Brazil: a retrospective cohort study

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ABSTRACT

Objective
To provide a comprehensive description of demographic, clinical, and radiographic characteristics; treatment and case outcomes; and risk factors associated with in-hospital death of patients hospitalized with COVID-19 in Brazil.

Design
Retrospective cohort study of hospitalized patients diagnosed with COVID-19.

Setting
Data from all hospitals across Brazil.

Participants
522,167 hospitalized patients in Brazil by December 14, 2020 with severe acute respiratory ilness, and a confirmed diagnosis for COVID-19.

Primary and Secondary Outcome Measures
Prevalence of symptoms and comorbidities were compared by clinical outcomes and intensive care unit (ICU) admission status. Survival was assessed using Kaplan Meier survival estimates. Risk factors associated with in-hospital death were evaluated with multivariable Cox proportional hazards regression.

Results
Of the 522,167 patients included in this study, 56.7% were discharged, 0.002% died of other causes, 30.7% died of causes associated with COVID-19, and 10.2% remained hospitalized. The median age of patients was 61 years (interquartile range [IQR], 47-73), and of non-survivors 71 years (IQR, 60-80); 292,570 patients (56.0%) were men. At least one comorbidity was present in 64.5% of patients and in 76.8% of non-survivors. From illness onset, the median times to hospital and ICU admission were 6 days (IQR, 3-9) and 7 days (IQR, 3-10), respectively; 15 days (IQR, 9-24) to death, and 15 days (IQR, 11-20) to hospital discharge. Risk factors for in-hospital death included old age, Black/Brown ethnoracial self-classification, ICU admission, being male, living in the North and Northeast regions, and various co-morbidities. Age had the highest hazard ratios of 5.51 (95% CI: 4.91-6.18) for patients ≥ 80, compared to those ≤ 20.

Conclusions
Characteristics of patients and risk factors for in-hospital mortality highlight inequities of COVID-19 outcomes in Brazil. As the pandemic continues to unfold, targeted policies that address those inequities are needed to mitigate the unequal burden of COVID-19.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The strength of this study is that it leverages Brazil's established national Influenza Epidemiological Surveillance Information System data to present comprehensive characteristics, clinical course, and risk factors for COVID-19 in-hospital deaths across Brazil.
- Administrative records lack details available in hospital medical records and may have accuracy and completeness problems.
- We did not have access to laboratory results other than COVID-19 tests (e.g., complete blood count) that would allow for a better characterization of the clinical course of the disease.
- COVID-19 deaths at home likely follow a different clinical course than deaths in the hospital and are not included in this analysis.
- In-hospital deaths due to COVID-19 are likely under-reported and are limited by the testing protocol and capacity of each hospital.

INTRODUCTION

On March 11 the World Health Organization declared COVID-19 as a pandemic. Caused by the novel coronavirus SARS-CoV-2, it emerged in China and quickly spread across the country and beyond. As of January 4, 2021, it was present in 222 countries and territories, with 83,910,386 confirmed cases and 1,839,660 confirmed deaths.[1] Brazil recorded the first confirmed COVID-19 case on February 26 and the first death on March 12, both in São Paulo State. In 24 days, the disease had spread to all Federal Units. As of January 4, 2021, 7,716,405 cases (9% of worldwide cases) and 195,725 deaths (over 10% of worldwide deaths) had been reported in Brazil, the second-highest in the world, behind only the US. These numbers are underestimated since most mild cases are not being tested and thus are not likely to be reported, and some deaths may be reported with ill-defined causes, or not reported at all.

Brazil has a comprehensive health information system,[2] with the systematic collection of births, deaths, hospitalizations, and diseases of mandatory notification, among others. However, a complete and linked registry of records combining data from ambulatory and inpatient care, laboratory and radiologic results, and outcome of the disease is not available. Therefore, there is limited information on the course of the disease for every case reported in Brazil.

Currently, the most detailed data available in Brazil refer to hospitalizations due to severe acute respiratory illness (SARI). Here, we use these data to provide a comprehensive description of demographic, clinical, and radiographic characteristics, treatment, case outcome, and risk factors associated with in-hospital death of patients hospitalized with SARI with a confirmed diagnosis for COVID-19, as of December 14, 2020. We analyze the largest retrospective number of cases (N=522,167) and we assess whether the Brazilian case is comparable to patterns previously described for other countries.

METHODS

Data Sources

We used de-identified records from the Influenza Epidemiological Surveillance Information System (*Sistema de Informação de Vigilância Epidemiológica da Gripe, SIVEP-Gripe*, in Portuguese), an information system of the Ministry of Health that captures all notifications of SARI hospitalizations in both public and private hospitals. The system is updated daily, and every two weeks a new dataset is made publicly available (https://opendatasus.saude.gov.br/nl/dataset). Here we analyzed records as of December 14, 2020 (N=1,029,684 notifications), after 15,419 duplicate records were removed by the Ministry of Health. Each record has data on patient's age, sex, place of residence and of hospitalization, ethnoracial self-classification,[3] pregnancy status, comorbidities, and symptoms; drug treatment; radiologic test results; and dates of illness onset, hospitalization, ICU admission, and outcome (death, release, still hospitalized). We considered only records of patients hospitalized with a confirmed diagnosis for COVID-19 (N = 522,167). Diagnosis followed the Ministry of Health guidelines.[4]

Statistical Analysis

Characteristics of inpatients were summarized in three groups: demographic, clinical and radiographic, and treatment and outcomes. Medians and interquartile ranges (IQR) were used to describe continuous variables, and counts and percentages to describe categorical variables. Differences between inpatients that needed and did not need ICU admission and those that survived and did not survive were assessed by Whitney U, χ^2, or Fisher's exact test, as

appropriate. No data imputation was performed for missing data (see online supplementary table 1 for information on data completeness).

Survival curves of inpatients at 60 days of hospitalization by age, sex, ethnoracial self-classification, region, and ICU admission were estimated using the Kaplan-Meier estimator and compared with the log-rank test. Factors associated with inpatient death were identified by univariable and multivariable logistic regression (excluding from the analysis those that remained hospitalized). Considering time to death as the outcome, hazard ratios were estimated using Cox proportional-hazards models. Based on previous studies[5-7] and on our available information, covariates included in both logistic and Cox models were age (0-19, 20-39, 40-59, 60-69, 70-79, and 80 or more years), sex, ethnoracial self-classification (White, Black/Brown, other, not reported), region (North – where Amazonia is located, Northeast, South, Southeast – where the cities of São Paulo and Rio de Janeiro are located, and Center-West), comorbidities (diabetes, asthma, chronic liver disease, chronic neurological disease, chronic lung disease, immunodeficiency, and chronic kidney disease), obesity, and ICU admission. The variable ethnoracial self-classification was missing in 23.1% of the records, and we added those as a separate category (not reported). Distances between municipalities of residence and hospitalization were calculated in ArcMap, version 10.6 (ESRI, Redlands, CA, USA). All analyses were performed in Stata, version 15.1 (Stata Corp., College Station, TX, USA), and R version 4.0.0 (RStudio Team, Boston, MA, USA).

Patient and public involvement

Our analysis used administrative records, and thus study participants were not involved in the design of the study. Public involvement was achieved through collaboration with the Ministry of

Health, with whom we defined the research questions to fill in knowledge gaps and inform decision making. Results were discussed and shared with the Ministry, and their wide dissemination with public health officials, researchers, and through the media will reach the broader public.

RESULTS

As of December 14, 2020, 522,167 patients had been hospitalized with confirmed COVID-19 since the beginning of the epidemic in Brazil. Of those, 296,002 (56.7%) were discharged, 1,004 (0.002%) died of other causes, 160,495 (30.7%) died of causes associated with COVID-19, 53,503 (10.2%) remained hospitalized. Clinical outcome was unknown for 11,126 (2.1%) patients (table 1). The cumulative curve of hospital admissions (online supplementary figure 1) shows the fast increase in severe cases that required hospitalization, following the steep increase in COVID-19 transmission in Brazil since the end of March. The median age of patients was 61 years (IQR, 47-73), and much higher for non-survivors, 71 years (IQR, 60-80), as shown by the age distribution in figures 1a-b. Patients aged 60 years or more represented 50.1% of hospitalizations, 59.0% of ICU admissions, and 74.0% of deaths associated with COVID-19. Patients were mostly males (56.0%) and from the Southeast region (49.3%). Among females, 2.5% were pregnant or puerperal at the time of hospitalization, and 7.5% of those died in the hospital. A total of 172,473 (33.0%) patients with median age of 65 years (IQR, 52-76) needed ICU admission. Of all hospitalizations, 37.7% of the patients were White, and 37.9% were Black/Brown. Among survivors, 38.8% were White, while among non-survivors 41.7% were Black/Brown. About 25% of the patients traveled a median of 32.0 km (IQR, 18.6-64.1) to be hospitalized in a municipality different from where they reside (table 1).

Table 1. Demographic characteristics of patients

Characteristic	All patients (N = 522,167)[a]	ICU admission (N = 172,473)	Non-ICU admission (N = 293,384)	Not reported (N = 56,310)	p-value	Survivor & non-COVID-19 death (N = 297,043)	Non-survivor (N = 160,495)[b]	Still in the hospital (N = 53,503)	p-value
Age									
Median (IQR) - years	61 (47-73)	65 (52-76)	59 (45-72)	61 (47-74)	<0.001	56 (42-68)	71 (60-80)	60 (46-72)	<0.001
Distribution, number (%)					<0.001				<0.001
0-19	13,136 (2.5)	3,211 (1.9)	8,517 (2.9)	1,408 (2.5)		9,994 (3.4)	985 (0.6)	1,628 (3.0)	
20-39	71,728 (13.7)	16,978 (9.8)	46,823 (16.0)	7,927 (14.1)		54,889 (18.5)	7,299 (4.6)	7,814 (14.6)	
40-59	170,266 (32.6)	50,445 (29.3)	101,922 (34.7)	17,899 (31.8)		114,769 (38.6)	33,405 (20.8)	18,196 (34.0)	
60-69	108,416 (20.8)	39,362 (22.8)	57,404 (19.6)	11,650 (20.7)		56,788 (19.1)	38,044 (23.7)	11,352 (21.2)	
70-79	90,800 (17.4)	35,944 (20.8)	44,943 (15.3)	9,913 (17.6)		38,304 (12.9)	41,883 (26.1)	8,942 (16.7)	
≥ 80	67,808 (13.0)	26,530 (15.4)	33,769 (11.5)	7,509 (13.3)		22,303 (7.5)	38,872 (24.2)	5,570 (10.4)	
Sex, number (%)					<0.001				<0.001
Male	292,570 (56.0)	100,399 (58.2)	161,377 (55.0)	30,794 (54.7)		163,967 (55.2)	92,376 (58.6)	30,146 (56.3)	
Female	229,513 (44.9)	72,060 (41.8)	131,964 (45.0)	25,489 (45.3)		133,028 (44.8)	68,101 (42.4)	23,345 (43.6)	
Pregnant, number (%)	4,441 (1.9)	802 (1.1)	3,249 (2.5)	390 (1.5)	<0.001	3,603 (2.7)	230 (0.3)	469 (2.0)	<0.001
Puerperal, number (%)	1,350 (0.6)	426 (0.6)	850 (0.6)	74 (0.3)	<0.001	965 (0.7)	204 (0.4)	148 (0.6)	<0.001
Ethnoracial, number (%)					<0.001				<0.001
White	196,035 (37.5)	67,619 (39.2)	114,339 (39.0)	14,077 (25.0)		115,358 (38.8)	58,487 (36.4)	19,257 (36.0)	
Black/Brown	198,096 (37.9)	61,450 (35.6)	114,378 (39.0)	22,268 (39.6)		106,312 (35.8)	66,889 (41.7)	19,891 (37.2)	
Other	7,237 (1.4)	2,135 (1.2)	4,191(1.4)	911 (1.6)		4,028 (1.4)	2,332 (1.5)	710 (1.3)	
Not reported	120,799 (23.1)	41,269 (23.9)	60,476 (20.6)	19,054 (33.8)		71,345 (24.0)	32,787 (20.4)	13,645 (25.5)	
Region of residence, number (%)					<0.001				<0.001
North	41,961 (8.0)	10,024 (5.8)	27,065 (9.2)	4,872 (8.7)		23,149 (7.8)	14,537 (9.1)	3,559 (6.7)	
Northeast	104,213 (20.0)	33,220 (19.3)	50,377 (17.2)	20,616 (36.6)		49,733 (16.7)	37,919 (23.6)	12,695 (23.7)	
Center-West	48,864 (9.4)	16,581 (9.6)	28,872 (9.8)	3,411 (6.1)		29,169 (9.8)	13,532 (8.4)	4,759 (8.9)	
Southeast	257,503 (49.3)	88,817 (51.5)	144,010 (49.1)	24,676 (43.8)		151,595 (51.0)	76,494 (47.7)	25,050 (46.8)	
South	69,590 (13.3)	23,814 (13.8)	43,042 (14.7)	2,734 (4.9)		43,380 (14.6)	17,997 (11.2)	7,439 (13.9)	
Foreigner	36 (0.0)	17 (0.0)	18 (0.0)	1 (0.0)		17 (0.0)	16 (0.0)	1 (0.0)	
Hospital in the same municipality of residence, number (%)					<0.001				<0.001
Yes	388,304 (74.4)	118,002 (68.4)	227,423 (77.5)	42,879 (76.2)		224,134 (75.5)	116,664 (72.7)	39,772 (74.3)	
No	133,827 (25.6)	54,454 (31.6)	65,943 (22.5)	13,430 (23.9)		72,892 (24.5)	43,815 (27.3)	13,730 (25.7)	
Distance (km) from residence to hospital[b]	32.0 (18.4-64.1)	35.6 (19.8-77.8)	29.4 (18.0-56.6)	25.8 (14.5-54.7)	<0.001	29.8 (18.1-57.8)	34.1 (19.1-71.9)	34.5 (18.8-75.9)	<0.001

[a] Includes 11,126 patients with unknown clinical outcome.

[b] Non-survivors are classified as those whose death was associated with COVID-19, according to the *SIVEP-Gripe* database. Those who had COVID-19 but died due to an unrelated cause are classified under "Survivor & non-COVID-19 death". Survivor N=296,002, non-COVID-19 death=1,041.

[c] Distances (measured in km) are calculated from the centroid of the notification municipality (consistent with municipality of hospitalization) to the centroid of the municipality of residence, using the South America Lambert Conformal Conic projection.

Comorbidities were observed in 64.5% of the patients, 74.6% of those who needed ICU admission, 76.8% of non-survivors, and 58.5% of the survivors and those whose death was not associated with COVID-19. With the exception of asthma, all comorbidities had a higher prevalence among non-survivors (compared to all patients). The most common comorbidities were chronic cardiovascular disease (34.5% of patients and 43.5% of non-survivors) and diabetes (25.7% of patients and 33.0% of non-survivors). Obesity was reported in 7.4% of the patients and 10.5% of those who needed ICU admission. The most common symptoms were fever, cough, shortness of breath, low oxygen saturation, and respiratory distress symptoms (table 2).

Table 2. Clinical and radiographic characteristics of patients

Characteristic	All patients (N = 522,167)[a]	ICU admission (N = 172,473)	Non-ICU admission (N = 293,384)	Not reported (N = 56,310)	p-value	Survivor & non-COVID-19 death (N = 297,043)	Non-survivor (N = 160,495)[b]	Still in the hospital (N = 53,503)	p-value
Any comorbidity, number (%)	336,909 (64.5)	128,590 (74.6)	179,847 (61.3)	28,472 (50.6)	<0.001	173,828 (58.5)	123,265 (76.8)	33,318 (62.3)	<0.001
Chronic cardiovascular disease	180,370 (34.5)	72,196 (41.9)	93,574 (31.9)	14,600 (25.9)	<0.001	89,402 (30.1)	69,768 (43.5)	17,980 (33.6)	<0.001
Chronic hematologic diseases	4,134 (0.8)	1,687 (1.0)	2,204 (0.8)	243 (0.4)	<0.001	1,957 (0.7)	1,739 (1.1)	365 (0.7)	<0.001
Chronic hepatic disease	4,732 (0.9)	2,101 (1.2)	2,309 (0.8)	322 (0.6)	<0.001	1,924 (0.7)	2,368 (1.5)	361 (0.7)	<0.001
Asthma	14,567 (2.8)	4,947 (2.9)	8,639 (2.9)	981 (1.7)	<0.001	9,130 (3.1)	3,634 (2.3)	1,514 (2.8)	<0.001
Diabetes	134,391 (25.7)	53,717 (31.2)	69,078 (23.6)	11,596 (20.6)	<0.001	65,941 (22.2)	52,958 (33.0)	12,844 (24.0)	<0.001
Chronic neurological disease	21,016 (4.0)	8,821 (5.1)	10,832 (3.7)	1,363 (2.4)	<0.001	8,113 (2.7)	10,943 (6.8)	1,622 (3.0)	<0.001
Chronic lung disease	20,140 (3.9)	9,249 (5.4)	9,483 (3.2)	1,408 (2.5)	<0.001	8,222 (2.8)	10,021 (6.2)	1,621 (3.0)	<0.001
Immunodeficiency	13,967 (2.7)	5,689 (3.3)	7,376 (2.5)	902 (1.6)	<0.001	6,351 (2.1)	6,283 (3.9)	1,132 (2.1)	<0.001
Chronic renal disease	21,725 (4.2)	10,684 (6.2)	9,429 (3.2)	1,512 (2.9)	<0.001	8,149 (2.7)	11,491 (7.2)	1,743 (3.3)	<0.001
Obesity	38,415 (7.4)	18,057 (10.5)	17,998 (6.1)	2,360 (4.2)	<0.001	20,993 (7.1)	12,765 (8.0)	4,005 (7.5)	<0.001
Others[c]	144,081 (27.6)	58,139 (33.7)	74,994 (25.6)	10,948 (19.4)	<0.001	72,598 (24.4)	55,866 (34.8)	13,042 (24.4)	<0.001
Symptoms, number (%)									
Fever	188,572 (64.3)	104,650 (60.7)	188,572 (64.3)	34,789 (61.8)	<0.001	194,578 (65.5)	93,933 (58.5)	32,586 (60.9)	<0.001
Cough	369,192 (70.7)	115,147 (66.7)	215,084 (73.3)	38,961 (69.2)	<0.001	219,433 (73.9)	105,252 (65.6)	36,717 (68.6)	<0.001
Sore throat	90,487 (17.3)	23,531 (13.6)	56,653 (19.3)	10,303 (18.3)	<0.001	56,741 (19.1)	22,982 (14.3)	8,872 (16.6)	<0.001
Shortness of breath	367,917 (70.5)	131,799 (76.4)	199,805 (68.1)	36,313 (64.5)	<0.001	200,051 (67.4)	124,724 (77.7)	35,709 (66.7)	<0.001
Respiratory distress syndrome	296,238 (56.7)	107,762 (62.5)	163,370 (55.7)	25,106 (44.7)	<0.001	157,412 (53.0)	104,555 (65.2)	28,046 (52.4)	<0.001
Oxygen saturation <95%	303,282 (58.1)	116,355 (67.5)	160,837 (54.8)	26,090 (46.3)	<0.001	156,349 (52.6)	111,097 (69.2)	29,704 (55.5)	<0.001
Diarrhea	71,069 (13.6)	20,340 (11.8)	44,411 (15.1)	6,318 (11.2)	<0.001	44,961 (15.1)	17,419 (10.9)	7,264 (13.6)	<0.001
Vomiting	41,974 (8.0)	11,950 (6.9)	26,177 (8.9)	3,847 (6.8)	<0.001	25,799 (8.7)	11,076 (6.9)	4,156 (7.8)	<0.001
Others[d]	179,222 (34.3)	58,268 (33.8)	105,646 (36.0)	15,308 (27.2)	<0.001	112,278 (37.8)	45,263 (28.2)	18,294 (34.2)	<0.001
Chest radiograph, number (%)					<0.001				<0.001
Normal	11,816 (2.3)	3,403 (2.0)	7,782 (2.7)	631 (1.1)		7,895 (2.7)	2,558 (1.6)	1,091 (2.0)	
Interstitial abnormalities	81,412 (15.6)	28,091 (16.3)	48,864 (16.7)	4,457 (7.9)		45,320 (15.3)	27,071 (16.9)	7,500 (14.0)	
Other[e]	85,870 (16.4)	35,844 (20.8)	47,185 (16.1)	2,841 (5.1)		246,250 (82.9)	132,429 (82.5)	47,639 (89.0)	

[a] Includes 11,126 patients with unknown clinical outcome.

[b] Non-survivors are classified as those whose death was associated with COVID-19, according to the *SIVEP-Gripe* database. Those who had COVID-19 but died due to an unrelated cause are classified under "Survivor & non-COVID-19 death". Survivor N=296,002, non-COVID-19 death=1,041.

[c] Other comorbidities that were not specifically asked about in the survey, but self-reported as "other" include, but are not limited to: hypertension, cancer, anemia, bronchitis, dyslipidemia, and pulmonary emphysema.

[d] Other symptoms that were not specifically asked about in the surveillance form, but self-reported as "other" include, but are not limited to: loss of taste, loss of smell, myalgia, weakness, body ache, fatigue, exhaustion, tachypnea, and syncope.

[e] Includes consolidation, mixed, and other.

The median time from illness onset to hospital admission was 6 days (IQR, 3-9), slightly shorter among non-survivors, 5 days (IQR, 2-8). Mechanical ventilation was needed by 62.2% of all patients, and by 75.6% of those who died. Invasive ventilation was more common in the ICU (44.0%). Oseltamivir, an antiviral medication, was the most common drug used during treatment (15.8% overall, and 17.6% among those in ICU), and the median time from illness onset to treatment was 5 days (IQR, 3-8). Of the patients that needed ICU, 51.8% died from causes associated with COVID-19, and 19.0% remained hospitalized after ICU discharge for 5 days (IQR, 2-10). The median time from illness onset to ICU admission was 7 days (IQR, 3-10), and the medium length of ICU stay was 8 days (IQR, 3-15) for all patients, 9 days (IQR, 4-16) for the deceased. Among the 160,495 patients who died of causes associated with COVID-19 by December 14, the median time from illness onset to death was 15 days (IQR, 9-24) (table 3). Medium length of hospital stay was 8 days (IQR, 4-17), but longer for those who needed ICU admission, 12 days (IQR, 6-22). The density of time from hospital admission to death is positively skewed, more so for those who did not get admitted to the ICU (figure 1c). Kaplan Meier curves (figure 1d and online supplementary figure 2) for a period of up to 60 days after hospital admission showed that survival curves were significantly different by age, region, sex, ethnoracial self-classification, and ICU admission.

Table 3. Treatment and outcomes of patients

Variable	All patients (N = 522,167)[a]	ICU admission (N = 172,473)	Non-ICU admission (N = 293,384)	Not reported (N = 56,310)	p-value	Survivor & non-COVID-19 death (N = 297,043)	Non-survivor (N = 160,495)	Still in the hospital (N = 53,503)	p-value
Treatment with drugs, number (%)					<0.001				<0.001
Oseltamivir	82,659 (15.8)	30,341 (17.6)	47,317 (16.1)	5,001 (8.9)		50,091 (16.9)	27,192 (16.9)	4,242 (7.9)	
Zanamivir	492 (0.1)	152 (0.1)	303 (0.1)	37 (0.1)		298 (0.1)	128 (0.1)	56 (0.1)	
Other	5,008 (1.0)	1,480 (0.9)	3,243 (1.1)	285 (0.5)		3,029 (1.0)	1,118 (0.7)	701 (1.3)	
Mechanical ventilation, number (%)					<0.001				<0.001
Invasive	90,189 (17.3)	75,915 (44.0)	12,019 (4.1)	2,255 (4.0)		17,263 (5.8)	66,652 (41.5)	5,238 (9.8)	
Noninvasive	234,554 (44.9)	65,281 (37.9)	157,913 (53.8)	11,360 (20.2)		148,930 (50.1)	54,652 (34.1)	25,925 (48.5)	
ICU admission, number (%)	172,473 (33.0)	172,473 (100.0)	-	-	-	65,102 (21.9)	89,264 (55.6)	15,614 (29.2)	<0.001
Remained hospitalized after ICU discharge, number (%)	32,770 (19.0)	32,770 (19.0)	-	-	-	27,775 (42.7)	3,243 (3.6)	1,303 (8.4)	<0.001
Median length (IQR), days	5 (2-10)	5 (2-10)	-	-	-	5 (2-9)	7 (2-16)	72 (21-139)	<0.001
Median times (IQR), days									
Illness onset to treatment with drugs	5 (3-8)	5 (3-8)	6 (3-9)	6 (3-8)	<0.001	6 (3-9)	5 (2-8)	6 (3-9)	<0.001
Illness onset to hospitalization	6 (3-9)	6 (3-9)	6 (3-10)	6 (2-9)	<0.001	7 (3-10)	5 (2-8)	6 (3-10)	<0.001
Illness onset to ICU admission	7 (3-10)	7 (3-10)	-	-	-	7 (4-10)	6 (3-10)	7 (3-10)	<0.001
Hospital admission to ICU admission	0 (0-1)	0 (0-1)	-	-	-	0 (0-1)	0 (0-1)	0 (0-0)	<0.001
Illness onset to death	15 (9-24)	17 (10-25)	13 (7-21)	12 (7-20)	<0.001	-	15 (9-24)	-	-
Illness onset to hospital discharge	15 (11-20)	18 (13-27)	14 (10-18)	16 (11-21)	<0.001	15 (11-20)	-	-	-
Hospital admission to death	9 (4-16)	10 (5-18)	7 (2-14)	5 (1-13)	<0.001	-	9 (4-16)	-	-
Hospital admission to ICU discharge	9 (4-17)	9 (4-17)	-	-	-	7 (4-14)	10 (5-10)	6 (2-14)	<0.001
ICU admission to death	9 (4-16)	9 (4-16)	-	-	-	-	9 (4-16)	-	-
Median length hospital stay (IQR), days	8 (4-17)	12 (6-22)	7 (4-13)	8 (3-18)	<0.001	7 (4-12)	9 (4-16)	79 (23-157)	<0.001
Median length ICU stay (IQR), days	8 (3-15)	8 (3-15)	-	-	-	6 (3-12)	9 (4-16)	4 (2-11)	<0.001
Clinical outcomes as of 12/14/2020, number (%)					<0.001				-
Cured and discharged from hospital	296,002 (56.7)	64,578 (37.4)	202,042 (68.9)	29,382 (52.2)		296,002 (99.7)	-	-	
Death due to other causes	1,041 (0.2)	524 (0.3)	443 (0.2)	74 (0.1)		1,041 (0.4)	-	-	
Death associated with COVID-19	160,495 (30.7)	89,264 (51.8)	53,282 (18.2)	17,949 (31.9)		-	160,495 (100.0)	-	
Still in the hospital	53,503 (10.3)	15,614 (9.1)	30,963 (10.6)	6,926 (12.3)		-	-	53,503 (100.0)	

[a] Includes 11,126 patients with unknown clinical outcome.

[b] Non-survivors are classified as those whose death was associated with COVID-19, according to the *SIVEP-Gripe* database. Those who had COVID-19 but died due to an unrelated cause are classified under "Survivor & non-COVID-19 death". Survivor N=296,002, non-COVID-19 death=1,041.

Univariable logistic analysis indicated that the odds of in-hospital death progressively increased with age, and were higher for patients who were male, non-white, from the North and Northeast regions, needed ICU care, were obese, and had diabetes and other comorbidities (table 4). The multivariable analysis included 168,936 records (65,670 non-survivors) that had no missing data for covariates. The odds of in-hospital death for males are 1.23 times that of females, and for those in the North and Northeast regions were, respectively, 1.83 and 1.48 times that of patients in the Southeast. The Cox proportional-hazards model included 176,559 records (64,809 non-survivors). Variables associated with in-hospital death were age, sex, ethnoracial self-classification, region, ICU care, and various co-morbidities. Age, however, had the highest hazard ratios, ranging from 1.67 (95% CI: 1.49-1.89) for those aged 20-39, to 5.51 (95% CI: 4.91-6.18) for those 80 or older, compared to patients younger than 20 years (table 4).

Table 4: Odds ratios (OR) and hazard ratios (HR) for death among hospitalized patients with confirmed COVID-19

Variables	Univariable OR[a] (95% CI)	p-value[b]	Multivariable OR (95% CI) N = 168,936	p-value[b]	HR (95% CI) for death within 60 days of hospitalization N = 176,559
Age (reference 0-19)					
20-39	1.35 (1.26,1.46)	< 0.001	1.66 (1.45, 1.91)	< 0.001	1.67 (1.48, 1.89)
40-59	2.94 (2.74, 3.15)	< 0.001	2.70 (2.37, 3.09)	< 0.001	2.21 (1.97, 2.48)
60-69	6.76 (6.30, 7.26)	< 0.001	5.15 (4.52, 5.88)	< 0.001	3.05 (2.72, 3.43)
70-79	11.05 (10.30, 11.86)	< 0.001	8.24 (7.24, 9.42)	< 0.001	3.90 (3.48, 4.38)
≥ 80	17.58 (16.37, 18.88)	< 0.001	14.52 (12.74, 16.59)	< 0.001	5.51 (4.91, 6.18)
Sex (reference Female)					
Male	1.10 (1.09, 1.11)	< 0.001	1.23 (1.20, 1.26)	< 0.001	1.09 (1.07, 1.10)
Ethnoracial self-classification (reference White)					
Black/Brown	1.25 (1.24, 1.27)	< 0.001	1.18 (1.15, 1.22)	< 0.001	1.08 (1.06, 1.10)
Other	1.18 (1.12, 1.25)	< 0.001	1.05 (0.95, 1.16)	0.309	1.02 (0.96, 1.10)
Not reported	0.9 (0.89, 0.92)	< 0.001	0.77 (0.74, 0.80)	< 0.001	0.79 (0.77, 0.81)
Region (reference Southeast)					
South	0.85 (0.83, 0.87)	< 0.001	0.89 (0.87, 0.92)	< 0.001	0.91 (0.89, 0.93)
Center-West	0.96 (0.94, 0.98)	< 0.001	1.04 (1.00, 1.08)	0.049	1.00 (0.97, 1.03)
North	1.31 (1.28, 1.34)	< 0.001	1.83 (1.75, 1.92)	< 0.001	1.34 (1.30, 1.39)
Northeast	1.61 (1.58, 1.64)	< 0.001	1.48 (1.43, 1.55)	< 0.001	1.10 (1.07, 1.12)
ICU	5.21 (5.14, 5.28)	< 0.001	5.20 (5.08, 5.32)	< 0.001	1.78 (1.75, 1.81)
Obesity	0.91 (0.88, 0.93)	< 0.001	1.23 (1.18, 1.27)	< 0.001	1.07 (1.04, 1.10)
Diabetes	1.32 (1.30, 1.35)	< 0.001	1.18 (1.15, 1.21)	< 0.001	1.08 (1.07, 1.10)
Asthma	0.59 (0.56, 0.61)	< 0.001	0.81 (0.77, 0.86)	< 0.001	0.88 (0.84, 0.92)
Chronic liver disease	1.87 (1.76, 1.99)	< 0.001	1.74 (1.59, 1.90)	< 0.001	1.33 (1.26, 1.40)
Chronic neurological disease	2.12 (2.06, 2.19)	< 0.001	1.65 (1.58, 1.73)	< 0.001	1.18 (1.15, 1.21)
Chronic lung disease	1.92 (1.86, 1.99)	< 0.001	1.46 (1.40, 1.53)	< 0.001	1.16 (1.13, 1.19)
Immunodeficiency	1.53 (1.47, 1.58)	< 0.001	1.93 (1.83, 2.04)	< 0.001	1.26 (1.22, 1.31)
Chronic kidney disease	2.23 (2.16, 2.30)	< 0.001	1.70 (1.63, 1.78)	< 0.001	1.17 (1.14, 1.21)

[a] The N varies for univariable OR, depending on the number of missing values for each variable.
[b] P-value from Wald test.

CONCLUSION

This study described demographic, clinical, and radiographic characteristics, treatment, case outcome, and risk factors associated with in-hospital death of 522,167 patients hospitalized with confirmed COVID-19 in Brazil. Results show that 56.7% were discharged, 0.002% died of other causes, 30.7% died of causes associated with COVID-19, and 10.2% remained in the hospital as of December 14. Patients were mostly older than 40 years, predominantly from the Southeast region, with about one fourth needing to travel to a different municipality for hospitalization. At least one comorbidity was present in 64.5% of patients and in 76.8% of the non-survivors. From illness onset, the median time to hospital and ICU admission was 6 and 7 days, respectively; 15 days to death (17 to those admitted to the ICU), and 15 days to hospital discharge (18 days to those admitted to the ICU). Risk factors for in-hospital death were older age, being male, of Black/Brown ethnoracial self-classification, living in the North or Northeast regions, with a history of ICU admission, and various co-morbidities.

Our results can be analyzed in light of findings from other countries. The use of mechanical ventilation was higher in Brazil (62.2% among all patients, 75.6% of the non-survivors) compared to patterns described for China (ranging from 17.2 to 38.7% of patients),[8-10] and Germany (17% of patients),[11] but lower than Italy (81.7% of all patients).[12] While ICU mortality in Italy was 26%,[12] in Brazil it was 51.8%. In Brazil, 33.0% of hospitalized patients were admitted to the ICU, against 16% in Italy,[13] and 19% in France.[14] In-hospital death was observed in 18.1% of patients in France,[14] 22% in Germany,[11] and 30.7% in Brazil. The time from illness onset to hospitalization in China[9] was 11 days (IQR, 8-14), but much shorter in Brazil, 6 days (IQR, 3-9). The length of hospital stay, however, was about 4 days longer in China.[9 15] These comparisons need to be taken with caution. First, studies from China had a smaller sample size,

and regional variability is very large, as reported for France.[14] In Brazil, for example, in-hospital death varied from 25.9% in the South region to 36.4% in the Northeast, and ICU mortality from 48.0% in the Southeast to 66.5% in the North. The time from illness to hospitalization was also longer in the North and Center-West regions, 7 days (IQR, 4-10).

Our results confirm previous findings regarding symptoms and comorbidities. Hypertension, a very common comorbidity in China[9] could not be measured from our data, but over one-third of the adult population in Brazil has that condition.[16] In Brazil, 35.5% of the patients reported no comorbidities, while in New York City this number was 6.1%,[17] and in China it was 52%.[9] Diabetes was reported in 19% of patients in China,[9] 33.8% in New York City,[17] and 25.7% in Brazil. Part of these differences reflects the disease burden in each locality, but also the lack of standardized data collection (e.g., conditions systematically collected in one country and only reported in the 'other' category in another country).

The observed associations of age, sex, obesity, and diabetes with in-hospital death corroborate previous findings.[5 6 14] The higher risk among non-white patients was previously reported in Brazil, the UK, and the US.[18-22] In Brazil, this reflects structural inequalities that made large fractions of the population more vulnerable to COVID-19 (e.g., people living in areas with precarious infrastructure, overcrowded households, regions with low supply of physicians and hospital services, and who depend on informal labor).[23 24] Those inequalities are also captured by a higher hazard ratio in the North and Northeast regions, where Brazil consistently reports worse socioeconomic indicators.[25] Currently, the North region has the lowest rates of hospital beds, ICU beds, and physicians per person.[26] Indeed, the region had the worst indicators in terms of mortality and time to hospitalization, and patients who were hospitalized in a municipality different from the one where they live had to travel 122.0 km (IQR, 58.3-258.6) while those in

the Southeast traveled 22.3 km (IQR, 16.1-36.3). Hospitalization in a different municipality occurs when the place of residence has no hospitals, has no available hospital beds, or when the closest hospital is actually outside the municipality of residence. In Brazil, the size of municipalities varies widely: 23% have 5,000 residents or less, and 5% have 100,000 or more residents. Of the 5,570 municipalities, 37% and 75% have no hospitals and no ICU care, respectively. A regionalization process guarantees that all the population has access to hospital care.[27] However, when hospitals reach capacity, as was observed in several cities in Brazil in late April and May, municipalities without hospitals and ICU units are unable to provide proper care, which may have contributed to higher COVID-19 mortality. Therefore, risk factors for in-hospital mortality due to COVID-19 expose local and structural inequalities.

This study has some limitations. First, we used administrative records captured in structured surveillance forms. Those lack details available in hospital medical records and may have accuracy and completeness problems. In addition, it limits the types of comorbidities and symptoms reported, as those listed under the 'other' category were not systematically collected from all cases (e.g., loss of taste and smell). Second, we did not have access to laboratory results other than COVID-19 tests (e.g., complete blood count). While this does not change any of our results, they would allow for a better characterization of the clinical course of the disease. Third, 23.1% of patients did not report information on ethnoracial self-classification, 10.8% did not have information on ICU admission, and for 2.1% there was no information on clinical outcome. This is not uncommon in the analysis of administrative records.[22] Here we report all records and included an additional category (ethnoracial self-classification not reported) in the risk factor analysis.

Despite these limitations, this study provides a comprehensive description of characteristics, outcomes, and risk factors for mortality of patients hospitalized with COVID-19 in Brazil, and the largest cohort of patients so far analyzed (N=522,167). Results shed light on commonalities and differences between Brazil and other countries affected by COVID-19, and highlight inequalities in disease outcomes. Most importantly, our results could be used to inform coordinated actions to target those who currently bear the highest morbidity and mortality burden. Currently, Brazil's response to COVID-19 did not comprehensively and effectively utilize its community-based primary health care program.[28-30] Brazil has a network of almost 270,000 community health workers that reach out to about 70% of the Brazilian population. These agents could actively identify vulnerable people who face higher risk of mortality, could act as agents of information to sensitize the population and boost adherence to control measures (e.g., use of masks), and could continue to deliver community-based primary care services that have been, for the most part, interrupted by the pandemic. These agents will also be important to support the delivery of vaccination (once it starts) to the most vulnerable. Currently, with more than 200,000 deaths and with hospital occupancy increasing at alarming rates, leveraging and strengthening the existing network of primary health care is paramount to contain the sustained and unequal burden of COVID-19 in Brazil.

Contributors: MCC and GVAF conceived the study, were responsible for data analysis and interpretation. MCC wrote the manuscript. GVAF and EMM acquired the data. GVAF and SG were responsible for data curation. SG ran the statistical models and contributed to writing. All authors edited and approved the final version of the manuscript.

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Data availability statement: The *SIVEP-Gripe* dataset is publicly available on the Ministry of Health's DATASUS website (https://opendatasus.saude.gov.br/nl/dataset).

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Figure 1: Age distribution of patients, density curves of length of time from hospital admission to death, and survival curve 60 days after hospital admission. (a) Age distribution of patients hospitalized. (b) Age distribution of in-hospital deaths. (c) Density of number of days from hospital admission to death up to 60 days after hospital admission, detailed by ICU admission status. (d) Survival curve estimated with Kaplan Meier and considering 60 days from hospital admission.

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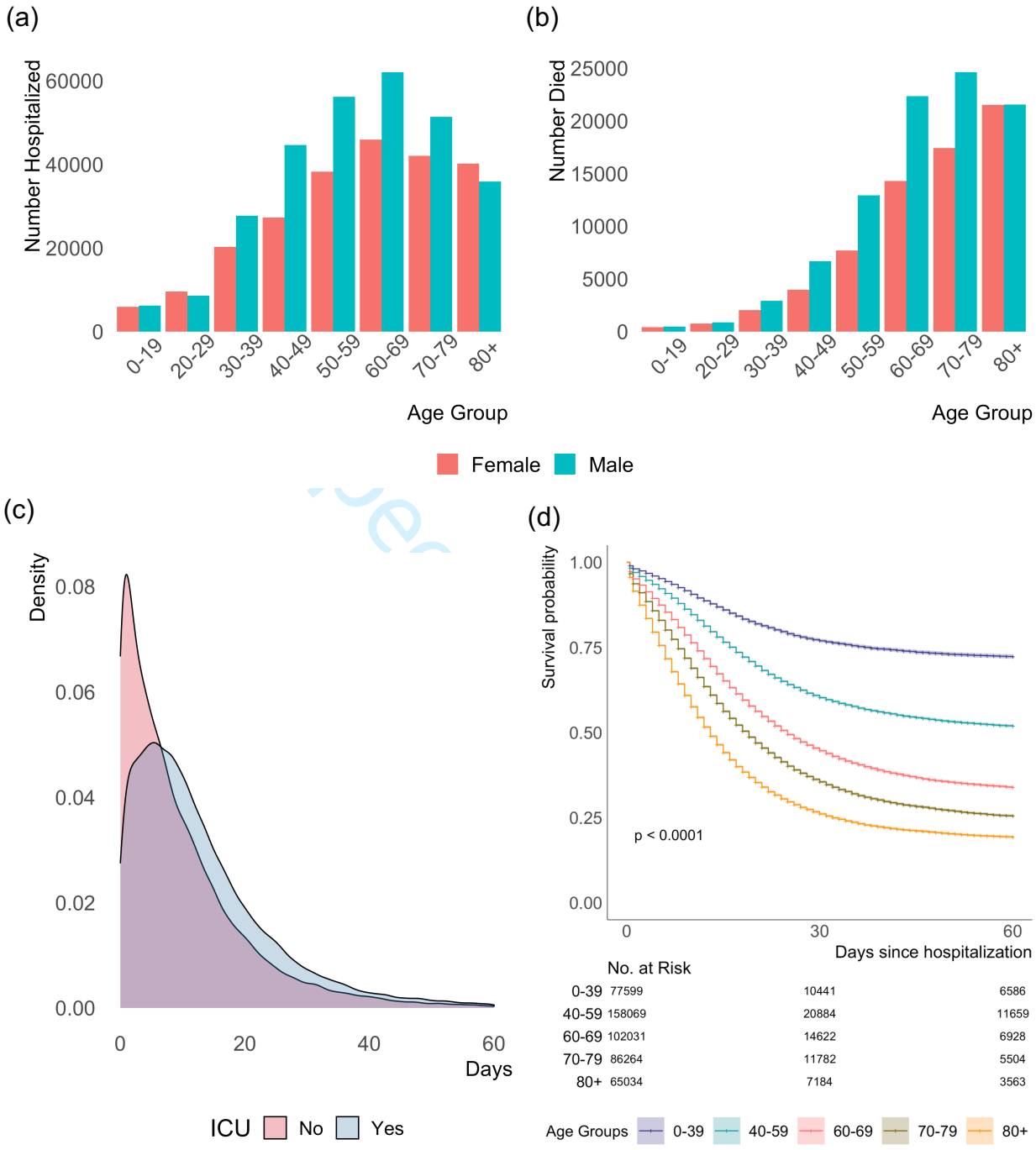

(a)
Number Hospitalized
60000
40000
20000
0
0-19
20-29
30-39
40-49
50-59
60-69
70-79
80+
Age Group
(b)
Number Died
25000
20000
15000
10000
5000
0
Age Group
Female
Male
(c)
Density
0.08
0.06
0.04
0.02
0.00
0
20
40
60
Days
ICU
No
Yes
(d)
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
30
60
Days since hospitalization
No. at Risk
0-39 77599 10441 6586
40-59 158069 20884 11659
60-69 102031 14622 6928
70-79 86264 11782 5504
80+ 65034 7184 3563
Age Groups
0-39
40-59
60-69
70-79
80+

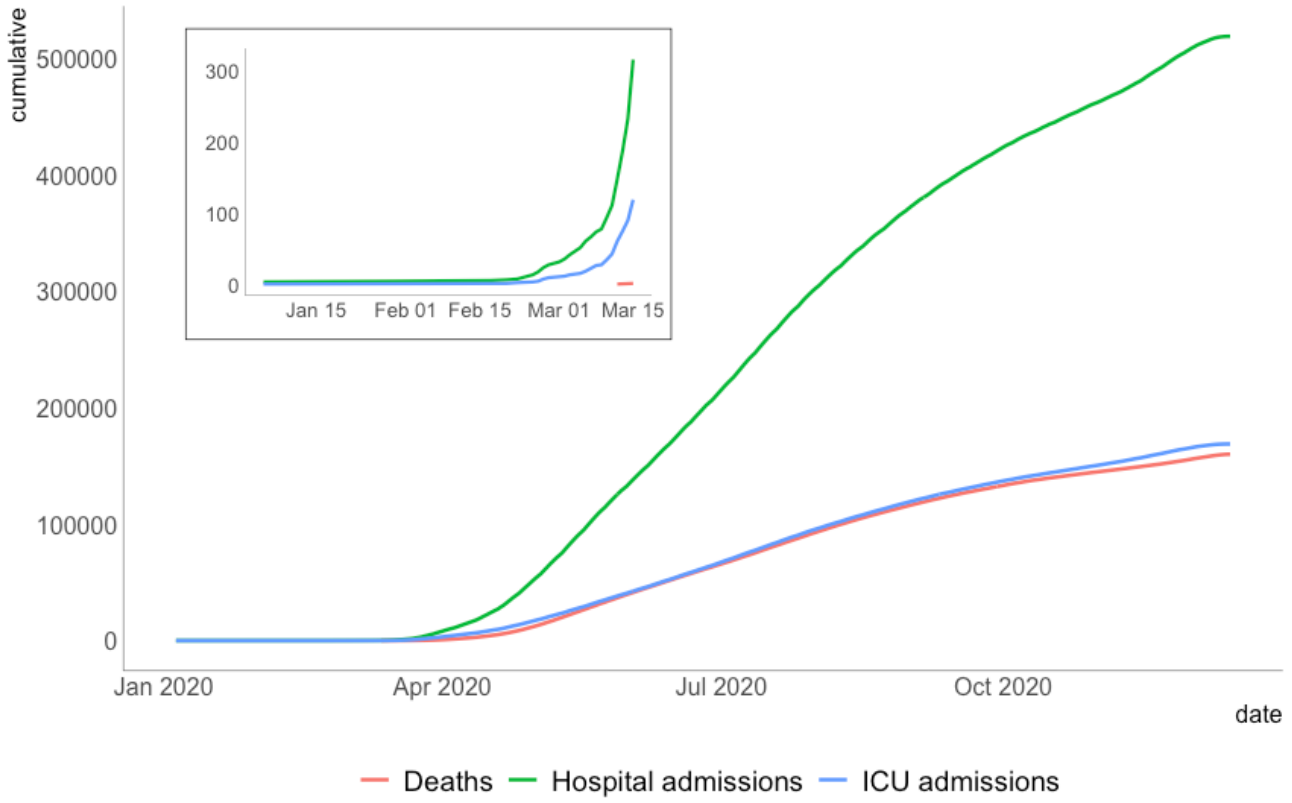
Supplementary material for "Characteristics, outcomes and risk factors for mortality of 522,167 patients hospitalized with COVID-19 in Brazil: a retrospective cohort study"

Supplementary Table 1: Data completeness in the dataset of hospitalized individuals with confirmed COVID-19 from SIVEP-Gripe data (as of December 14, 2020)

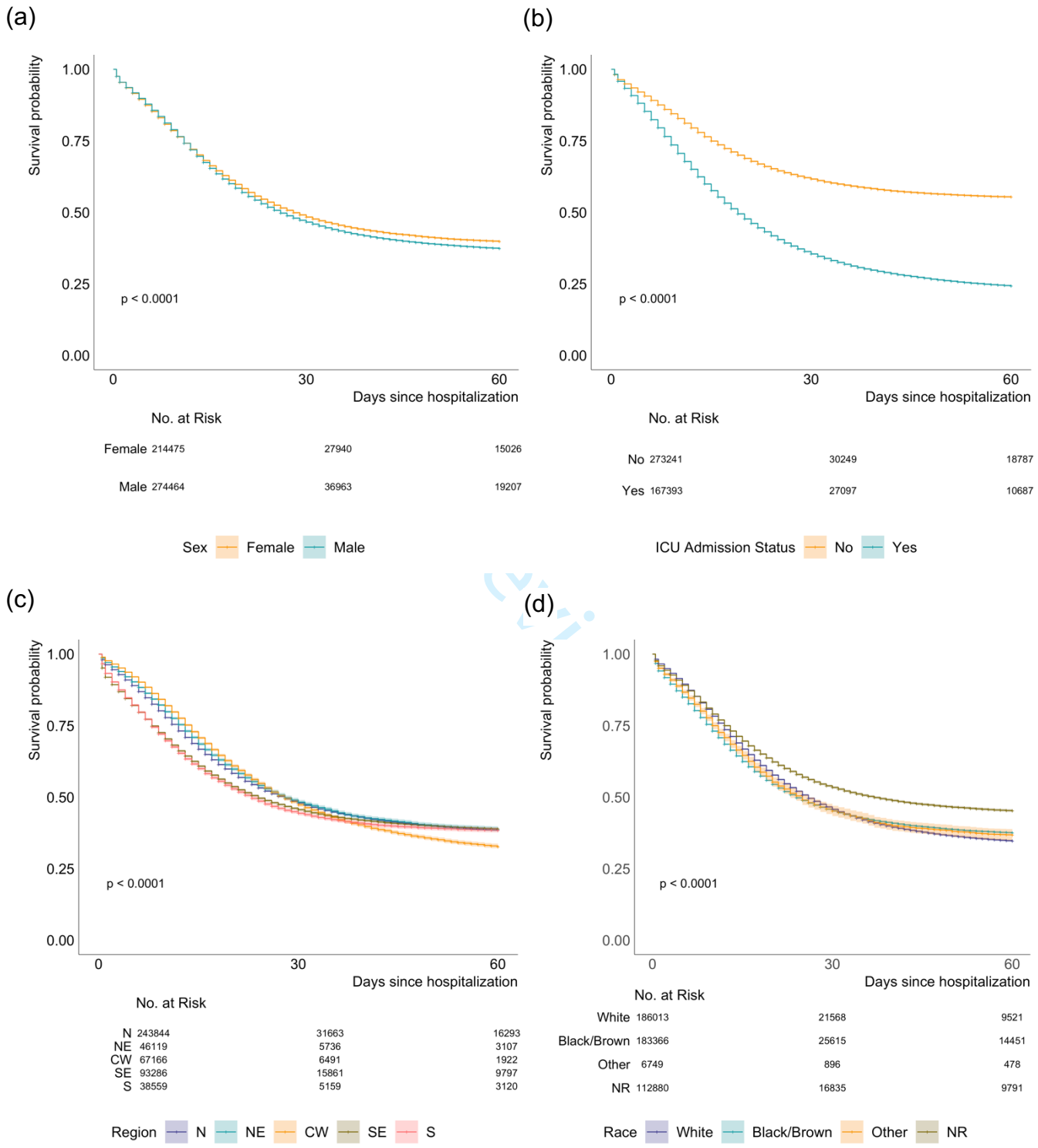
Variable	Missing	N	% Complete
Hospitalization	0	522,167	100%
Final diagnosis of the case	0	522,167	100%
Age informed by patient	0	522,167	100%
Type of age (day, month, year)	0	522,167	100%
Sex	84	522,167	100%
Gestational age	26,081	299,513	91%
Puerperal[a]	133,695	299,513	55%
Ethnoracial self-classification	120,799	522,167	77%
Federal unit of residence	0	522,167	100%
Municipality of residence[b]	36	522,167	100%
Municipality of notification	0	522,167	100%
Comorbidities[a]			
Chronic cardiovascular disease	246,121	522,167	53%
Chronic hematologic diseases	314,925	522,167	40%
Chronic hepatic disease	315,473	522,167	40%
Asthma	311,743	522,167	40%
Diabetes	264,470	522,167	49%
Chronic neurological disease	309,103	522,167	41%
Chronic lung disease	309,631	522,167	41%
Immunodeficiency	312,874	522,167	40%
Chronic renal disease	309,780	522,167	41%
Obesity	306,964	522,167	41%
Other comorbidities	272,160	522,167	48%
Symptoms[a]			
Fever	65,355	522,167	87%
Cough	56,324	522,167	89%
Sore throat	140,061	522,167	73%
Shortness of breath	56,843	522,167	89%
Respiratory distress syndrome	90,093	522,167	83%
Other symptoms descriptive	272,160	522,167	48%
Chest radiograph result	222,990	522,167	57%
Type of drug treatment[a]	434,008	522,167	17%
Mechanical ventilation	75,907	522,167	85%
ICU admission	56,310	522,167	89%
Date of ICU discharge[c]	46,919	522,167	91%
Date of hospital discharge of death[c]	31,755	522,167	94%
Date of onset of illness	0	522,167	100%
Date of treatment with drugs	6,993	93,688	93%
Date of hospitalization[c]	3,170	522,167	99%
Date of ICU admission[c]	3,580	172,473	98%
Date of case closed	8,457	468,664	98%
Clinical outcome (discharge, death, still in hospital)	11,126	522,167	98%

a. Unlike other fields (such as age and sex), comorbidities, symptoms, peruperal, and drugs are not mandatory. Non-response does not necessarily mean missing information, but absence of those conditions.
b. The 36 observations missing municipality of residence are foreigners.
c. Missingness in several date variables could be resolved by cross-checking with other variables. Doing so reduced missingness by 0.04-10.3 percentage points from the original missingness shown above.

Supplementary Figure 1: Cumulative number of COVID-19 hospitalizations, ICU admissions, and deaths. Although hospitalizations occurred early in January, confirmed laboratory results were only made available in late February.



Supplementary Figure 2: Survival curves (Kaplan Meier) 60 days after hospital admission:
Note: N = North, NE = Northeast, CW = Center-West, SE = Southeast, S = South



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	7-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7-10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*7-10*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-14
		(*b*) Report category boundaries when continuous variables were categorized	7-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Characteristics, outcomes and risk factors for mortality of 522,167 patients hospitalized with COVID-19 in Brazil: a retrospective cohort study

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Characteristics, outcomes and risk factors for mortality of 522,167 patients hospitalized with COVID-19 in Brazil: a retrospective cohort study

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ABSTRACT

Objective
To provide a comprehensive description of demographic, clinical, and radiographic characteristics; treatment and case outcomes; and risk factors associated with in-hospital death of patients hospitalized with COVID-19 in Brazil.

Design
Retrospective cohort study of hospitalized patients diagnosed with COVID-19.

Setting
Data from all hospitals across Brazil.

Participants
522,167 hospitalized patients in Brazil by December 14, 2020 with severe acute respiratory illness, and a confirmed diagnosis for COVID-19.

Primary and Secondary Outcome Measures
Prevalence of symptoms and comorbidities were compared by clinical outcomes and intensive care unit (ICU) admission status. Survival was assessed using Kaplan Meier survival estimates. Risk factors associated with in-hospital death were evaluated with multivariable Cox proportional hazards regression.

Results
Of the 522,167 patients included in this study, 56.7% were discharged, 0.002% died of other causes, 30.7% died of causes associated with COVID-19, and 10.2% remained hospitalized. The median age of patients was 61 years (interquartile range [IQR], 47-73), and of non-survivors 71 years (IQR, 60-80); 292,570 patients (56.0%) were men. At least one comorbidity was present in 64.5% of patients and in 76.8% of non-survivors. From illness onset, the median times to hospital and ICU admission were 6 days (IQR, 3-9) and 7 days (IQR, 3-10), respectively; 15 days (IQR, 9-24) to death, and 15 days (IQR, 11-20) to hospital discharge. Risk factors for in-hospital death included old age, Black/Brown ethnoracial self-classification, ICU admission, being male, living in the North and Northeast regions, and various co-morbidities. Age had the highest hazard ratios of 5.51 (95% CI: 4.91-6.18) for patients ≥ 80, compared to those ≤ 20.

Conclusions
Characteristics of patients and risk factors for in-hospital mortality highlight inequities of COVID-19 outcomes in Brazil. As the pandemic continues to unfold, targeted policies that address those inequities are needed to mitigate the unequal burden of COVID-19.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The strength of this study is that it leverages Brazil's established national Influenza Epidemiological Surveillance Information System data to present comprehensive characteristics, clinical course, and risk factors for COVID-19 in-hospital deaths across Brazil.
- Administrative records lack details available in hospital medical records and may have accuracy and completeness problems.
- We did not have access to laboratory results other than COVID-19 tests (e.g., complete blood count) that would allow for a better characterization of the clinical course of the disease.
- COVID-19 deaths at home likely follow a different clinical course than deaths in the hospital and are not included in this analysis.
- In-hospital deaths due to COVID-19 are likely under-reported and are limited by the testing protocol and capacity of each hospital.

INTRODUCTION

On March 11, 2020 the World Health Organization declared COVID-19 as a pandemic. Caused by the novel coronavirus SARS-CoV-2, it emerged in China and quickly spread across the country and beyond. As of February 16, 2021, it was present in 223 countries and territories, with 108,822,960 confirmed cases and 2,403,641 confirmed deaths.[1] Brazil recorded the first confirmed COVID-19 case on February 26, 2020 and the first death on March 12, both in São Paulo State. In 24 days, the disease had spread to all Federal Units. As of February 16, 2021, 9,834,513 cases (9% of worldwide cases) and 239,245 deaths (10% of worldwide deaths) had been reported in Brazil, the second-highest in the world, behind only the US. These numbers are underestimated since most mild cases are not being tested and thus are not likely to be reported, and some deaths may be reported with ill-defined causes, or not reported at all.

Brazil has a comprehensive health information system,[2] with the systematic collection of births, deaths, hospitalizations, and diseases of mandatory notification, among others. However, a complete and linked registry of records combining data from ambulatory and inpatient care, laboratory and radiologic results, and outcome of the disease is not available. Therefore, there is limited information on the course of the disease for every case reported in Brazil.

Currently, the most detailed data available in Brazil refer to hospitalizations due to severe acute respiratory illness (SARI). Here, we use these data to provide a comprehensive description of demographic, clinical, and radiographic characteristics, treatment, case outcome, and risk factors associated with in-hospital death of patients hospitalized with SARI with a confirmed diagnosis for COVID-19, as of December 14, 2020. We analyze the largest retrospective number of cases (N=522,167) and we assess whether the Brazilian case is comparable to patterns previously described for other countries.

METHODS

Data Sources

We used de-identified records from the Influenza Epidemiological Surveillance Information System (*Sistema de Informação de Vigilância Epidemiológica da Gripe, SIVEP-Gripe*, in Portuguese), an information system of the Ministry of Health that captures all notifications of SARI hospitalizations in both public and private hospitals. The system is updated daily, and every two weeks a new dataset is made publicly available (https://opendatasus.saude.gov.br/nl/dataset). Here we analyzed records as of December 14, 2020 (N=1,029,684 notifications), after 15,419 duplicate records were removed by the Ministry of Health. Each record has data on patient's age, sex, place of residence and of hospitalization, ethnoracial self-classification,[3] pregnancy status, comorbidities, and symptoms; drug treatment; radiologic test results; and dates of illness onset, hospitalization, ICU admission, and outcome (death, release, still hospitalized). We considered only records of patients hospitalized with a confirmed diagnosis for COVID-19 (N = 522,167). Diagnosis followed the Ministry of Health guidelines.[4]

Statistical Analysis

Characteristics of inpatients were summarized in three groups: demographic, clinical and radiographic, and treatment and outcomes. Medians and interquartile ranges (IQR) were used to describe continuous variables, and counts and percentages to describe categorical variables. Differences between inpatients that needed and did not need ICU admission and those that survived and did not survive were assessed by Whitney U, χ^2, or Fisher's exact test, as

appropriate. No data imputation was performed for missing data (see online supplementary table 1 for information on data completeness).

Survival curves of inpatients at 60 days of hospitalization by age, sex, ethnoracial self-classification, region, and ICU admission were estimated using the Kaplan-Meier estimator and compared with the log-rank test. Factors associated with inpatient death were identified by univariable and multivariable logistic regression (excluding from the analysis those that remained hospitalized). Considering time to death as the outcome, hazard ratios were estimated using Cox proportional-hazards models. Based on previous studies[5-7] and on our available information, covariates included in both logistic and Cox models were age (0-19, 20-39, 40-59, 60-69, 70-79, and 80 or more years), sex, ethnoracial self-classification (White, Black/Brown, other, not reported), region (North – where Amazonia is located, Northeast, South, Southeast – where the cities of São Paulo and Rio de Janeiro are located, and Center-West), comorbidities (diabetes, asthma, chronic liver disease, chronic neurological disease, chronic lung disease, immunodeficiency, and chronic kidney disease), obesity, and ICU admission. The variable ethnoracial self-classification was missing in 23.1% of the records, and we added those as a separate category (not reported). Distances between municipalities of residence and hospitalization were calculated in ArcMap, version 10.6 (ESRI, Redlands, CA, USA). All analyses were performed in Stata, version 15.1 (Stata Corp., College Station, TX, USA), and R version 4.0.0 (RStudio Team, Boston, MA, USA).

Patient and public involvement

Our analysis used administrative records, and thus study participants were not involved in the design of the study. Public involvement was achieved through collaboration with the Ministry of

Health, with whom we defined the research questions to fill in knowledge gaps and inform decision making. Results were discussed and shared with the Ministry, and their wide dissemination with public health officials, researchers, and through the media will reach the broader public.

RESULTS

As of December 14, 2020, 522,167 patients had been hospitalized with confirmed COVID-19 since the beginning of the epidemic in Brazil. Of those, 296,002 (56.7%) were discharged, 1,004 (0.002%) died of other causes, 160,495 (30.7%) died of causes associated with COVID-19, 53,503 (10.2%) remained hospitalized. Clinical outcome was unknown for 11,126 (2.1%) patients (table 1). The cumulative curve of hospital admissions (online supplementary figure 1) shows the fast increase in severe cases that required hospitalization, following the steep increase in COVID-19 transmission in Brazil since the end of March. The median age of patients was 61 years (IQR, 47-73), and much higher for non-survivors, 71 years (IQR, 60-80), as shown by the age distribution in figures 1a-b. Patients aged 60 years or more represented 50.1% of hospitalizations, 59.0% of ICU admissions, and 74.0% of deaths associated with COVID-19. Patients were mostly males (56.0%) and from the Southeast region (49.3%). Among females, 2.5% were pregnant or puerperal at the time of hospitalization, and 7.5% of those died in the hospital. A total of 172,473 (33.0%) patients with median age of 65 years (IQR, 52-76) needed ICU admission. Of all hospitalizations, 37.7% of the patients were White, and 37.9% were Black/Brown. Among survivors, 38.8% were White, while among non-survivors 41.7% were Black/Brown. About 25% of the patients traveled a median of 32.0 km (IQR, 18.6-64.1) to be hospitalized in a municipality different from where they reside (table 1).

Table 1. Demographic characteristics of patients

Characteristic	All patients (N = 522,167)[a]	ICU admission (N = 172,473)	Non-ICU admission (N = 293,384)	Not reported (N = 56,310)	p-value	Survivor & non-COVID-19 death (N = 297,043)	Non-survivor (N = 160,495)[b]	Still in the hospital (N = 53,503)	p-value
Age									
Median (IQR) - years	61 (47-73)	65 (52-76)	59 (45-72)	61 (47-74)	<0.001	56 (42-68)	71 (60-80)	60 (46-72)	<0.001
Distribution, number (%)					<0.001				<0.001
0-19	13,136 (2.5)	3,211 (1.9)	8,517 (2.9)	1,408 (2.5)		9,994 (3.4)	985 (0.6)	1,628 (3.0)	
20-39	71,728 (13.7)	16,978 (9.8)	46,823 (16.0)	7,927 (14.1)		54,889 (18.5)	7,299 (4.6)	7,814 (14.6)	
40-59	170,266 (32.6)	50,445 (29.3)	101,922 (34.7)	17,899 (31.8)		114,769 (38.6)	33,405 (20.8)	18,196 (34.0)	
60-69	108,416 (20.8)	39,362 (22.8)	57,404 (19.6)	11,650 (20.7)		56,788 (19.1)	38,044 (23.7)	11,352 (21.2)	
70-79	90,800 (17.4)	35,944 (20.8)	44,943 (15.3)	9,913 (17.6)		38,304 (12.9)	41,883 (26.1)	8,942 (16.7)	
≥ 80	67,808 (13.0)	26,530 (15.4)	33,769 (11.5)	7,509 (13.3)		22,303 (7.5)	38,872 (24.2)	5,570 (10.4)	
Sex, number (%)					<0.001				<0.001
Male	292,570 (56.0)	100,399 (58.2)	161,377 (55.0)	30,794 (54.7)		163,967 (55.2)	92,376 (58.6)	30,146 (56.3)	
Female	229,513 (44.9)	72,060 (41.8)	131,964 (45.0)	25,489 (45.3)		133,028 (44.8)	68,101 (42.4)	23,345 (43.6)	
Pregnant, number (%)	4,441 (1.9)	802 (1.1)	3,249 (2.5)	390 (1.5)	<0.001	3,603 (2.7)	230 (0.3)	469 (2.0)	<0.001
Puerperal, number (%)	1,350 (0.6)	426 (0.6)	850 (0.6)	74 (0.3)	<0.001	965 (0.7)	204 (0.4)	148 (0.6)	<0.001
Ethnoracial, number (%)					<0.001				<0.001
White	196,035 (37.5)	67,619 (39.2)	114,339 (39.0)	14,077 (25.0)		115,358 (38.8)	58,487 (36.4)	19,257 (36.0)	
Black/Brown	198,096 (37.9)	61,450 (35.6)	114,378 (39.0)	22,268 (39.6)		106,312 (35.8)	66,889 (41.7)	19,891 (37.2)	
Other	7,237 (1.4)	2,135 (1.2)	4,191(1.4)	911 (1.6)		4,028 (1.4)	2,332 (1.5)	710 (1.3)	
Not reported	120,799 (23.1)	41,269 (23.9)	60,476 (20.6)	19,054 (33.8)		71,345 (24.0)	32,787 (20.4)	13,645 (25.5)	
Region of residence, number (%)					<0.001				<0.001
North	41,961 (8.0)	10,024 (5.8)	27,065 (9.2)	4,872 (8.7)		23,149 (7.8)	14,537 (9.1)	3,559 (6.7)	
Northeast	104,213 (20.0)	33,220 (19.3)	50,377 (17.2)	20,616 (36.6)		49,733 (16.7)	37,919 (23.6)	12,695 (23.7)	
Center-West	48,864 (9.4)	16,581 (9.6)	28,872 (9.8)	3,411 (6.1)		29,169 (9.8)	13,532 (8.4)	4,759 (8.9)	
Southeast	257,503 (49.3)	88,817 (51.5)	144,010 (49.1)	24,676 (43.8)		151,595 (51.0)	76,494 (47.7)	25,050 (46.8)	
South	69,590 (13.3)	23,814 (13.8)	43,042 (14.7)	2,734 (4.9)		43,380 (14.6)	17,997 (11.2)	7,439 (13.9)	
Foreigner	36 (0.0)	17 (0.0)	18 (0.0)	1 (0.0)		17 (0.0)	16 (0.0)	1 (0.0)	
Hospital in the same municipality of residence, number (%)					<0.001				<0.001
Yes	388,304 (74.4)	118,002 (68.4)	227,423 (77.5)	42,879 (76.2)		224,134 (75.5)	116,664 (72.7)	39,772 (74.3)	
No	133,827 (25.6)	54,454 (31.6)	65,943 (22.5)	13,430 (23.9)		72,892 (24.5)	43,815 (27.3)	13,730 (25.7)	
Distance (km) from residence to hospital[b]	32.0 (18.4-64.1)	35.6 (19.8-77.8)	29.4 (18.0-56.6)	25.8 (14.5-54.7)	<0.001	29.8 (18.1-57.8)	34.1 (19.1-71.9)	34.5 (18.8-75.9)	<0.001

[a] Includes 11,126 patients with unknown clinical outcome.

[b] Non-survivors are classified as those whose death was associated with COVID-19, according to the *SIVEP-Gripe* database. Those who had COVID-19 but died due to an unrelated cause are classified under "Survivor & non-COVID-19 death". Survivor N=296,002, non-COVID-19 death=1,041.

[c] Distances (measured in km) are calculated from the centroid of the notification municipality (consistent with municipality of hospitalization) to the centroid of the municipality of residence, using the South America Lambert Conformal Conic projection.

Comorbidities were observed in 64.5% of the patients, 74.6% of those who needed ICU admission, 76.8% of non-survivors, and 58.5% of the survivors and those whose death was not associated with COVID-19. With the exception of asthma, all comorbidities had a higher prevalence among non-survivors (compared to all patients). The most common comorbidities were chronic cardiovascular disease (34.5% of patients and 43.5% of non-survivors) and diabetes (25.7% of patients and 33.0% of non-survivors). Obesity was reported in 7.4% of the patients and 10.5% of those who needed ICU admission. The most common symptoms were fever, cough, shortness of breath, low oxygen saturation, and respiratory distress symptoms (table 2).

Table 2. Clinical and radiographic characteristics of patients

Characteristic	All patients (N = 522,167)[a]	ICU admission (N = 172,473)	Non-ICU admission (N = 293,384)	Not reported (N = 56,310)	p-value	Survivor & non-COVID-19 death (N = 297,043)	Non-survivor (N = 160,495)[b]	Still in the hospital (N = 53,503)	p-value
Any comorbidity, number (%)	336,909 (64.5)	128,590 (74.6)	179,847 (61.3)	28,472 (50.6)	<0.001	173,828 (58.5)	123,265 (76.8)	33,318 (62.3)	<0.001
Chronic cardiovascular disease	180,370 (34.5)	72,196 (41.9)	93,574 (31.9)	14,600 (25.9)	<0.001	89,402 (30.1)	69,768 (43.5)	17,980 (33.6)	<0.001
Chronic hematologic diseases	4,134 (0.8)	1,687 (1.0)	2,204 (0.8)	243 (0.4)	<0.001	1,957 (0.7)	1,739 (1.1)	365 (0.7)	<0.001
Chronic hepatic disease	4,732 (0.9)	2,101 (1.2)	2,309 (0.8)	322 (0.6)	<0.001	1,924 (0.7)	2,368 (1.5)	361 (0.7)	<0.001
Asthma	14,567 (2.8)	4,947 (2.9)	8,639 (2.9)	981 (1.7)	<0.001	9,130 (3.1)	3,634 (2.3)	1,514 (2.8)	<0.001
Diabetes	134,391 (25.7)	53,717 (31.2)	69,078 (23.6)	11,596 (20.6)	<0.001	65,941 (22.2)	52,958 (33.0)	12,844 (24.0)	<0.001
Chronic neurological disease	21,016 (4.0)	8,821 (5.1)	10,832 (3.7)	1,363 (2.4)	<0.001	8,113 (2.7)	10,943 (6.8)	1,622 (3.0)	<0.001
Chronic lung disease	20,140 (3.9)	9,249 (5.4)	9,483 (3.2)	1,408 (2.5)	<0.001	8,222 (2.8)	10,021 (6.2)	1,621 (3.0)	<0.001
Immunodeficiency	13,967 (2.7)	5,689 (3.3)	7,376 (2.5)	902 (1.6)	<0.001	6,351 (2.1)	6,283 (3.9)	1,132 (2.1)	<0.001
Chronic renal disease	21,725 (4.2)	10,684 (6.2)	9,429 (3.2)	1,512 (2.9)	<0.001	8,149 (2.7)	11,491 (7.2)	1,743 (3.3)	<0.001
Obesity	38,415 (7.4)	18,057 (10.5)	17,998 (6.1)	2,360 (4.2)	<0.001	20,993 (7.1)	12,765 (8.0)	4,005 (7.5)	<0.001
Others[c]	144,081 (27.6)	58,139 (33.7)	74,994 (25.6)	10,948 (19.4)	<0.001	72,598 (24.4)	55,866 (34.8)	13,042 (24.4)	<0.001
Symptoms, number (%)									
Fever	188,572 (64.3)	104,650 (60.7)	188,572 (64.3)	34,789 (61.8)	<0.001	194,578 (65.5)	93,933 (58.5)	32,586 (60.9)	<0.001
Cough	369,192 (70.7)	115,147 (66.7)	215,084 (73.3)	38,961 (69.2)	<0.001	219,433 (73.9)	105,252 (65.6)	36,717 (68.6)	<0.001
Sore throat	90,487 (17.3)	23,531 (13.6)	56,653 (19.3)	10,303 (18.3)	<0.001	56,741 (19.1)	22,982 (14.3)	8,872 (16.6)	<0.001
Shortness of breath	367,917 (70.5)	131,799 (76.4)	199,805 (68.1)	36,313 (64.5)	<0.001	200,051 (67.4)	124,724 (77.7)	35,709 (66.7)	<0.001
Respiratory distress syndrome	296,238 (56.7)	107,762 (62.5)	163,370 (55.7)	25,106 (44.7)	<0.001	157,412 (53.0)	104,555 (65.2)	28,046 (52.4)	<0.001
Oxygen saturation <95%	303,282 (58.1)	116,355 (67.5)	160,837 (54.8)	26,090 (46.3)	<0.001	156,349 (52.6)	111,097 (69.2)	29,704 (55.5)	<0.001
Diarrhea	71,069 (13.6)	20,340 (11.8)	44,411 (15.1)	6,318 (11.2)	<0.001	44,961 (15.1)	17,419 (10.9)	7,264 (13.6)	<0.001
Vomiting	41,974 (8.0)	11,950 (6.9)	26,177 (8.9)	3,847 (6.8)	<0.001	25,799 (8.7)	11,076 (6.9)	4,156 (7.8)	<0.001
Others[d]	179,222 (34.3)	58,268 (33.8)	105,646 (36.0)	15,308 (27.2)	<0.001	112,278 (37.8)	45,263 (28.2)	18,294 (34.2)	<0.001
Chest radiograph, number (%)					<0.001				<0.001
Normal	11,816 (2.3)	3,403 (2.0)	7,782 (2.7)	631 (1.1)		7,895 (2.7)	2,558 (1.6)	1,091 (2.0)	
Interstitial abnormalities	81,412 (15.6)	28,091 (16.3)	48,864 (16.7)	4,457 (7.9)		45,320 (15.3)	27,071 (16.9)	7,500 (14.0)	
Other[e]	85,870 (16.4)	35,844 (20.8)	47,185 (16.1)	2,841 (5.1)		246,250 (82.9)	132,429 (82.5)	47,639 (89.0)	

[a] Includes 11,126 patients with unknown clinical outcome.

[b] Non-survivors are classified as those whose death was associated with COVID-19, according to the *SIVEP-Gripe* database. Those who had COVID-19 but died due to an unrelated cause are classified under "Survivor & non-COVID-19 death". Survivor N=296,002, non-COVID-19 death=1,041.

[c] Other comorbidities that were not specifically asked about in the survey, but self-reported as "other" include, but are not limited to: hypertension, cancer, anemia, bronchitis, dyslipidemia, and pulmonary emphysema.

[d] Other symptoms that were not specifically asked about in the surveillance form, but self-reported as "other" include, but are not limited to: loss of taste, loss of smell, myalgia, weakness, body ache, fatigue, exhaustion, tachypnea, and syncope.

[e] Includes consolidation, mixed, and other.

The median time from illness onset to hospital admission was 6 days (IQR, 3-9), slightly shorter among non-survivors, 5 days (IQR, 2-8). Mechanical ventilation was needed by 62.2% of all patients, and by 75.6% of those who died. Invasive ventilation was more common in the ICU (44.0%). Oseltamivir, an antiviral medication, was the most common drug used during treatment (15.8% overall, and 17.6% among those in ICU), and the median time from illness onset to treatment was 5 days (IQR, 3-8). Of the patients that needed ICU, 51.8% died from causes associated with COVID-19, and 19.0% remained hospitalized after ICU discharge for 5 days (IQR, 2-10). The median time from illness onset to ICU admission was 7 days (IQR, 3-10), and the medium length of ICU stay was 8 days (IQR, 3-15) for all patients, 9 days (IQR, 4-16) for the deceased. Among the 160,495 patients who died of causes associated with COVID-19 by December 14, the median time from illness onset to death was 15 days (IQR, 9-24) (table 3). Medium length of hospital stay was 8 days (IQR, 4-17), but longer for those who needed ICU admission, 12 days (IQR, 6-22). The density of time from hospital admission to death is positively skewed, more so for those who did not get admitted to the ICU (figure 1c). Kaplan Meier curves (figure 1d and online supplementary figure 2) for a period of up to 60 days after hospital admission showed that survival curves were significantly different by age, region, sex, ethnoracial self-classification, and ICU admission.

Table 3. Treatment and outcomes of patients

Variable	All patients (N = 522,167)[a]	ICU admission (N = 172,473)	Non-ICU admission (N = 293,384)	Not reported (N = 56,310)	p-value	Survivor & non-COVID-19 death (N = 297,043)	Non-survivor (N = 160,495)	Still in the hospital (N = 53,503)	p-value
Treatment with drugs, number (%)					<0.001				<0.001
Oseltamivir	82,659 (15.8)	30,341 (17.6)	47,317 (16.1)	5,001 (8.9)		50,091 (16.9)	27,192 (16.9)	4,242 (7.9)	
Zanamivir	492 (0.1)	152 (0.1)	303 (0.1)	37 (0.1)		298 (0.1)	128 (0.1)	56 (0.1)	
Other	5,008 (1.0)	1,480 (0.9)	3,243 (1.1)	285 (0.5)		3,029 (1.0)	1,118 (0.7)	701 (1.3)	
Mechanical ventilation, number (%)					<0.001				<0.001
Invasive	90,189 (17.3)	75,915 (44.0)	12,019 (4.1)	2,255 (4.0)		17,263 (5.8)	66,652 (41.5)	5,238 (9.8)	
Noninvasive	234,554 (44.9)	65,281 (37.9)	157,913 (53.8)	11,360 (20.2)		148,930 (50.1)	54,652 (34.1)	25,925 (48.5)	
ICU admission, number (%)	172,473 (33.0)	172,473 (100.0)	-	-	-	65,102 (21.9)	89,264 (55.6)	15,614 (29.2)	<0.001
Remained hospitalized after ICU discharge, number (%)	32,770 (19.0)	32,770 (19.0)	-	-	-	27,775 (42.7)	3,243 (3.6)	1,303 (8.4)	<0.001
Median length (IQR), days	5 (2-10)	5 (2-10)	-	-	-	5 (2-9)	7 (2-16)	72 (21-139)	<0.001
Median times (IQR), days									
Illness onset to treatment with drugs	5 (3-8)	5 (3-8)	6 (3-9)	6 (3-8)	<0.001	6 (3-9)	5 (2-8)	6 (3-9)	<0.001
Illness onset to hospitalization	6 (3-9)	6 (3-9)	6 (3-10)	6 (2-9)	<0.001	7 (3-10)	5 (2-8)	6 (3-10)	<0.001
Illness onset to ICU admission	7 (3-10)	7 (3-10)	-	-	-	7 (4-10)	6 (3-10)	7 (3-10)	<0.001
Hospital admission to ICU admission	0 (0-1)	0 (0-1)	-	-	-	0 (0-1)	0 (0-1)	0 (0-0)	<0.001
Illness onset to death	15 (9-24)	17 (10-25)	13 (7-21)	12 (7-20)	<0.001	-	15 (9-24)	-	-
Illness onset to hospital discharge	15 (11-20)	18 (13-27)	14 (10-18)	16 (11-21)	<0.001	15 (11-20)	-	-	-
Hospital admission to death	9 (4-16)	10 (5-18)	7 (2-14)	5 (1-13)	<0.001	-	9 (4-16)	-	-
Hospital admission to ICU discharge	9 (4-17)	9 (4-17)	-	-	-	7 (4-14)	10 (5-10)	6 (2-14)	<0.001
ICU admission to death	9 (4-16)	9 (4-16)	-	-	-	-	9 (4-16)	-	-
Median length hospital stay (IQR), days	8 (4-17)	12 (6-22)	7 (4-13)	8 (3-18)	<0.001	7 (4-12)	9 (4-16)	79 (23-157)	<0.001
Median length ICU stay (IQR), days	8 (3-15)	8 (3-15)	-	-	-	6 (3-12)	9 (4-16)	4 (2-11)	<0.001
Clinical outcomes as of 12/14/2020, number (%)					<0.001				-
Cured and discharged from hospital	296,002 (56.7)	64,578 (37.4)	202,042 (68.9)	29,382 (52.2)		296,002 (99.7)	-	-	
Death due to other causes	1,041 (0.2)	524 (0.3)	443 (0.2)	74 (0.1)		1,041 (0.4)	-	-	
Death associated with COVID-19	160,495 (30.7)	89,264 (51.8)	53,282 (18.2)	17,949 (31.9)		-	160,495 (100.0)	-	
Still in the hospital	53,503 (10.3)	15,614 (9.1)	30,963 (10.6)	6,926 (12.3)		-	-	53,503 (100.0)	

[a] Includes 11,126 patients with unknown clinical outcome.

[b] Non-survivors are classified as those whose death was associated with COVID-19, according to the *SIVEP-Gripe* database. Those who had COVID-19 but died due to an unrelated cause are classified under "Survivor & non-COVID-19 death". Survivor N=296,002, non-COVID-19 death=1,041.

Univariable logistic analysis indicated that the odds of in-hospital death progressively increased with age, and were higher for patients who were male, non-white, from the North and Northeast regions, needed ICU care, were obese, and had diabetes and other comorbidities (table 4). The multivariable analysis included 168,936 records (65,670 non-survivors) that had no missing data for covariates. The odds of in-hospital death for males are 1.23 times that of females, and for those in the North and Northeast regions were, respectively, 1.83 and 1.48 times that of patients in the Southeast. The Cox proportional-hazards model included 176,559 records (64,809 non-survivors). Variables associated with in-hospital death were age, sex, ethnoracial self-classification, region, ICU care, and various co-morbidities. Age, however, had the highest hazard ratios, ranging from 1.67 (95% CI: 1.49-1.89) for those aged 20-39, to 5.51 (95% CI: 4.91-6.18) for those 80 or older, compared to patients younger than 20 years (table 4).

Table 4: Odds ratios (OR) and hazard ratios (HR) for death among hospitalized patients with confirmed COVID-19

Variables	Univariable OR[a] (95% CI)	p-value[b]	Multivariable OR (95% CI) N = 168,936	p-value[b]	HR (95% CI) for death within 60 days of hospitalization N = 176,559
Age (reference 0-19)					
20-39	1.35 (1.26,1.46)	< 0.001	1.66 (1.45, 1.91)	< 0.001	1.67 (1.48, 1.89)
40-59	2.94 (2.74, 3.15)	< 0.001	2.70 (2.37, 3.09)	< 0.001	2.21 (1.97, 2.48)
60-69	6.76 (6.30, 7.26)	< 0.001	5.15 (4.52, 5.88)	< 0.001	3.05 (2.72, 3.43)
70-79	11.05 (10.30, 11.86)	< 0.001	8.24 (7.24, 9.42)	< 0.001	3.90 (3.48, 4.38)
≥ 80	17.58 (16.37, 18.88)	< 0.001	14.52 (12.74, 16.59)	< 0.001	5.51 (4.91, 6.18)
Sex (reference Female)					
Male	1.10 (1.09, 1.11)	< 0.001	1.23 (1.20, 1.26)	< 0.001	1.09 (1.07, 1.10)
Ethnoracial self-classification (reference White)					
Black/Brown	1.25 (1.24, 1.27)	< 0.001	1.18 (1.15, 1.22)	< 0.001	1.08 (1.06, 1.10)
Other	1.18 (1.12, 1.25)	< 0.001	1.05 (0.95, 1.16)	0.309	1.02 (0.96, 1.10)
Not reported	0.9 (0.89, 0.92)	< 0.001	0.77 (0.74, 0.80)	< 0.001	0.79 (0.77, 0.81)
Region (reference Southeast)					
South	0.85 (0.83, 0.87)	< 0.001	0.89 (0.87, 0.92)	< 0.001	0.91 (0.89, 0.93)
Center-West	0.96 (0.94, 0.98)	< 0.001	1.04 (1.00, 1.08)	0.049	1.00 (0.97, 1.03)
North	1.31 (1.28, 1.34)	< 0.001	1.83 (1.75, 1.92)	< 0.001	1.34 (1.30, 1.39)
Northeast	1.61 (1.58, 1.64)	< 0.001	1.48 (1.43, 1.55)	< 0.001	1.10 (1.07, 1.12)
ICU	5.21 (5.14, 5.28)	< 0.001	5.20 (5.08, 5.32)	< 0.001	1.78 (1.75, 1.81)
Obesity	0.91 (0.88, 0.93)	< 0.001	1.23 (1.18, 1.27)	< 0.001	1.07 (1.04, 1.10)
Diabetes	1.32 (1.30, 1.35)	< 0.001	1.18 (1.15, 1.21)	< 0.001	1.08 (1.07, 1.10)
Asthma	0.59 (0.56, 0.61)	< 0.001	0.81 (0.77, 0.86)	< 0.001	0.88 (0.84, 0.92)
Chronic liver disease	1.87 (1.76, 1.99)	< 0.001	1.74 (1.59, 1.90)	< 0.001	1.33 (1.26, 1.40)
Chronic neurological disease	2.12 (2.06, 2.19)	< 0.001	1.65 (1.58, 1.73)	< 0.001	1.18 (1.15, 1.21)
Chronic lung disease	1.92 (1.86, 1.99)	< 0.001	1.46 (1.40, 1.53)	< 0.001	1.16 (1.13, 1.19)
Immunodeficiency	1.53 (1.47, 1.58)	< 0.001	1.93 (1.83, 2.04)	< 0.001	1.26 (1.22, 1.31)
Chronic kidney disease	2.23 (2.16, 2.30)	< 0.001	1.70 (1.63, 1.78)	< 0.001	1.17 (1.14, 1.21)

[a] The N varies for univariable OR, depending on the number of missing values for each variable.
[b] P-value from Wald test.

DISCUSSION

This study described demographic, clinical, and radiographic characteristics, treatment, case outcome, and risk factors associated with in-hospital death of 522,167 patients hospitalized with confirmed COVID-19 in Brazil. Results show that 56.7% were discharged, 0.002% died of other causes, 30.7% died of causes associated with COVID-19, and 10.2% remained in the hospital as of December 14. Patients were mostly older than 40 years, predominantly from the Southeast region, with about one fourth needing to travel to a different municipality for hospitalization. At least one comorbidity was present in 64.5% of patients and in 76.8% of the non-survivors. From illness onset, the median time to hospital and ICU admission was 6 and 7 days, respectively; 15 days to death (17 to those admitted to the ICU), and 15 days to hospital discharge (18 days to those admitted to the ICU). Risk factors for in-hospital death were older age, being male, of Black/Brown ethnoracial self-classification, living in the North or Northeast regions, with a history of ICU admission, and various co-morbidities.

Our results can be analyzed in light of findings from other countries. The use of mechanical ventilation was higher in Brazil (62.2% among all patients, 75.6% of the non-survivors) compared to patterns described for China (ranging from 17.2 to 38.7% of patients),[8-10] and Germany (17% of patients),[11] but lower than Italy (81.7% of all patients).[12] While ICU mortality in Italy was 26%,[12] in Brazil it was 51.8%. In Brazil, 33.0% of hospitalized patients were admitted to the ICU, against 16% in Italy,[13] and 19% in France.[14] In-hospital death was observed in 18.1% of patients in France,[14] 22% in Germany,[11] and 30.7% in Brazil. The time from illness onset to hospitalization in China[9] was 11 days (IQR, 8-14), but much shorter in Brazil, 6 days (IQR, 3-9). The length of hospital stay, however, was about 4 days longer in China.[9 15] These comparisons need to be taken with caution. First, studies from China had a smaller sample size,

and regional variability is very large, as reported for France.[14] In Brazil, for example, in-hospital death varied from 25.9% in the South region to 36.4% in the Northeast, and ICU mortality from 48.0% in the Southeast to 66.5% in the North. The time from illness to hospitalization was also longer in the North and Center-West regions, 7 days (IQR, 4-10).

Our results confirm previous findings regarding symptoms and comorbidities. Hypertension, a very common comorbidity in China[9] could not be measured from our data, but over one-third of the adult population in Brazil has that condition.[16] In Brazil, 35.5% of the patients reported no comorbidities, while in New York City this number was 6.1%,[17] and in China it was 52%.[9] Diabetes was reported in 19% of patients in China,[9] 33.8% in New York City,[17] and 25.7% in Brazil. Part of these differences reflects the disease burden in each locality, but also the lack of standardized data collection (e.g., conditions systematically collected in one country and only reported in the 'other' category in another country).

The observed associations of age, sex, obesity, and diabetes with in-hospital death corroborate previous findings.[5 6 14] The higher risk among non-white patients was previously reported in Brazil, the UK, and the US.[18-22] In Brazil, this reflects structural inequalities that made large fractions of the population more vulnerable to COVID-19 (e.g., people living in areas with precarious infrastructure, overcrowded households, regions with low supply of physicians and hospital services, and who depend on informal labor).[23 24] Those inequalities are also captured by a higher hazard ratio in the North and Northeast regions, where Brazil consistently reports worse socioeconomic indicators.[25] Currently, the North region has the lowest rates of hospital beds, ICU beds, and physicians per person.[26] Indeed, the region had the worst indicators in terms of mortality and time to hospitalization, and patients who were hospitalized in a municipality different from the one where they live had to travel 122.0 km (IQR, 58.3-258.6) while those in

the Southeast traveled 22.3 km (IQR, 16.1-36.3). Hospitalization in a different municipality occurs when the place of residence has no hospitals, has no available hospital beds, or when the closest hospital is actually outside the municipality of residence. In Brazil, the size of municipalities varies widely: 23% have 5,000 residents or less, and 5% have 100,000 or more residents. Of the 5,570 municipalities, 37% and 75% have no hospitals and no ICU care, respectively. A regionalization process guarantees that all the population has access to hospital care.[27] However, when hospitals reach capacity, as was observed in several cities in Brazil in late April and May, municipalities without hospitals and ICU units are unable to provide proper care, which may have contributed to higher COVID-19 mortality. Therefore, risk factors for in-hospital mortality due to COVID-19 expose local and structural inequalities.

This study has some limitations. First, we used administrative records captured in structured surveillance forms. Those lack details available in hospital medical records and may have accuracy and completeness problems. In addition, it limits the types of comorbidities and symptoms reported, as those listed under the 'other' category were not systematically collected from all cases (e.g., loss of taste and smell). Second, we did not have access to laboratory results other than COVID-19 tests (e.g., complete blood count). While this does not change any of our results, they would allow for a better characterization of the clinical course of the disease. Third, 23.1% of patients did not report information on ethnoracial self-classification, 10.8% did not have information on ICU admission, and for 2.1% there was no information on clinical outcome. This is not uncommon in the analysis of administrative records.[22] Here we report all records and included an additional category (ethnoracial self-classification not reported) in the risk factor analysis.

Despite these limitations, this study provides a comprehensive description of characteristics, outcomes, and risk factors for mortality of patients hospitalized with COVID-19 in Brazil, and the largest cohort of patients so far analyzed (N=522,167). Results shed light on commonalities and differences between Brazil and other countries affected by COVID-19, and highlight inequalities in disease outcomes. Most importantly, our results could be used to inform coordinated actions to target those who currently bear the highest morbidity and mortality burden. Currently, Brazil's response to COVID-19 did not comprehensively and effectively utilize its community-based primary health care program.[28-30] Brazil has a network of almost 270,000 community health workers that reach out to about 70% of the Brazilian population. These agents could actively identify vulnerable people who face higher risk of mortality, could act as agents of information to sensitize the population and boost adherence to control measures (e.g., use of masks), and could continue to deliver community-based primary care services that have been, for the most part, interrupted by the pandemic. These agents will also be important to support the delivery of vaccination (once it starts) to the most vulnerable. Currently, with more than 200,000 deaths and with hospital occupancy increasing at alarming rates, leveraging and strengthening the existing network of primary health care is paramount to contain the sustained and unequal burden of COVID-19 in Brazil.

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Figure 1: Age distribution of patients, density curves of length of time from hospital admission to death, and survival curve 60 days after hospital admission. (a) Age distribution of patients hospitalized. (b) Age distribution of in-hospital deaths. (c) Density of number of days from hospital admission to death up to 60 days after hospital admission, detailed by ICU admission status. (d) Survival curve estimated with Kaplan Meier and considering 60 days from hospital admission.

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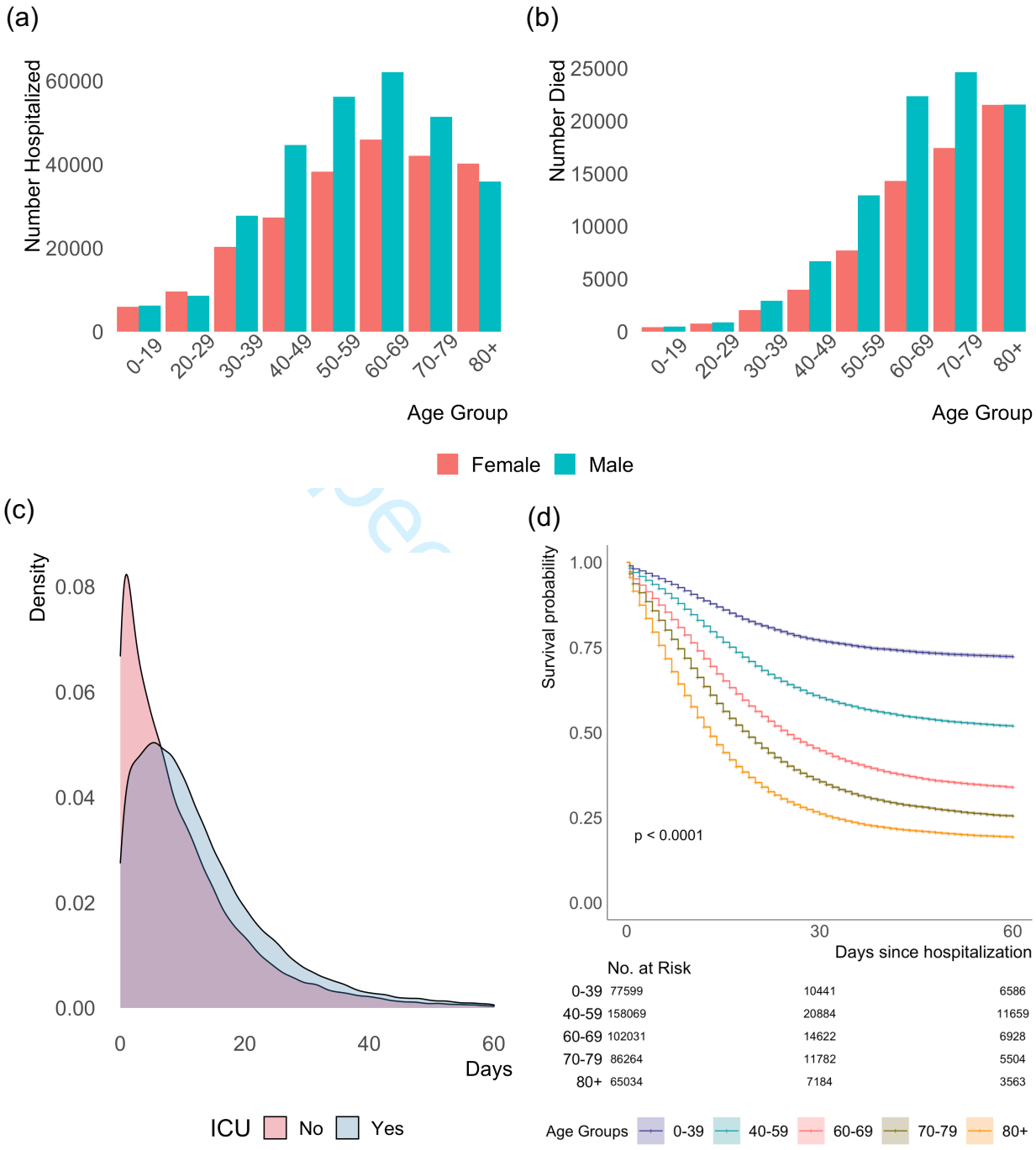

(a)
Number Hospitalized
60000
40000
20000
0
0-19
20-29
30-39
40-49
50-59
60-69
70-79
80+
Age Group
(b)
Number Died
25000
20000
15000
10000
5000
0
Age Group
Female
Male
(c)
Density
0.08
0.06
0.04
0.02
0.00
0
20
40
60
Days
ICU
No
Yes
(d)
Survival probability
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
30
60
Days since hospitalization
No. at Risk
0-39 77599 10441 6586
40-59 158069 20884 11659
60-69 102031 14622 6928
70-79 86264 11782 5504
80+ 65034 7184 3563
Age Groups
0-39
40-59
60-69
70-79
80+

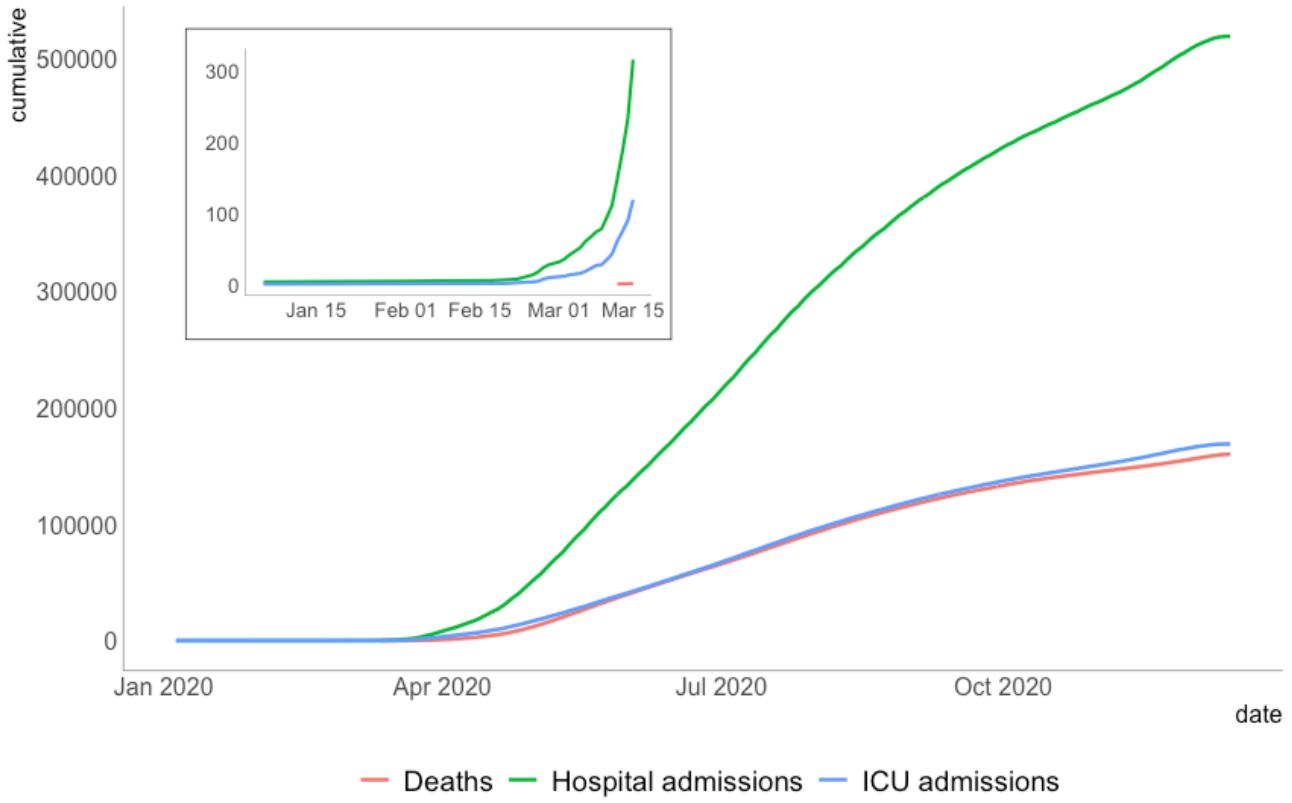
Supplementary material for "Characteristics, outcomes and risk factors for mortality of 522,167 patients hospitalized with COVID-19 in Brazil: a retrospective cohort study"

Supplementary Table 1: Data completeness in the dataset of hospitalized individuals with confirmed COVID-19 from SIVEP-Gripe data (as of December 14, 2020)

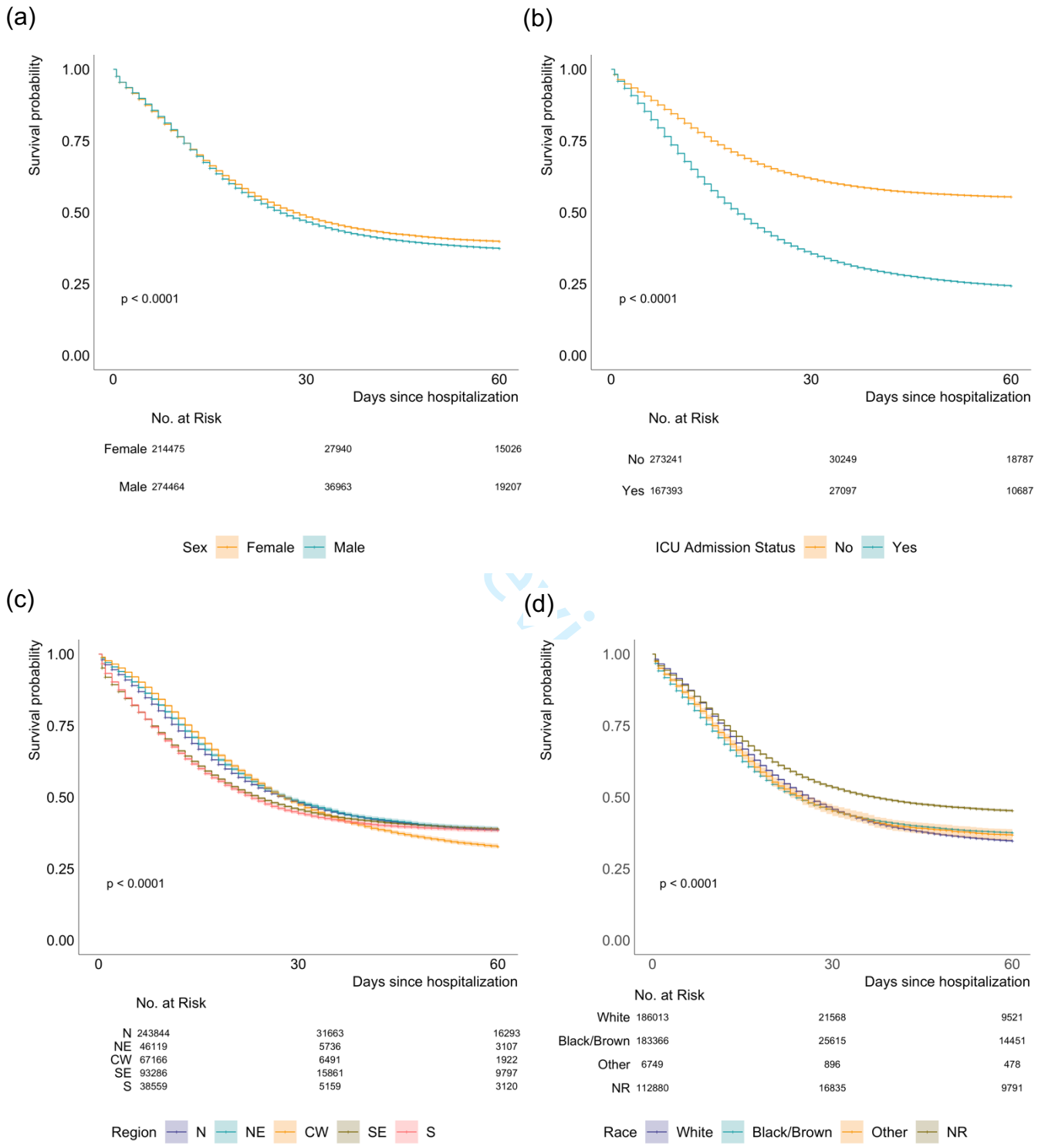
Variable	Missing	N	% Complete
Hospitalization	0	522,167	100%
Final diagnosis of the case	0	522,167	100%
Age informed by patient	0	522,167	100%
Type of age (day, month, year)	0	522,167	100%
Sex	84	522,167	100%
Gestational age	26,081	299,513	91%
Puerperal[a]	133,695	299,513	55%
Ethnoracial self-classification	120,799	522,167	77%
Federal unit of residence	0	522,167	100%
Municipality of residence[b]	36	522,167	100%
Municipality of notification	0	522,167	100%
Comorbidities[a]			
Chronic cardiovascular disease	246,121	522,167	53%
Chronic hematologic diseases	314,925	522,167	40%
Chronic hepatic disease	315,473	522,167	40%
Asthma	311,743	522,167	40%
Diabetes	264,470	522,167	49%
Chronic neurological disease	309,103	522,167	41%
Chronic lung disease	309,631	522,167	41%
Immunodeficiency	312,874	522,167	40%
Chronic renal disease	309,780	522,167	41%
Obesity	306,964	522,167	41%
Other comorbidities	272,160	522,167	48%
Symptoms[a]			
Fever	65,355	522,167	87%
Cough	56,324	522,167	89%
Sore throat	140,061	522,167	73%
Shortness of breath	56,843	522,167	89%
Respiratory distress syndrome	90,093	522,167	83%
Other symptoms descriptive	272,160	522,167	48%
Chest radiograph result	222,990	522,167	57%
Type of drug treatment[a]	434,008	522,167	17%
Mechanical ventilation	75,907	522,167	85%
ICU admission	56,310	522,167	89%
Date of ICU discharge[c]	46,919	522,167	91%
Date of hospital discharge of death[c]	31,755	522,167	94%
Date of onset of illness	0	522,167	100%
Date of treatment with drugs	6,993	93,688	93%
Date of hospitalization[c]	3,170	522,167	99%
Date of ICU admission[c]	3,580	172,473	98%
Date of case closed	8,457	468,664	98%
Clinical outcome (discharge, death, still in hospital)	11,126	522,167	98%

a. Unlike other fields (such as age and sex), comorbidities, symptoms, peruperal, and drugs are not mandatory. Non-response does not necessarily mean missing information, but absence of those conditions.
b. The 36 observations missing municipality of residence are foreigners.
c. Missingness in several date variables could be resolved by cross-checking with other variables. Doing so reduced missingness by 0.04-10.3 percentage points from the original missingness shown above.

Supplementary Figure 1: Cumulative number of COVID-19 hospitalizations, ICU admissions, and deaths. Although hospitalizations occurred early in January, confirmed laboratory results were only made available in late February.



Supplementary Figure 2: Survival curves (Kaplan Meier) 60 days after hospital admission:
Note: N = North, NE = Northeast, CW = Center-West, SE = Southeast, S = South



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-9
		(b) Indicate number of participants with missing data for each variable of interest	7-8
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*7-10*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*7-10*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-14
		(*b*) Report category boundaries when continuous variables were categorized	7-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.