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Differences in mortality of cancer patients with COVID-19 in a Brazilian cancer center

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ABSTRACT

Introduction: To analyze COVID-19 mortality in cancer patients and associated factors such as age, sex, type of insurance, situation at COVID-19 diagnosis, and cancer histology during the pandemic at a cancer center in Brazil.

Methods: Cross-sectional study carried out from April 02, 2020 to August 31, 2020 at A.C. Camargo Cancer Center (ACCCC), in São Paulo, Brazil. Cases were extracted from the Hospital Cancer Registry. COVID-19 lethality rates by histology were calculated; multiple logistic regression was used to identify factors associated with COVID-19 mortality. The log-rank test was applied to compare the survival curves for each variable.

Results: Of the 411 patients analyzed, 51 (12.4%) died due to COVID-19. Death occurred at an average age of 63 years. The fatality rate was higher for lung (0.333) and hematological (0.213) cancers and was associated with age over 60 years. The greatest chances of death from COVID-19 were in cases of lung (odds ratio, OR, 4.05, 95% confidence interval, CI 1.33–12.34) and hematological (OR 2.17, 95% CI 0.96–4.90) cancers, and in patients currently undergoing cancer treatment (OR 2.77, 95% CI 1.25–6.13). There were no statistical differences in survival by sex, age group, type of insurance, situation at the diagnosis of COVID-19, and histology of cancer for COVID-19.

Conclusions: Mortality due to COVID-19 in cancer patients is heterogeneous. These findings reinforce the need for individualized strategies for the management of different types of cancer that reduce the risk of death from COVID-19.

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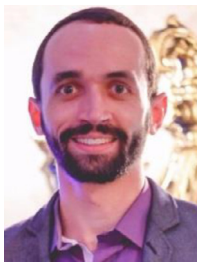

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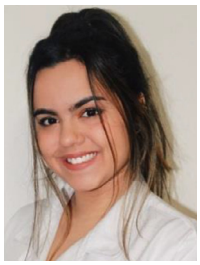

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Introduction

COVID-19 is a disease caused by a novel coronavirus, SARS-CoV-2, first reported in China in late 2019 [1]. Its rapid spread led the World Health Organization (WHO) to declare it a pandemic in March 2020 [2].

In Brazil, the first case was reported on February 26 and the first death on March 12, 2020, in São Paulo [3,4]. By May of 2020, Brazil was considered one of the epicenters of the global COVID-19 pandemic, while the state of São Paulo was considered the national epicenter, with the highest number of deaths [5].

Epidemiological and clinical evidence points to a greater risk of serious outcomes of COVID-19 in elderly patients, men, smokers, and patients with comorbidities such as hypertension, diabetes, obesity, and cancer [6-22] [See **Text Box** and Table 1]. Cancer patients are more vulnerable to complications and death when infected with SARS-CoV-2. This is due to a combination of factors including immunosuppressive therapies, age over 60, use of corticosteroids, presence of comorbidities, advanced metastatic cancer, and coexisting lung cancer. [23,24,25]. However, as mortality due to COVID-19 is different for each type of cancer, it is not accurate to classify all cancer patients as equally susceptible [6]. Some studies have shown higher mortality from COVID-19 in patients with lung and hematological cancers [6,7,8,9,13,14,16,17,21]; others have not [10,11].

In Brazil, few studies have evaluated COVID-19 mortality in cancer patients. An analysis carried out at the National Cancer Institute (INCA) from April 30, 2020 to May 26, 2020 identified a COVID-19 mortality rate of 33.1% in patients with a diagnosis of cancer [11]. In New York, the Montefiore Health System identified a 28% mortality rate [9], while at the Memorial Sloan Kettering Cancer Center mortality was reported to be 9% [12]. In France, the 15% death rate among cancer patients at Gustave Roussy was similar to that seen in the general population [13]. Therefore, the mortality of COVID-19 patients appears to differ between cancer treatment centers.

. TEXT BOX

- Patients with cancer have a higher risk of coronavirus disease 2019 (COVID-19) than noncancer patients – although all analyses confounded by older age of cancer patients and their attendant co-morbidities [7,11].
- Patients with a diagnosis of cancer appear to do worse [7,9,12,14,15,17,19,22].
- Different tumor types appear to confer differing susceptibility to SARS-CoV-2 infection and COVID-19 phenotypes [6].
- Advancing age is associated with worse outcomes [8,9,10,11,12,15,19], this study.
- Patient with a diagnosis of hematological malignancies seem to do worse [6,9,11,13,14,17,21], this study.
- Amongst solid tumors, lung cancer appears to do worse [7,11,13,14,16,27], this study.
- Amongst solid tumors, advanced cancer appears to do worse [7,11,13,19].
- Data suggests chemotherapy may worsen outcomes [6,8,13,15,17,18,20], this study, but not all studies agree [12].
- Data suggests surgery may worsen outcomes [7,15,17] but not all studies agree [10].
- Radiotherapy does not appear to worsen outcomes [7].

Table 1
Key references describing patients with a diagnosis of cancer and COVID-19.

Reference	Description	Results	Comments
Lee et al. [6]	• Compared adult patients with cancer enrolled in the UK Coronavirus Cancer Monitoring Project (UKCCMP) cohort between March 18 and May 8, 2020, with a parallel UK cancer control population from the UK Office for National Statistics not diagnosed with a COVID-19 infection (2017 data).	• 319/1044 (30·6%) patients in the UKCCMP cohort died; 295 (92·5%) due to COVID-19 • All-cause case-fatality rate in patients with a diagnosis of cancer after SARS-CoV-2 infection significantly associated with increasing age: 0.10 in patients 40–49 yr old and 0·48 in ≥ 80 yr • Diagnosis of leukemia, lymphoma, and myeloma associated with more severe COVID-19 trajectories than diagnosis of solid organ tumors (OR, 1.57, 95%CI 1.15-2.15; $P < .0043$). • Compared with rest of the UKCCMP cohort, patients with a diagnosis of leukemia had significantly increased case-fatality rate (OR, 2.25, 95%CI 1.13–4.57; $P = .023$)	• Patients with hematological malignancies who had recent chemotherapy had an increased risk of death during COVID-19-associated hospital admission (OR 2.09, 95% CI 1·09–4.08; $P = .028$). • Different tumor types appear to confer differing susceptibility to SARS-CoV-2 infection and COVID-19 phenotypes
Dai et al. [7]	• Multicenter study of 105 patients with cancer and 536 age-matched patients without a diagnosis of cancer with confirmed with COVID-19	• Patients with diagnoses of COVID-19 and cancer had higher risks in all severe outcomes • Patients with diagnoses of hematologic, lung, or metastatic stage IV cancer had the highest frequency of severe events • Compared with patients without cancer – Patients without metastatic cancer had similar frequencies of severe conditions – Patients with a diagnosis of cancer who underwent surgery had higher risks of having severe events – Patients receiving only radiotherapy for their cancer did not demonstrate significant differences in severe events	• Findings indicate that at least some patients with cancer appear more vulnerable to SARS-CoV-2 infection
Garassino et al. [8]	• 200 patients with COVID-19 and thoracic cancers from eight countries enrolled between March 26 and April 12, 2020 in the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry, a multicenter observational study, • Eligibility criteria were any thoracic cancer (NSCLC, SCLC, mesothelioma, thymic epithelial tumors, and other pulmonary neuroendocrine neoplasms) and a diagnosis of COVID-19	• Median age = 68.0 yr (61.8–75.0) • 142/196 (72%) with ECOG PS 0-1 • 147/199 (74%) on therapy at the time of COVID-19 diagnosis • 112/197 (57%) on first-line treatment • 152/200 (76%) hospitalized • 66/200 (33%) died. • 13/134 (10%) admitted to ICU; remaining 121 hospitalized, but not admitted to ICU • Risk factors for death [univariable analysis]: – ≥65 yr (OR, 1.88, 95%CI, 1.00–3.62) – Current or former smoker (OR, 4.24, 95%CI, 1.70–12.95) – Receiving treatment with chemotherapy alone (OR, 2.54, 1.09–6.11) – Presence of any comorbidities (OR, 2.65, 95%CI, 1.09-7.46) were associated with increased risk of death.	• Data suggest high mortality and low admission to intensive care in patients with thoracic cancer • Access to intensive care should be discussed in a multidisciplinary setting based on cancer specific mortality and patients' preference.
Mehta et al. [9]	• 218 patients with a diagnosis of cancer and COVID-19 between March 18, 2020, to April 8, 2020,	• 61/218 (28%) patients with cancer died from COVID-19 • CFR for hematologic malignancies = 20/54 (37%) • CFR for solid malignancies = 41/164 (25%) • CFR for lung cancer = 6/11 (55%) • In multivariate analysis increased mortality was significantly associated with – Older age – Multiple comorbidities – Need for ICU support – Elevated levels of D-dimer – Elevated levels of lactate dehydrogenase – Elevated levels of lactate • Age-adjusted CFRs in patients with cancer compared with noncancer patients found a significant increase in CFR for patients with cancer.	• Data suggest need for proactive strategies to reduce infection and improve early identification in vulnerable cancer patient population

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Table 1 (*continued*)

Reference	Description	Results	Comments
Kuderer et al. [10]	• De-identified data on 928/1035 records of patients with active or previous malignancy, ≥18 yr old, with confirmed SARS-CoV-2 infection from the USA, Canada, and Spain from the COVID-19 and Cancer Consortium (CCC19) database for whom baseline data were added between March 17 and April 16, 2020. • Note: This study is registered with ClinicalTrials.gov, NCT04354701 and is ongoing	• Median age = 66 yr (IQR 57–76) • 279/928 (30%) ≥75 yr old • At analysis on May 7, 2020, 121/928 (13%) had died • Independent factors associated with increased 30-day mortality: – Increased age (per 10 yr; partially adjusted OR 1.84, 95%CI 1.53–2.21) – Male sex (OR, 1.63, 95%CI, 1.07–2.48) – Smoking status (former smoker versus never smoked: OR, 1.60, 95%CI, 1.03–2.47) – Number of comorbidities (two vs none: OR, 4·50, 95%CI, 1.33–15.28) – ECOG PS ≥ 2 (2 vs 0 or 1: OR, 3.89, 95%CI, 2.11–7.18) – Active cancer (progressing vs remission: OR, 5.20, 95%CI, 2.77–9.77) • Race and ethnicity, obesity status, cancer type, type of anticancer therapy, and recent surgery were not associated with mortality.	• Among patients with cancer and COVID-19, 30-day all-cause mortality was high and associated with general risk factors and risk factors unique to patients with cancer.
Melo et al. [11]	• 181 patients with COVID-19 confirmed by RT-PCR identified in a retrospective search of the electronic medical records of cancer inpatients admitted to the Brazilian National Cancer Institute from April 30, 2020 to May 26, 2020 patients	• Mean age = 55.3 yr (SD ± 21.1) • Comorbidities in 110/181 (60.8%) • Metastatic disease accounted for 90/181 (49.7%) • Most common complications: – Respiratory failure 70/181 (38.7%) – Septic shock 40/81 (22.1%) – Acute kidney injury (33/181 (18.2%) – 60/181 (33.1%) died due to COVID-19 complications • CFR solid tumors = 52/138 (37.7%) • CFR hematological malignancies = 8/34 (23.5%) • COVID-19-specific mortality according to univariate analysis significantly associated with: – Age ≥75 yr (P = .002) – Metastatic cancer (P <.001) – Two or more sites of metastases (P < .001) – Presence of lung metastases (P < .001) – Presence of bone metastases (P = .001) – Noncurative treatment or best supportive care intent (P < .001) – Higher C-reactive protein levels (P = .002) – Admission due to COVID-19 (P = .009) – Antibiotics use (P = .02) • COVID-19-specific mortality according to multivariate analysis significantly associated with: – Cases with admission due to symptoms of COVID-19 (P = .027) – Two or more metastatic sites (P < .001)	• The rates of complications and COVID-19-specific death were significantly high in cancer patients
Robilotti et al. [12]	• Patient with a diagnosis of cancer and COVID-19 followed at Memorial Sloan Kettering Cancer Center	• 40% out of 423 patients with cancer were hospitalized for COVID-19 illness • 20% developed severe respiratory illness • 9% required mechanical ventilation • 9% died • Factor predictive of hospitalization and severe disease on multivariate analysis: – Age ≥ 65 yr – Treatment with ICI within 90 d • Factors not predictive of hospitalization and severe disease on multivariate analysis: – Receipt of chemotherapy within 30 d – Major surgery	• COVID-19 illness is associated with higher rates of hospitalization and severe outcomes in patients with cancer. • But risk factors may not be uniform. A many patient receiving ICI have lung cancer and its associated predisposing factors, the association between ICI and COVID-19 outcomes will need interrogation in tumor-specific cohorts.

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Table 1 (*continued*)

Reference	Description	Results	Comments
Barlesi et al. [13]	• 137 patients with cancer infected with SARS-CoV-2 treated at Institut de Cancérologie Gustave Roussy from March 14 to April 15, 2020. • Median follow-up time 13 d	• 119/137 solid tumors • 60% had advanced disease; 40% in remission or being treated for localized disease • >20% asymptomatic for COVID-19 • ~25% exhibited clinical worsening • 11% admitted to the ICU • ~15% death related to COVID-19 • Predictors of clinical worsening – ECOG PS ≥1 – Diagnosis of a hematological cancer – Having received chemotherapy within the last 3 mo. • Among patients treated with chemotherapy, those with metastatic disease had an increased risk of death; those with localized disease did not	• 14.6% mortality rate of patients with cancer and COVID-19 at Gustave Roussy was comparable to estimated 18.3% mortality rates from COVID-19 in the Paris area and 17.9% in France overall at the time of the study.
Venkatesulu et al. [14]	• Systematic search of PubMed/MEDLINE, Embase, Cochrane Central, Google Scholar, and MedRxiv for studies on cancer patients with COVID-19 • Meta-analysis of 181,323 patients from 26 studies involving 23,736 cancer patients	• Cancer patients with COVID-19 had higher likelihood of death (OR 2.54), largely driven by mortality among patients in China. • Cancer patients more likely to be intubated, although ICU admission rates not statistically significant • Mortality highest in hematological malignancies (OR 2.43) followed by lung cancer (OR 1.8) • No association between receipt of a particular type of oncologic therapy and mortality	• Cancer patients with COVID-19 disease are at increased risk of mortality and morbidity
Liang et al. [15]	• A prospective cohort to monitor COVID-19 cases throughout China. As of the data cutoff on Jan 31, 2020, 2007 cases from 575 hospitals in 31 provincial administrative regions. • 18/1590 (1%; 95%CI 0.61–1.65) had a history of cancer	• Patients with cancer had higher risk of severe events compared with patients without cancer (7/18 [39%] vs 124/1572 [8%]; Fisher's exact $P = .0003$) • Patients who underwent chemotherapy or surgery in the previous month had a numerically higher risk (3/4 [75%] of clinically severe events than did those not receiving chemotherapy or surgery (6/14 [43%] • Among patients with cancer, older age only risk factor for severe events (OR 1·43, 95% CI 0.97–2.12; $P = .072$). • Patients with lung cancer (1/5 [20%]) did not have higher probability of severe events compared with patients with other cancers of 8/13 [62%]; $P = .294$). • Patients with cancer deteriorated more rapidly than those without cancer (median time to severe events 13 d [IQR 6–15] vs 43 d [20–not reached]; $P < .0001$; hazard ratio 3·56, 95% CI 1.65–7.69, after adjusting for age).	• Found that patients with cancer might have a higher risk of COVID-19 than individuals without cancer • Patients with cancer had poorer outcomes from COVID-19.
Luo et al. [16]	• 102 consecutive patients with lung cancer and confirmed diagnosis of COVID-19 at a single center from 12 March 2020 to 6 May 2020	• COVID-19 severe in patients with lung cancer (62% hospitalized, 25% died); although severe, COVID-19 accounted for only 11% of lung cancer deaths during the pandemic • Determinants of COVID-19 severity largely patient-specific features, including: – Smoking status [OR for severe COVID-19 = 2.9, 95%CI 1.07–9.44 comparing the median (23.5 pack-yr) to never-smoker – Chronic obstructive pulmonary disease (OR, 3.87, 95%CI, 1.35–9.68) • Cancer-specific features that did not impact severity: – Prior thoracic surgery/radiation – Recent systemic therapies • Most patients recovered from COVID-19, including 25% patients initially requiring intubation	• COVID-19 associated with high burden of severity in patients with lung cancer. • Patient-specific features, rather than cancer-specific features or treatments, greatest determinants of severity.

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Table 1 (*continued*)

Reference	Description	Results	Comments
Jee et al. [17]	• Clinical characteristics and outcomes of 309 patients with cancer and concurrent COVID-19 treated at Memorial Sloan Kettering Cancer Center until March 31, 2020 and observed for clinical end points until April 13, 2020.	• Associations consistent in a multivariable model and in multiple sensitivity analyses: – Cytotoxic chemotherapy administration with a severe or critical COVID-19 event (HR, 1.10; 95%CI, 0.73–1.60). – Hematologic malignancy with increased COVID-19 severity (HR, 1.90; 95%CI, 1.30–2.80) – Lung cancer with higher rates of severe or critical COVID-19 events (HR, 2.0; 95%CI, 1.20–3.30). – Lymphopenia at COVID-19 diagnosis a with higher rates of severe or critical illness (HR, 2.10; 95%CI, 1.50–3.10). – Baseline neutropenia 14–90 d before COVID-19 diagnosis with worse outcomes (HR, 4.20; 95%CI, 1.70–11.00). • Rate of adverse events lower in a time-matched population of patients with cancer without COVID-19	• Recent cytotoxic chemotherapy treatment was not associated with adverse COVID-19 outcomes • Patients with active hematologic or lung malignancies, peri-COVID-19 lymphopenia, or baseline neutropenia had worse COVID-19 outcomes.
Yekedüz et al. [18]	• 16 studies included in a meta-analysis drawn from a MEDLINE database searched on September 01, 2020 with primary endpoints of severe disease and death in cancer patients treated within the last 30 d before COVID-19 diagnosis	• Chemotherapy within 30 d before COVID-19 diagnosis increased risk of death in cancer patients after adjusting for confounding variables (OR, 1.85; 95%CI, 1.26–2.71); but not risk of ever COVID disease • Targeted therapies, immunotherapy, surgery and radiotherapy did not increase the severe disease and death risk in cancer patients with COVID-19	• Chemotherapy increased risk of death from COVID-19 in cancer patients, • There was no safety concern for immunotherapy, targeted therapies, surgery and radiotherapy.
Elkrief et al. [19]	• 252 patients (N = 249 adult and N = 3 pediatric) patients with cancer and diagnosis of COVID-19 prospectively identified between March 3 and May 23, 2020 in the provinces of Quebec and British Columbia in Canada. • 106/252 (42.1%) received active anticancer treatment in the 3 mo before COVID-19 diagnosis	• During a median follow-up of 25 d, 33/252 (13.1%) required admission to the ICU, and 71/252 (28.2%) died • 47/252 (19.1%) had hospital-acquired COVID-19 • Median OS shorter with hospital-acquired infection than that in a contemporary community-acquired population (27 d vs unreached (HR, 2.3, 95%CI: 1.2–4.4, $P = .0006$. • Factors associated with death in a multivariate analysis: – Hospital-acquired COVID-19 – Older age – Low ECOG PS – Advanced stage of cancer	• Important to treat patients with cancer in COVID-free units. • Validated age and advanced cancer as negative predictive factors for COVID-19 severity in patients with cancer.
Zhang et al. [20]	• Multicenter retrospective study to investigate clinical manifestations and outcomes of patients with cancer diagnosed with COVID-19. • 107 patients with a diagnosis of cancer treated at 5 hospitals in Wuhan City, China, between January 5 and March 18, 2020.	• 37/107 (34.6%) receiving active anticancer treatment when diagnosed with COVID-19; 70/107 (65.4%) on follow-up. • 56/107 (52.3%) developed severe COVID-19 • Comparison of outcomes in those receiving and not receiving treatment: – Rate of severe COVID-19 higher in those receiving anticancer treatment (64.9% vs 45.7) – Inferior OS in those receiving anticancer treatment (HR, 3.365; 95%CI, 1.455–7.782 [$P = .005$]) • Detrimental effect of anticancer treatment on OS independent of exposure to systemic therapy (CFR 33.3% [systemic therapy] vs 43.8% [nonsystemic therapy]	• >50.0% of infected patients with cancer are susceptible to severe COVID-19 • Risk aggravated by simultaneous anticancer treatment and portends for a worse survival
Mato et al. [21]	• 198 CLL patients diagnosed with symptomatic COVID-19 across 43 international centers • 90% admitted to hospital	• Median age at COVID-19 diagnosis 70.5 yr • 90/198 (45%) were receiving active CLL therapy most commonly Bruton tyrosine kinase inhibitors (n = 68/90 [76%) • CFR 33% at median follow-up of 16 d • Comparing those under “watch-and-wait” and those under treatment: • Rates of admission 89% versus. 90% • Intensive care unit admission (35% vs 36%) • Intubation (33% vs 25%) • Mortality (37% vs 32%) • CLL-directed treatment with BTKi's at COVID-19 diagnosis did not impact survival (CFR 34% vs 35%), though the BTKi was held during the COVID-19 course for most patients	• CLL patients admitted with COVID-19, regardless of disease phase or treatment status, are at high risk of death

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Table 1 (*continued*)

Reference	Description	Results	Comments
Saini et al. [22]	• Systematic review and pooled analysis to provide estimates of the mortality rate among patients with both cancer and COVID-19. • Systematic literature search up to July 16, 2020 identified 52 studies in peer-reviewed publications, preprints and conference proceedings • Primary endpoint = CFR, defined as the rate of death among patients with cancer and COVID-19.	• 18,650 patients with both COVID-19 and cancer selected for the pooled analysis • 4243 deaths were recorded • Probability of death 25.6% (95%CI: 22.0%-29.5%; $I^2 = 8.9\%$)	• Patients with cancer who develop COVID-19 have high probability of mortality

CFR = case fatality rate; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; ICIs = immune checkpoint inhibitors; NCLC = nonsmall cell lung cancer; OR = odds ratio; SCLC = small cell lung cancer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

The A.C. Camargo Cancer Center (ACCCC) is a collaborative private-public oncology treatment center in the state of São Paulo, with treatment, teaching, and research units. Having been in operation for over 60 years, it is the primary oncologic reference in South America and attends an average of 8,000 new cases of cancer annually [26]. An ACCCC crisis committee was created on March 13, 2020 to implement a safe flow for coping with COVID-19, with the objective of treating patients and ensuring the safety of the professionals involved [27].

Therefore, analyzing COVID-19 mortality in cancer patients, identifying risk topographies, the situation at COVID-19 diagnosis, and factors such as age and sex in patients treated at a cancer center, can outline the profile of Brazilian patients in one of the largest treatment centers in the country and thus form health policies adapted to the Brazilian reality.

Methods

This is a retrospective cross-sectional study that analyzed mortality, age, sex, type of insurance, situation at the diagnosis of COVID-19, and histology of COVID-19 positive cancer patients. The period of analysis was from April 2 to August 31, 2020. The cases were extracted from the ACCCC Hospital Cancer Registry. The ACCCC is a private hospital, considered a tertiary referral center for cancer that maintains a partnership contract with both public and private health systems.

The variables analyzed were sex, categorized age (<60 years and ≥60 years), type of insurance (public or private), situation at diagnosis of COVID-19 (in follow-up, in treatment, or palliative), and cancer histology. Histology was classified using the International Classification of Diseases for Oncology, Third Edition (ICD-O3) codes as follows: hematological (C42, C77), breast (C50), digestive organs (C15-C17, C22-C26), lung (C34), colorectal (C18-C21), prostate (C61), urinary tract (C64-C68), organs respiratory and intrathoracic, except lung (C30-C39), female genitals (C51-C58), soft tissue (C49), lip, oral cavity and pharynx (C00-C14), and central nervous system (CNS) (C69-C72).

According to the WHO a death from COVID-19 is defined for surveillance purposes as a death resulting from a clinically compatible disease, in a confirmed case of COVID-19 by RT-PCR, unless there is a clear alternative cause of death that cannot be associated with COVID-19 [28]. This was the COVID-19 mortality criterion defined for the cases described here.

Statistical analysis

Absolute and relative frequencies were calculated for each variable. Categorical variables were compared using the chi-squared test, using a significance level of 5%. The mortality rate for COVID-19 was calculated for each cancer histology by dividing the number of COVID-19 deaths by the total number of cases. Lethality graphics by age group were made using Microsoft Excel.

Survival rates were calculated considering the dates of diagnosis and death by COVID-19. Survival analyses at 10, 20, and 30 days were applied to the following variables: sex, age group, type of insurance, situation at the diagnosis of COVID-19, and cancer histology. The log-rank test was performed to compare the survival curves for each variable, using a significance level of 0.05.

To estimate the odds ratio (OR) and 95% confidence interval by histology (hematological and lung) and situation at the diagnosis of COVID-19, adjusted for potential confounding factors age and sex, multiple logistic regression was performed. Solid tumors were used as reference, and a P-value <0.05 was defined as significant. The type of insurance variable did not enter the multiple analysis because it presented a value of $P > 0.20$ in the univariate analysis. Analyses were performed using STATA 15 (College Station, Texas, 2017) and Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp., Armonk, NY, USA).

Ethical approval

This study was approved by the Research Ethics Committee of the Antônio Prudente Foundation, A. C. Camargo Cancer Center, reference number 2462/17.

Results

In the studied period, 411 patients were diagnosed with COVID-19, 51 of whom died (12.4%), and 16 of whom were excluded from analysis because they presented nonmelanoma skin cancer. The average age of patients with COVID-19 was 56.9 years; 52.3% (215/411) were aged <60 years, 56.9% (234/411) were female, 68% (281/411) were attended by the private health system, and 64.7% (266/411) were undergoing cancer treatment at the time of COVID-19 diagnosis.

The demographic and clinical data of patients who died from COVID-19 were compared with those who survived. It was observed that the majority of patients were female in both groups 52.9% (27) and 57.5% (207), respectively. Of the patients who died, 66.7% (34) were ≥60 years old, mean age 63 years, while in the surviving group 55.0% (198) were <60 years old with a mean age of 56 years. In both groups, the majority of patients were covered by private health insurance 64.7% (33) and 68.9% (248), and 74.5% (38), and 63.3% (228) were currently undergoing cancer treatment. Significant differences were observed between deaths and survivors for age group, histology, and treatment situation (Table 2).

The fatality rate in cancer patients after COVID-19 infection was highest among patients with lung cancer (0.333) and hematological cancers (0.213) (Table 3), and in the 70–79 age group (Fig. 1).

Table 2
Sociodemographic and clinical data of the A.C. Camargo Cancer Center COVID-19 cohort, from April to August, 2020, São Paulo – SP, Brazil.

	Died from COVID-19 (n = 51)	Survived COVID-19 (n = 360)	P[a]
Sex			
Female	27 (52.9%)	207 (57.5%)	.538
Male	24 (47.1%)	153 (42.5%)	
Age group			
Average (± SD)	63.0 (±13.0)	56.0 (±15.1)	.004
<60	17 (33.3%)	198 (55.0%)	
≥60	34 (66.7%)	162 (45.0%)	
Histology (ICD-O3)			
Hematological (C42, C77)	10 (19.6%)	37 (10.3%)	.032
Breast (C50)	8 (15.7%)	85 (23.6%)	
Digestive organs (C15-C17, C22-C26)	8 (15.7%)	32 (8.9%)	
Lung (C34)	6 (11.8%)	12 (3.3%)	
Colorectal (C18-C21)	4 (7.8%)	48 (13.3%)	
Prostate (C61)	4 (7.8%)	36 (10.0%)	
Urinary tract (C64-C68)	4 (7.8%)	23 (6.4%)	
Respiratory and intrathoracic organs, not lung (C30-C39)	2 (3.9%)	2 (0.6%)	
Female genital organs (C51-C58)	2 (3.9%)	24 (6.7%)	
Soft tissues (C49)	1 (1.9%)	11 (3.1%)	
Lip, oral cavity, and pharynx (C00-C14)	1 (1.9%)	18 (5.0%)	
SNC (C69-C72)	1 (1.9%)	5 (1.4%)	
Bone and articular cartilage (C40-C41)	-	2 (0.6%)	
Male genital organs (C60-C63)	-	9 (2.5%)	
Endocrine glands (C73-C75)	-	16 (4.4%)	
Type of insurance			
Private	33 (64.7%)	248 (68.9%)	.548
Public	18 (35.3%)	112 (31.1%)	
Situation at diagnosis of COVID-19			
In follow-up	9 (17.7%)	129 (35.8%)	<.001
In treatment	38 (74.5%)	228 (63.3%)	
Palliative	4 (7.8%)	3 (0.8%)	

[a] Pearson Chi-squared test.

Table 3
COVID-19 case-fatality rate by cancer histology (ICD-O3) at the A.C. Camargo Cancer Center, from April to August, 2020, São Paulo – SP, Brazil.

Histology (ICD-O3)	Deaths	Total	Case–fatality rate
Hematological (C42, C77)	10	47	**0.213**
Breast (C50)	8	93	0.086
Digestive organs (C15-C17, C22-C26)	8	40	0.200
Lung (C34)	6	18	**0.333**
Colorectal (C18-C21)	4	52	0.077
Prostate (C61)	4	40	0.100
Urinary tract (C64-C68)	4	27	0.148
Respiratory and intrathoracic Organs, not lung (C30-C39)	2	4	0.500
Female genital organs (C51-C58)	2	26	0.077
Soft tissues (C49)	1	12	0.083
Lip, oral cavity, and pharynx (C00-C14)	1	19	0.053
SNC (C69-C72)	1	6	0.167

*COVID-19 topographies without deaths were excluded from the analysis.

In univariate analysis, a greater chance of death from COVID-19 was observed in patients over 60 years of age (OR 2.44 [1.31; 4.53]), those undergoing cancer treatment (OR 2.38 [1.11; 5.09]) or in palliative care (OR 19.01 [3.69; 98.75]), and in those with lung cancer (OR 4.44 [1.56; 12.57]), or hematological malignancies (OR 2.40 [1.09; 5.24]). In the multiple analysis, a greater chance of death from COVID-19 was observed in patients over 60 years of age (OR 2.26 [1.18; 4.35]), in cancer treatment (OR 2.77 [1.25; 6.13]) and in palliative care (OR 17.66 [3.13; 99.59]), with lung cancer (OR 4.05 [1.33; 12.34]) and hematological malignancies (OR 2.17 [0.96; 4.90]). Sex and type of treatment were not associated with COVID-19 mortality in either analysis (Table 4).

The highest overall survival in cancer patients with COVID-19 were in women, other solid tumors, and in those undergoing follow-up. However, no significant differences were observed in survival by sex, age group, tumor site, type of insurance, and situation at diagnosis of COVID-19 (Supplemental Table 1; Supplemental Figure 1).

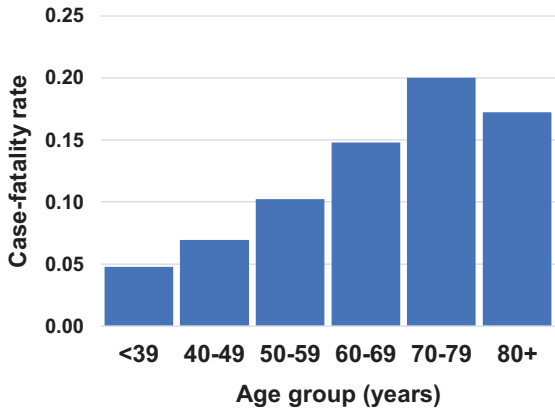

Fig. 1. Case-fatality rate by COVID-19 in cancer patients by age group, in the A.C. Camargo Cancer Center from April to August, 2020, São Paulo – SP, Brazil.

Discussion

In the present study, mortality due to COVID-19 in cancer patients was most associated with lung and hematological cancers, and particularly for patients undergoing cancer treatment in the age group above 60 years. There were no differences in survival by sex, age group, histology, type of insurance, or situation at diagnosis of COVID-19. A systematic review with meta-analysis showed that cancer patients affected by COVID-19 have a higher chance of death (OR 2.54 [1.47; 4.42]) and are 10 years older, than the general population. The most frequent neoplasms observed in that study were hematological (34.3%), breast (29%), and lung (27.3%) [14].

Other studies have also demonstrated higher mortality from COVID-19 in cancer patients, with reported mortality ranging from 9% to 50% [7,9,12,14,15,17,19,22]. The results of the present study fall on the lower end of this spectrum, with a 12.4% mortality. The highest prevalence of mortality was observed in studies of Liang et al. [15]. who analyzed 18 patients (50% died), Garassino et al. [8] 200 (33,3%), Melo et al. [11] 181 (33.1%), Mehta et al. [9] 218 (28%), and Luo et al. [16] 69 (24%). Whereas, the lowest prevalence of mortality was found in studies of Barlesi et al. [13] 137 (15%), Dai et al. [7] 154 (11,4%), and Robilotti et al. [12] 423 (9%), as well, in this study in which 411 patients were analyzed and 12.4% (51) died due to COVID-19 (Table 5). Given the diversity of the population studied one cannot and should not infer any signifcance to these differences.

In this study we reported that patients with hematological cancers had 2.17 times the chance of death from COVID-19, which parralleles results of a UK study (OR 1.57) [6]; as well as those of a systematic review (OR 2.39) [14]. However, in the USA, Canada and Spain (OR 1.40) [10]; as in a Brazilian study (OR 1.0) [11] there was no increase in mortality in COVID-19 patients with hematological cancers. It is thought that patients with hematological cancers are more vulnerable to severe outcomes due to immunosuppression caused by intense treatment with myelosuppressants or in the cae of chronic lymphocytic leukemia, their intrinsic immunosuppression [21]. Lymphopenia and basal neutropenia are additional factors that can increase the risk of worse outcomes and are frequently observed in individuals with hematological cancers [6,17,29].

Table 4
Univariate and adjusted analysis of COVID-19 mortality, in the A.C. Camargo Cancer Center, from April to August, 2020, São Paulo – SP, Brazil.

Variables	OR[a] univariate (95% CI)	*P*	OR[a] adjusted (95% CI)	*P*
Histology (ICD-O3)				
Other Solid Tumors	1		1	
Hematological (C42, C77)	**2.40 (1.09–5.24)**	**.029**	**2.17 (0.96–4.90)**	**.062**
Lung (C34)	**4.44 (1.56–12.57)**	**.005**	**4.05 (1.33–12.34)**	**.014**
Sex				
Female	1		1	
Male	0.83 (0.46–1.49)	.539	0.88 (0.47–1.66)	.709
Age group				
<60	**1**		1	
≥60	**2.44 (1.31–4.53)**	**.005**	**2.26 (1.18–4.35)**	**.014**
Type of insurance				
Public	1		-	-
Private	0.83 (0.45–1.53)	.548	-	-
Situation at diagnosis of COVID-19				
In follow-up	1		-	-
In treatment	**2.38 (1.11–5.09)**	**.024**	**2.77 (1.25–6.13)**	**.011**
Palliative	**19.01 (3.69–98.75)**	**.001**	**17.66 (3.13–99.59)**	**.001**

Other Solid Tumors = (C50, C15-C17, C22-C26, C18-C21, C61, C64-C68, C30-C39, C51-C58, C49, C00-C14, C69-C72).
The values in bold are significant.
[a] OR = Odds Ratio. Multivariable corrections were made for patient age and sex.

Table 5
Case-fatality by COVID-19 in cancer patients in selected studies.

COVID-19/Cancer	N patients (% death)
Liang et al. [15]	18 (50%)
Garassino et al. [8]	200 (33,3%)
Melo et al. [11]	181 (33,1%)
Mehta et al. [9]	218 (28%)
Luo et al. [16]	69 (24%)
Barlesi et al. [13]	137 (15%)
Fernandes et al. (2021)	**411 (12,4%)**
Dai et al. [7]	154 (11,4%)
Robilotti et al. [12]	423 (9%)

The values in bold are significant.

Lung cancer patients are more vulnerable to COVID-19 and the data suggests their outcomes are worse [16]. The chances of death were reported here to be increased by 4.05 times, somewhat higher than the chances reported by a meta-analysis (OR 1.83) [14]. In contrast, a study in the United Kingdom found no increase in lung cancer mortality (OR 1.41) [6]. In this study, 66% of patients diagnosed with lung cancer and who died of COVID-19 were smokers or ex-smokers. The high prevalence of smoking can be attributed as a risk factor associated with mortality. The TERAVOLT study, which analyzed data from patients with chest cancer (76% nonsmall cell lung cancer), found that smoking history was associated with an increased risk of death [8]. According to the THOCOoP cooperative group, patients with lung cancer represent a population particularly vulnerable to COVID-19, due to smoking, low immunity, and the presence of comorbidities such as chronic obstructive pulmonary disease (COPD). They suggest that treatment should be maintained with special care and that avoiding patient exposure to SARS-CoV-2 is paramount [30].

A systematic review revealed that patients undergoing cancer treatment, such as chemotherapy, had a higher risk of death from COVID-19 [18], which aligns with our own findings that patients who had received chemotherapy in the previous 30 days were more vulnerable to death from COVID-19. However, another systematic review found no association between the receipt of any type of cancer therapy and mortality from SARS-CoV-2 [14]. Different cancer therapies are believed to have different effects on the risk of serious outcomes for COVID-19 [31].

The patients in the present study had a mean age (56.9 years) lower than that of a recent systematic review (65.1 years) [14] and similar to that of another study conducted in Brazil (55.3 years) [11]. This lower average age is due to a higher prevalence of visits by young women with breast cancer at the ACCCC. However, even in our cohort, age over 60 years was associated with higher mortality from COVID-19, similar to the findings of other studies [6,11,32], and may be due to a less efficient immune response in the elderly [33,34].

Male cancer patients have been reported to have more severe COVID-19 outcomes [10,23,24]. This increase in mortality in men is related to a higher number of comorbidities, prevalence of smoking, alcohol consumption, and occupational exposures [35,36,37]. In the present study, differences in mortality due to COVID-19 between the sexes were not identified, as reported in other studies [9,11,19]. Sex hormones are believed to be important in the immune response; estrogen is known to act as an immune booster, but androgens need to be further investigated for their interaction with COVID-19 [38,39].

Cancer patients develop severe COVID-19 outcomes in less time than cancer-free patients do [15]. Studies in China have reported lower survival in patients with lung cancer and COVID-19 compared to people without cancer [7], as well as in patients undergoing cancer treatment compared to patients who are in the follow-up [20]. A study carried out in Canada identified a lower survival rate in elderly patients with advanced stage IV disease [19], with age greater than or equal to 75 years associated with low survival in a patient with chronic lymphocytic leukemia [21]. However, in the present study there were no differences in survival by sex, age group, tumor site, type of insurance, or situation at the diagnosis of COVID-19.

The ACCCC is a public-private treatment center in which increased COVID-19 related mortality from lung and hematological cancer has been observed. These findings are unlike what was observed in a study carried out at INCA, a public referral center for cancer treatment in Brazil, supervised by the Ministry of Health [11]. At the ACCCC, no difference in mortality was observed in terms of access to public versus private care, which demonstrates equity in treatment, without a difference in patient survival.

These results demonstrate the importance of studies in cancer patients since it is a population at higher risk of death from COVID-19. A total of 411 patients were analyzed at a cancer center where most of the care is provided by the private system. Detailed studies on the clinical profiles, comorbidities, and staging should be investigated to better understand mortality and mechanisms of COVID-19 in this risk group. Our study has limitations, as it is a cross-sectional study limited in time, but still presents useful in-

formation on mortality due to COVID-19 in cancer patients at the largest cancer center in Latin America.

Conclusion

We observed that cancer patients have a greater chance of death associated with COVID-19 if they have hematological or lung cancers, are in the age group above 60 years, and if they are currently undergoing cancer treatment. There was no difference in mortality regarding sex or type of insurance. From these data we conclude that cancer patients are not affected equally by COVID-19. Consequently one can envision that deployment of different strategies for individual cancer patients will be needed to reduce the chance of death while also maintaining oncologic care.

Author contributions

Gisele A. Fernandes: Conceptualization, Methodology, Software, Writing- Original draft preparation, Writing- Reviewing and Editing, Visualization, Investigation. **Maria P. Curado**: Conceptualization, Methodology, Writing- Original draft preparation, Supervision, Writing- Reviewing and Editing, Visualization, Investigation. **Diego R. M. Silva:** Data curation, Methodology, Software. **Ivan L.A.F. Silva:** Data curation, Writing- Original draft preparation, Supervision, Visualization, Investigation. **Diego Feriani:** Data curation, Writing- Original draft preparation, Visualization, Investigation. **Juliana S. Canteras:** Data curation. **Rodrigo R. Silva:** Data curation. **Paola E. Arantes:** Data curation.

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Declaration of competing interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1053/j.seminoncol.2021.01.003.

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