Original Article

Higher Severity and Risk of In-Hospital Mortality for COVID-19 Patients With Cancer During the Year 2020 in Brazil: A Countrywide Analysis of Secondary Data

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BACKGROUND: Coronavirus disease 2019 (COVID-19) and cancer are serious public health problems worldwide. However, little is known about the risk factors of in-hospital mortality among COVID-19 patients with and without cancer in Brazil. The objective of this study was to evaluate the risk factors of in-hospital mortality among COVID-19 patients with and without cancer and to compare mortality according to gender and topography during the year 2020 in Brazil. **METHODS:** This was a secondary data study of hospitalized adult patients with a diagnosis of COVID-19 by real-time polymerase chain reaction testing in Brazil. The data were collected from the Influenza Epidemiological Surveillance Information System. **RESULTS:** This study analyzed data from 322,817 patients. The prevalence of cancer in patients with COVID-19 was 2.3%. COVID-19 patients with neurological diseases and cancer had the most lethal comorbidities in both sexes. COVID-19 patients with cancer were more likely to be older (median age, 67 vs 62 years; $P < .001$), to have a longer hospital stay (13.1 vs 11.5 days; $P < .001$), to be admitted to the intensive care unit (45.3% vs 39.6%; $P < .001$), to receive more invasive mechanical ventilation (27.1% vs 21.9%), and to have a higher risk of death (adjusted odds ratio [aOR], 1.94; 95% confidence interval [CI], 1.83-2.06; $P < .001$) than those without cancer. Patients with hematological neoplasia (aOR, 2.85; 95% CI, 2.41-3.38; $P < .001$) had a higher risk of mortality than those with solid tumors (aOR, 1.83; 95% CI, 1.72-1.95; $P < .001$) in both sexes. **CONCLUSIONS:** Brazilian COVID-19 patients with cancer have higher disease severity and a higher risk of mortality than those without cancer. ***Cancer* 2021;127:4240-4248**. © *2021 American Cancer Society*.

KEYWORDS: Brazil, cancer, coronavirus disease 2019 (COVID-19), mortality, prevalence, risk factors.

INTRODUCTION

The emergence of coronavirus disease 2019 (COVID-19) has caused an unprecedented public health crisis in the world since December 2019. Up to December 31, 2020, the World Health Organization reported more than 82 million confirmed cases and approximately 1.8 million deaths in the world. In the same period, Brazil reported more than 7.6 million confirmed cases and almost 195,000 deaths.[1] Cancer is also a serious public health problem, and it is increasing as a leading cause of mortality because of the aging population and the prevalence of important risk factors as well as a marked decline in mortality due to stroke and heart disease.[2,3]

Patients with cancer have been associated with higher risks of viral infection, the development of COVID-19–related complications, and mortality.[4-7] COVID-19 patients with cancer are at increased risk for mortality according to age, gender, and comorbidities.[8,9] Male COVID-19 patients with[10] or without cancer[11,12] have greater severity and mortality. Nevertheless, the prevalence of cancer in patients with COVID-19 is usually low, approximately 2%,[13] and the mortality of COVID-19 patients with and without cancer in developing countries such as Brazil remains poorly explored.

Furthermore, mortality due to COVID-19 in patients with cancer could be heterogeneous. Cancer patients with different tumor types could have differing susceptibility to severe acute respiratory syndrome coronavirus 2 infections and mortality, so it would be not accurate to classify all patients with cancer as equally vulnerable.[9] In a pioneering Brazilian study, COVID-19 patients with lung and hematological cancers were found to have a greater risk of death when they were undergoing oncological treatment.[14] However, these studies failed to determine the risk of mortality in COVID-19 patients with cancer according to gender and in different topographies. Recently, 2 other Brazilian studies using a large nationwide surveillance database showed higher in-hospital mortality for COVID-19 patients who were from the northern and northeastern regions of the country, who were brown- and black-skinned,[15] who

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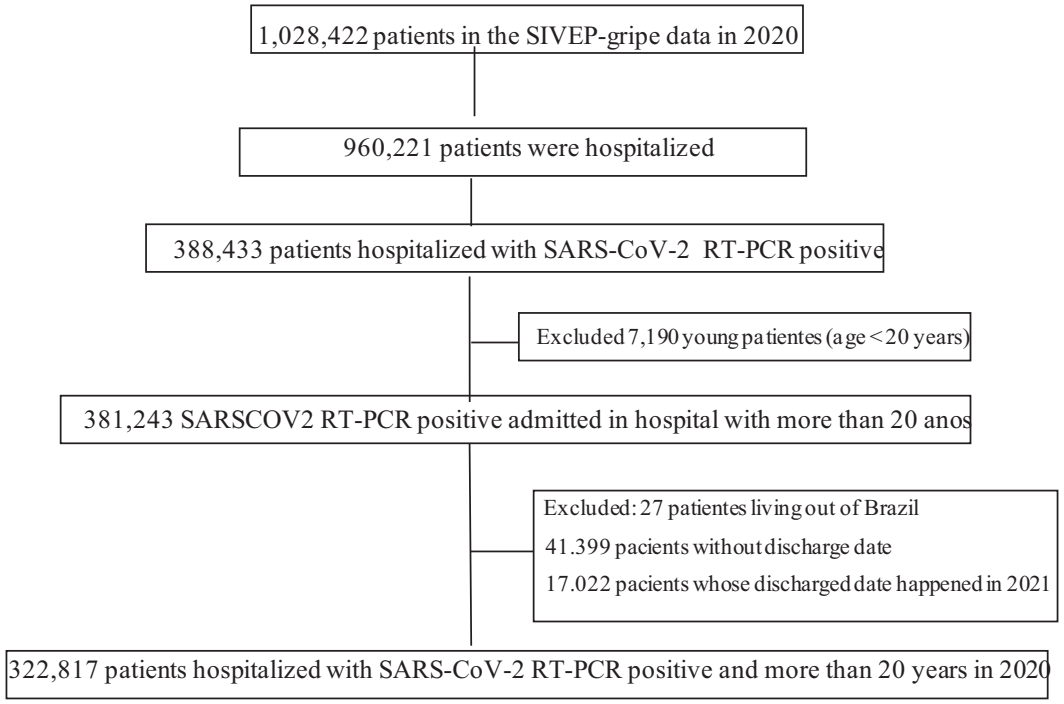

Figure 1. Flowchart of the SIVEP-Gripe data used in this study. RT-PCR indicates real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SIVEP-Gripe, Sistema de Informação de Vigilância Epidemiológica da Gripe.

were older, and who were admitted to the intensive care unit (ICU).[16] However, these studies did not evaluate the risk of mortality in COVID-19 patients with cancer. Therefore, this study was aimed at evaluating the prevalence of patients with cancer as well as the severity and risk factors of in-hospital mortality among COVID-19 patients and at analyzing mortality according to gender and topography.

MATERIALS AND METHODS

Study Design

This was a secondary data study of hospitalized adult patients with a diagnosis of COVID-19 in Brazil. The data were retrieved from the Influenza Epidemiological Surveillance Information System (Sistema de Informação de Vigilância Epidemiológica da Gripe [SIVEP-Gripe] in Portuguese). This system is used by the epidemiological surveillance of states and municipalities to insert the files of severe acute respiratory syndrome cases seen in hospitals and emergency care units (Unidades de Pronto Atendimento in Portuguese). Data were publicly available online at https://covid.saude.gov.br and were retrieved on January 17, 2021.

Patients were included in the study if they had COVID-19 confirmed by real-time polymerase chain reaction testing and were admitted between March 1 and December 31, 2020. Patients younger than 20 years, patients living outside Brazil, patients without discharge date data, and patients whose discharge date happened after December 31, 2020, were excluded from the analysis (Fig. 1).

The following demographic, epidemiological, and clinical variables were evaluated: age at diagnosis, sex, self-reported ethnicity/skin color (according to the Brazilian Institute of Geography and Statistics), self-reported level of education, main symptoms of COVID-19, and presence of comorbidities potentially associated with the severity of COVID-19 (with an emphasis on cancer topographies). In addition, data were collected upon ICU admission on the following: mortality, need for respiratory support (noninvasive vs invasive), time in the ICU, hospital length of stay, and hospital mortality.

Statistical Analysis

Data were analyzed with SPSS version 24.0. The analysis was performed with valid data only. A descriptive analysis of the study population was performed with mean and standard deviation measures for continuous variables and with absolute and relative frequency distributions for categorical variables. The Kolmogorov-Smirnov test was used to check the normal distribution of continuous variables.

TABLE 1. Demographic Characteristics of COVID-19 Patients With and Without Cancer in Brazil in 2020

Characteristic	All Patients (n = 322,816 [100%])	Cancer (n = 7406 [2.3%])	No Cancer (n = 315,410 [97.7%])	P[a]
Age (n = 322,816)				
Mean ± SD, y	61 ± 17	66 ± 16	61 ± 145	<.001
Median, y	62	67	62	
Age groups (n = 322,816), No. (%)				<.001
20-39 y	39,690 (12.3)	421 (5.7)	39,269 (12.5)	
40-49 y	45,010 (13.9)	627 (8.5)	44,383 (14.1)	
50-59 y	59,847 (18.5)	1155 (11.6)	58,692 (18.6)	
60-69 y	68,881 (21.3)	1969 (26.6)	66,852 (21.2)	
70-79 y	60,132 (18.6)	1905 (25.7)	58,227 (18.5)	
≥80 y	49,316 (15.3)	1328 (17.9)	47,988 (15.2)	
Sex (n = 322,774), No. (%)				<.001
Male	181,419 (56.2)	3896 (52.6)	177,523 (56.3)	
Female	141,355 (43.8)	3509 (47.4)	137,846 (43.7)	
Ethnicity/skin color (n = 245,117), No. (%)				<.001
White	134,759 (55)	3529 (62.2)	131,230 (54.8)	
Brown-skinned	90,891 (37.1)	1675 (29.5)	89,216 (37.3)	
Black	15,314 (6.2)	376 (6.6)	14,938 (6.2)	
Asian	3539 (1.4)	91 (1.6)	3448 (1.4)	
Indigenous	614 (0.3)	610 (0.3)	4 (0.1)	
Level of education (n = 115,730), No. (%)				<.001
Illiterate	6780 (5.9)	153 (5.6)	6627 (5.9)	
Up to high school	52,360 (45.3)	1458 (53)	50,902 (45.1)	
High school	37,056 (32)	715 (26)	36,341 (32.2)	
College or university	19,534 (16.9)	426 (15.5)	19,108 (16.9)	

Abbreviations: COVID-19, coronavirus disease 2019; SD, standard deviation.
[a]χ^2 test.

The *t* test was used to compare continuous variables, and the χ^2 test was performed with the objective of comparing the categorical data. Differences were considered significant when the *P* value was <.05. A logistic regression analysis was used to explore the association between the comorbidities, with an emphasis on cancer topographies, and the risk of death. The variables whose associations with outcomes in univariate analyses exhibited *P* values < .15 were sequentially tested in a multivariate model; we started with the variable most strongly associated with the risk of death and continued until no other variable reached significance.[17] Variables with $P < .05$ were maintained in the final model.

Ethics

Ethics committee approval was not required because only secondary data available on the internet were used in this study.

RESULTS

In total, 322,816 COVID-19 patients were identified; 56.2% were men, the mean age was 61 ± 17 years, and the most frequent skin color was white (55% of cases). In the total population studied, 2.3% of the patients had a history of cancer. Comparing COVID-19 patients with and without cancer showed that patients with cancer were older (median, 67 vs 62 years), and a majority of the patients with cancer were White (62.2% vs 54.8% of patients without cancer) with a level of education up to high school (53.0% vs 45.1% of patients without cancer; Table 1).

As for symptoms related to COVID-19, the most frequent were cough (79.7%), dyspnea (79.6%), and fever (71.6%). COVID-19 patients without cancer showed a higher frequency of most symptoms ($P < .001$). Most patients had chronic heart disease (66.5%) and diabetes (52.2%), and with the exception of pulmonary disease and immunosuppression, comorbidities were more frequently reported in noncancer patients ($P < .001$). Of all patients, 39.7% were admitted to the ICU, and 22.1% of the patients were subjected to invasive mechanical ventilation. Overall in-hospital mortality was 37%, and ICU mortality was 64%. COVID-19 patients with cancer had longer hospital stays than those without cancer (13.1 vs 11.5 days; $P < .001$). The overall in-hospital mortality rate was 37.0%, and it was higher among patients with cancer (60.5% vs 36.5%; $P < .001$; Table 2). COVID-19 patients with cancer more frequently needed admission to the ICU (45.3% vs 39.6%) and invasive ventilatory support (27.1% vs 21.9%) than patients with cancer ($P < .001$; Table 2). There were temporal trends of higher mortality, more frequent admissions to the ICU, and a greater need for invasive respiratory support in COVID-19

TABLE 2. Symptoms, Comorbidities, In-Hospital Mortality, Admissions to the ICU, and Respiratory Support Among COVID-19 Patients With and Without Cancer in Brazil in 2020

Characteristic	All Patients (n = 322,816 [100%]), No. (%)	Cancer (n = 7406 [2.3%]), No. (%)	No Cancer (n = 315,410 [97.7%]), No. (%)	P^a
Symptoms				
Cough (n = 289,197)	230,361 (79.7)	4398 (69.7)	225,963 (79.6)	<.001
Dyspnea (n = 289,120)	230,078 (79.6)	5094 (77.7)	224,984 (86)	<.001
Fever (n = 283,316)	202,929 (71.6)	3949 (63.2)	198,980 (71.8)	<.001
Oxygen saturation < 95% (n = 273,849)	193,997 (70.8)	4747 (73.8)	189,250 (70.8)	<.001
Respiratory distress (n = 268,673)	183,762 (68.4)	4053 (66.3)	179,709 (68.4)	<.001
Weakness (n = 125,913)	35,651 (28.3)	774 (29.7)	34,877 (28.3)	<.001
Odynophagia (n = 238,012)	54,384 (22.8)	773 (14)	53,651 (23)	<.001
Diarrhea (n = 236,197)	44,387 (18.8)	891 (16.8)	43,496 (18.8)	<.001
Loss of taste (n = 122,357)	17,487 (14.3)	201 (8.2)	17,286 (14.4)	<.001
Loss of smell (n = 122,756)	17,428 (14.2)	197 (8)	17,286 (14.3)	<.001
Vomit (n = 230,995)	24,932 (10.8)	676 (13)	24,256 (10.7)	<.001
Abdominal pain (n = 121,679)	8491 (7)	243 (9.7)	8248 (6.9)	<.001
Comorbidities				
Chronic heart disease (n = 179,251)	119,413 (66.5)	2405 (47.5)	116,738 (67)	<.001
Diabetes (n = 167,078)	87,201 (52.2)	1561 (33.1)	85,640 (52.7)	<.001
Obesity (n = 137,262)	20,992 (15.3)	257 (6.3)	20,735 (15.6)	<.001
Renal disease (n = 138,617)	14,916 (10.8)	460 (10.8)	14,456 (10.8)	.458
Neurological disease (n = 138,924)	14,340 (10.3)	320 (7.6)	14,020 (10.4)	<.001
Pulmonary disease (n = 138,481)	13,683 (9.9)	521 (12.3)	13,162 (9.8)	<.001
Immunosuppression (n = 136,393)	9569 (7)	1846 (39.6)	7723 (5.9)	<.001
Asthma (n = 136,605)	8962 (6.6)	129 (3.1)	8833 (6.7)	<.001
Liver disease (n = 134,674)	3161 (2.3)	146 (3.6)	3015 (2.3)	<.001
Hospitalization (n = 322,816)				
In-hospital mortality	119,545 (37)	4479 (60.5)	115,066 (36.5)	<.001
Length of hospital stay, mean, d	11.5	13.1	11.5	<.001
ICU admission and mortality				
Admission to ICU (n = 293,441)	116,640 (39.7)	3159 (45.3)	113,481 (39.6)	<.001
In-ICU mortality (n = 106,401)	68,052 (64)	2392 (57.1)	65,660 (64.2)	<.001
Length of ICU stay, mean, d	11.1	10.9	11.1	.526
Respiratory support (n = 281,050)				<.001
None	72,245 (22.3)	1480 (22.3)	70,765 (25.8)	
Noninvasive	146,806 (52.2)	3360 (50.6)	143,446 (52.3)	
Invasive	61,999 (22.1)	1802 (27.1)	60,197 (21.9)	

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit.
[a]χ^2 test.

patients with cancer in comparison with those without cancer ($P < .001$; Fig. 2).

When all patients were evaluated by different comorbidities, the percentual of death for COVID-19 patients was 25% and 43% without comorbidities and with at least 1 comorbidity, respectively. Different comorbidities were associated with different chances of death, with neurological disease, cancer, chronic renal disease, chronic hepatic disease, and chronic pulmonary disease being the 5 most lethal comorbidities reported in sequence in both sexes and when they were analyzed separately (Fig. 3).

An analysis of the adjusted risk of mortality of COVID-19 patients showed that patients with cancer had a 1.94 times greater risk of death (95% confidence interval [CI], 1.83-2.06; $P < .001$). When they were stratified by sex, a high risk of mortality in patients with cancer was also observed among men (adjusted odds ratio [aOR], 1.78; 95% CI, 1.64-1.94; $P < .001$) and among women (aOR, 2.02; 95% CI, 1.86-2.19; $P < .001$; Table 3).

When we considered the topography of cancer, after adjustments, patients with hematological cancer had a 2.85 times higher risk of death (95% CI, 2.41-3.38; $P < .001$), and those with solid tumors had a 1.83 times higher risk (95% CI, 1.72-1.95; $P < .001$; Table 4). A graphical representation of the aORs for the 10 most frequent cancer topographies in this study is shown in Figure 4.

DISCUSSION

In this study, data were analyzed from 322,816 hospitalized COVID-19 patients in Brazil during the year 2020, and it showed that cancer was one of the worst comorbidities related to death in COVID-19 patients in Brazil, even after adjustments for age, sex, and comorbidities.

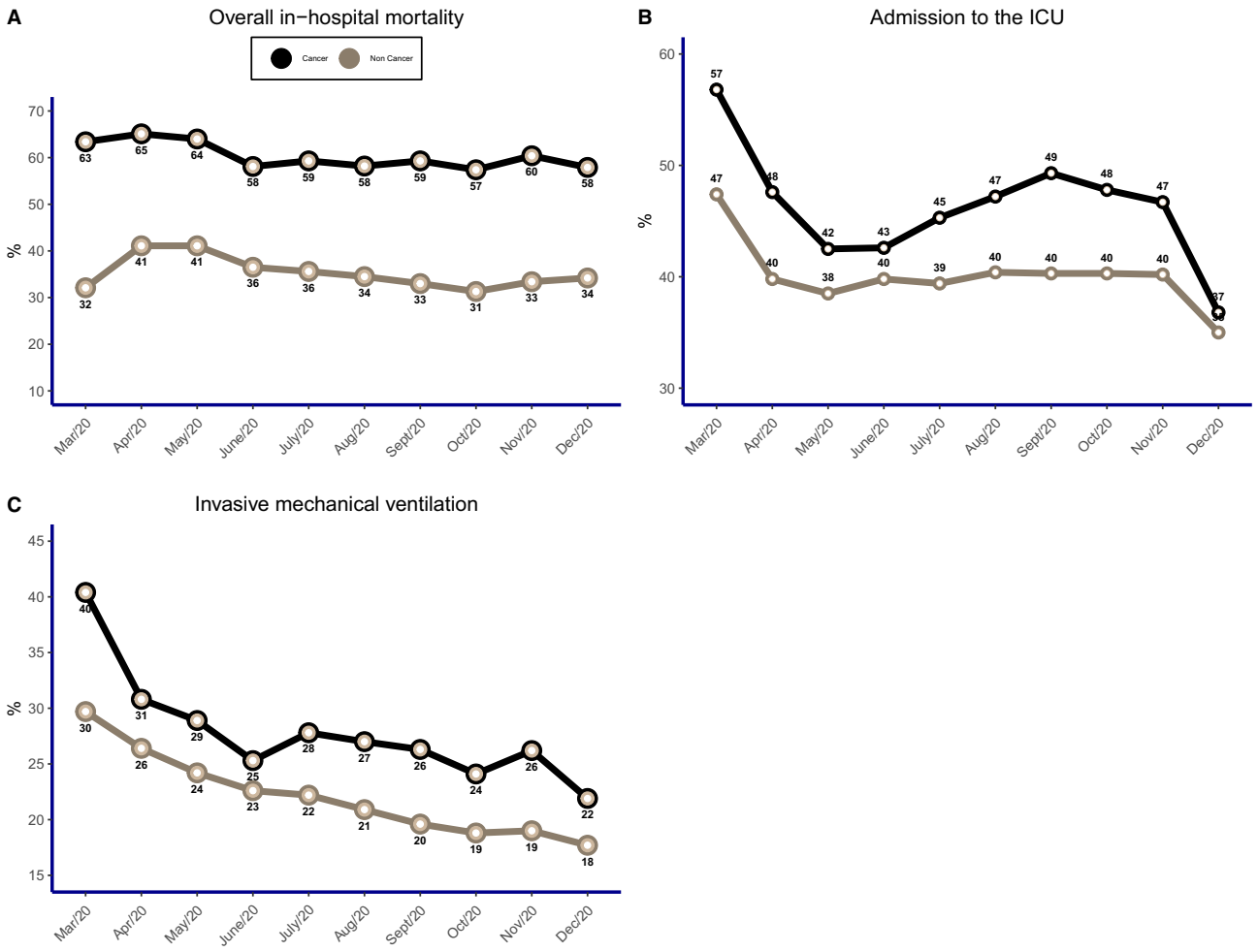

Figure 2. Percent distributions according to cancer patients versus noncancer patients: (A) overall in-hospital mortality ($P < .001$), (B) admission to the ICU ($P < .001$), and (C) invasive mechanical ventilation ($P < .001$). ICU indicates intensive care unit.

COVID-19 patients with cancer had greater disease severity, they were associated with being older, more often admitted to the ICU, received more invasive mechanical ventilation, and had higher mortality rates than noncancer patients during the entire evaluated period.

The frequency of COVID-19 patients with cancer has ranged from 0.8% to 10.6% of cases in different studies.[18-22] A meta-analysis showed a frequency of approximately 2% for cancer in COVID-19 patients, especially in large studies with more than 100 patients included.[13] Fifteen percent to 17.7% of COVID-19 patients with cancer needed ICU admission, and 10% to 19.3% required invasive mechanical ventilation.[4,8] A systematic review and meta-analysis showed that the need to be admitted to the ICU was more often reported in patients with cancer than those without cancer (3220 events; RR, 1.56; 95% CI, 1.31-1.87; $P < .0001$).[23] In this study, we identified 2.3% of the cases as being COVID-19 patients with cancer, and they had longer hospital stays, a higher frequency of ICU admissions (45%), and a greater need for mechanical ventilation support (27%), albeit with lower ICU mortality in comparison with those without cancer. Furthermore, the symptoms of COVID-19 patients could not be differentiated between patients with cancer and patients without cancer. The clinical diagnosis of COVID-19 is a challenge because it is often superimposed on the symptoms of neoplasia and/or treatment toxicity. In Latin America (including Brazil), the infrastructure of diagnosis, treatment, and support for patients with cancer is considered insufficient because of low funding and the heterogeneous distribution of resources and services[24]; this could explain why patients with cancer have had later health assistance.

Patients with cancer have higher mortality in comparison with COVID-19 patients without cancer. In

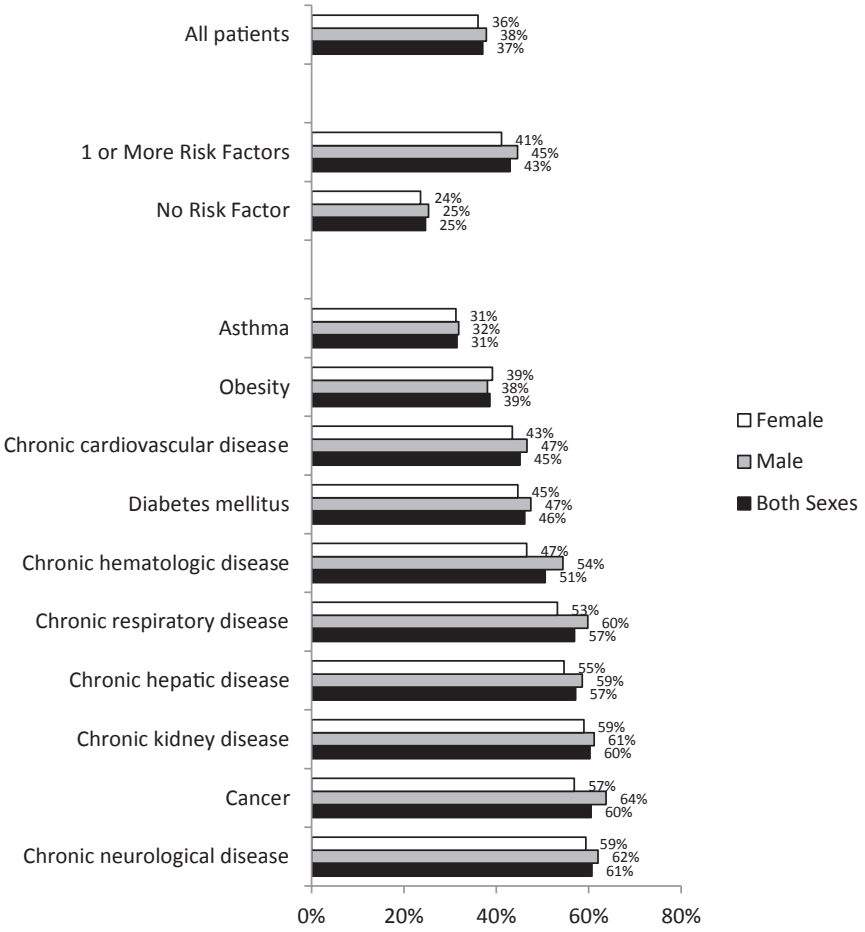

Figure 3. Percent distributions of the lethality of different comorbidities according to sex.

a previous study, the risk of death in the hospital for COVID-19 patients with cancer was higher because of older age, male sex, chronic renal disease, and obesity.[25] Cancer patients with COVID-19 also had an independent risk factor of mortality, with an almost 2-fold higher risk than COVID-19 patients without cancer, even after adjustments for age, gender, and different comorbidities.[26] In our analysis, female patients had a slightly higher risk of death than male patients after adjustments because breast cancer, reported in 15% of cases, was the most common topography identified.

COVID-19 patients with different tumor types have distinct vulnerabilities and mortalities. Hematological malignancies were associated with greater severity and mortality[8] in comparison with patients with solid tumors or COVID-19 patients without cancer,[27] but recent chemotherapy incurred an increased risk of death during COVID-19–associated hospital admissions.[28] In a Brazilian study, patients with lung or hematological cancer and patients under oncological treatment had a higher risk of death among patients with COVID-19.[14] Mortality due to COVID-19 in patients with cancer could be heterogeneous for different kinds of primary tumors, and individualized strategies for preventing or reducing the risk of mortality in COVID-19 patients with cancer are necessary.

Patients with cancer have more vulnerable clinical conditions, which are associated with greater severity and lethality due to COVID-19.[8] They are often older, immunosuppressed, and poorly nourished and have different comorbidities and adverse effects caused by oncological treatment.[5,7,8,14] Hematological malignancies, associated with greater susceptibility due to immune system impairment, have been associated with a poor prognosis for COVID-19 patients with cancer.[8,14,28] Oncological treatments have also been related to the risk of mortality due to COVID-19.[8,14] Although oncological patients have not been included in clinical trials that have evaluated

TABLE 3. Risk of Mortality for COVID-19 Patients in Brazil in 2020

Variable	Univariate Analysis	*P*	Multivariate Analysis	*P*
Cancer (both sexes)[a]				
Yes	2.66 (2.54-2.80)	<.001	1.94 (1.83-2.06)	<.001
No	1.0		1.0	
Cancer (male)[b]				
Yes	2.96 (2.77-3.16)	<.001	1.78 (1.64-1.94)	<.001
No	1.0		1.0	
Cancer (female)[c]				
Yes	2.39 (2.239-2.56)	<.001	2.02 (1.86-2.19)	<.001
No	1.0		1.0	

Abbreviation: COVID-19, coronavirus disease 2019.
[a]Adjusted by age, pulmonary disease, hematological disease, and cardiovascular disease.
[b]Adjusted by age, schooling, neurological disease, renal disease, pulmonary disease, hematological disease, and cardiovascular disease.
[c]Adjusted by neurological disease, pulmonary disease, hematological disease, and cardiovascular disease.

TABLE 4. Risk of Mortality for COVID-19 Patients With Different Types of Cancer in Brazil in 2020

Variable	Univariate Analysis	*P*	Multivariate Analysis	*P*
Cancer (both sexes)[a]				
Hematological	3.27 (2.86-2.80)	<.001	2.85 (2.41-3.38)	<.001
Solid tumors	2.59 (2.46-2.72)		1.83 (1.72-1.95)	
No	1.0		1.0	
Cancer (male)[b]				
Hematological	3.24 (2.70-3.90)	<.001	2.90 (2.30-3.70)	<.001
Other solid tumors	2,92 (2.72-3.14)		1.83 (1.57-1.86)	
No	1.0		1.0	
Cancer (female)[c]				
Hematological	3.32 (2.73-4.03)	<.001	2.67 (2.12-3.39)	<.001
Other solid tumors	2.29 (2.13-2.46)		1.87 (1.71-2.04)	
No	1.0		1.0	

Abbreviation: COVID-19, coronavirus disease 2019.
[a]Adjusted by age, pulmonary disease, hematological disease, and cardiovascular disease.
[b]Adjusted by age, schooling, neurological disease, renal disease, pulmonary disease, hematological disease, and cardiovascular disease.
[c]Adjusted by neurological disease, pulmonary disease, hematological disease, and cardiovascular disease.

different vaccines against COVID-19,[29-31] American and European oncological societies have recommended that patients with cancer be vaccinated when vaccines are available.[32,33] So, it would be desirable for oncological patients to have priority in different immunization programs because they are more susceptible to COVID-19 and other infectious diseases.

Besides that, there was a negative impact of the COVID-19 pandemic on screening, diagnosis, and treatment for patients with cancer in 2020.[34] There may have been progression of cancer or impaired survival if treatments were delayed. Oncological procedures were reduced or postponed during the pandemic.[35,36] Also, there were delays because patients were afraid of the pandemic, there were travel restrictions and quarantines, and they experienced worsening clinical conditions.[37] As a matter of fact, the COVID-19 pandemic affected oncologists' decision-making for cancer because they used less chemotherapy, immune checkpoint inhibitors, and steroids and recommended second- or third-line therapies, especially in metastatic staging.[38]

This study has some limitations. First, the SIVEP-Gripe national data do not include information about staging, clinical performance, or oncological treatment; these aspects are very important for determining the prognosis in patients with cancer. Second, the quality of the data on the original forms from which the data were obtained may be open to criticism. However, as all cases of suspected COVID-19 should have been notified in Brazil, we can expect that in-hospital cases were better informed because it was necessary to access a free real-time polymerase chain reaction swab test for each patient. Third, patient comorbidities were not defined by clear criteria, so we cannot be sure about levels of severity and treatment. However, this register is highly representative of the Brazilian population with COVID-19 as a whole, and its analysis could be very important for improving epidemiological knowledge of COVID-19 patients who have different conditions (ie, frequency and risk of death). This information could provide important support for better decision-making by governments, institutions, and/or health professionals during the COVID-19 pandemic.

This is the largest population-based study conducted in Brazil that has evaluated prevalence, temporal trends, morbidity, length of hospital stay, cancer topographies, and mortality risk among COVID-19 patients with and without cancer throughout the year 2020. Previous population-based studies in this country failed to determine these aspects involving COVID-19 patients with cancer, who must be considered a priority for receiving immunizations, including the vaccine against COVID-19, as well as diagnostic procedures and oncological modalities of treatment during the COVID-19 pandemic.

In conclusion, this Brazilian study showed that COVID-19 patients with cancer were older, had greater disease severity, stayed longer in the hospital, had a greater

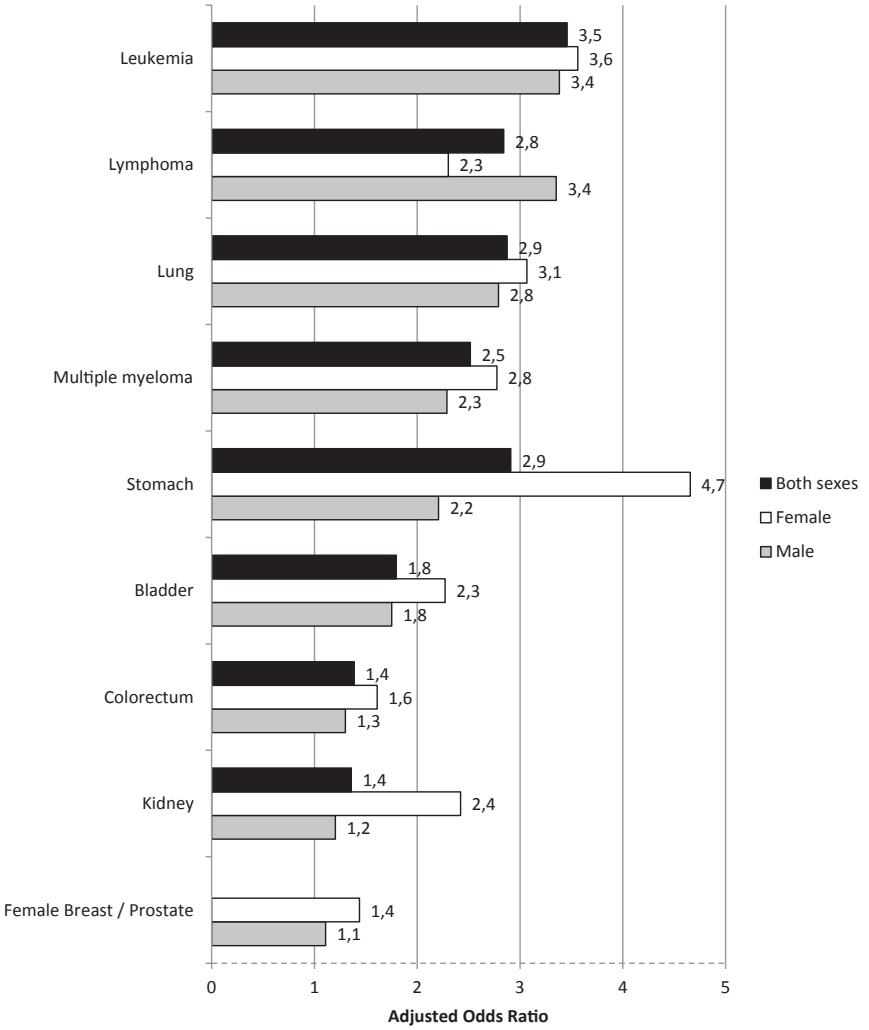

Figure 4. Adjusted odds ratios and 95% confidence intervals for mortality in patients with coronavirus disease 2019 according to the topography of cancer.

need for ICU admission, and had more need for invasive mechanic ventilation during their hospital stay beyond all oncological support in the year 2020. Furthermore, COVID-19 patients with cancer and hematological topographies had a higher risk of death comparing with those without cancer and those with solid tumors, respectively, even with adjustments for age, sex, and different comorbidities.

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CONFLICT OF INTEREST DISCLOSURES
The authors made no disclosures.

AUTHOR CONTRIBUTIONS
Guilherme Jorge Costa: Literature search, study design, data collection, data analysis, data interpretation, and writing. **Carla Rameri Alexandre Silva de Azevedo:** Literature search, data interpretation, and review and editing. **José Iran Costa Júnior:** Literature search, data interpretation, and review and editing. **Anke Bergmann:** Literature search, data analysis, data interpretation, and review and editing. **Luiz Claudio Santos Thuler:** Literature search, study design, data analysis, data interpretation, and review and editing. All the authors have participated directly, written the manuscript, approved the version to be published, and agreed to be accountable for all aspects of the work.

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