Palliative Care and COVID-19 Pandemic: Retrospective Study of Factors Associated With Infection and Death at an Oncological Palliative Care Reference Center

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Abstract

Background: Advanced cancer patients are part of a group likely to be more susceptible to COVID-19. **Aims:** To describe the profile of advanced cancer inpatients to an exclusive Palliative Care Unit (PCU) with the diagnosis of COVID-19, and to evaluate the factors associated with death in these cases. **Design:** Retrospective cohort study with data from advanced cancer inpatients to an exclusive PCU, from March to July 2020, with severe acute respiratory syndrome. Diagnostic of COVID-19 and death were the dependent variables. Logistic regression analyses were performed, with the odds ratio (OR) and 95% confidence interval (CI). **Results:** One hundred fifty-five patients were selected. The mean age was 60.9 ($\pm$13.4) years old and the most prevalent tumor type was breast (30.3%). Eighty-three (53.5%) patients had a diagnostic confirmation of COVID-19. Having diabetes mellitus (OR: 2.2; 95% CI: 1.1-6.6) and having received chemotherapy in less than 30 days before admission (OR: 3.8; 95% CI: 1.2-12.2) were associated factors to diagnosis of COVID-19. Among those infected, 81.9% died and, patients with Karnofsky Performance Status (KPS) < 30% (OR: 14.8; 95% CI 2.7-21.6) and C-reactive protein (CRP) >21.6mg/L (OR: 9.3; 95% CI 1.1-27.8), had a greater chance of achieving this outcome. **Conclusion:** Advanced cancer patients who underwent chemotherapy in less than 30 days before admission and who had diabetes mellitus were more likely to develop Coronavirus 2019 disease. Among the confirmed cases, those hospitalized with worse KPS and bigger CRP were more likely to die.

Keywords

coronavirus, palliative care, neoplasms, hospital mortality, advanced cancer, prognosis

Introduction

The Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, was recognized as a new health issue in December 2019. Since then, it has been spread around the world and WHO declared COVID-19 a pandemic in March 2020.[1] The first case of disease in Brazil was detected on February 26, 2020. Since then, the country had a non-integrated response and is the third most infected country in the world, with more than 145.000 deaths.[2] Although most patients will have a mild disease, a small part will develop severe problems, such as severe acute respiratory syndrome (SARS), shock, thromboembolism, and organ failure.[3,4]

Initial reports have suggested that cancer patients might be at increased risk of contracting the virus and developing severe COVID-19. Moreover, these patients presented higher mortality. This difference can be explained by an immune compromised status, due to the cancer itself, surgery or antineoplastic

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therapy, and steroids chronic use. Patients with malignity disease are often older, have one or more comorbidities, and are in continuous contact with the healthcare.[4-6]

Palliative care aims to improve quality of life to those with a life-threatening disease. It includes keeping pain and other symptoms to a minimum level, integrating the psychological and spiritual aspects of patient care. The palliative care services must respond briefly during an unexpected epidemic, seeking new ways of working in order to maintain these goals.[7,8] Although palliative care is getting stronger in Brazil, specialized services are in small number, irregular, and isolated.[9,10]

This article aims to describe the profile of advanced cancer inpatients to an exclusive Palliative Care Unit (PCU) with the diagnosis of COVID-19, and to evaluate the factors associated with death in these cases.

Methods

This is a clinical, observational, retrospective cohort study, with all advanced cancer patients admitted to the exclusive PCU at the National Cancer Institute José Alencar Gomes da Silva (INCA), in Brazil, from March 19 to July 30, 2020, with suspicion or confirmation of infection by COVID-19. The patients had generalized malignant disease or advanced local tumor growth and were not receiving any antineoplastic treatment with control intent. Intubation, usually adopted in severe cases of COVID 19, is not part of the medical approach for this group. The data extracted from the medical records during the months of June to August 2020. The study was approved by the INCA Ethics Committee and exempted the need of individual consent (CAAE: 31053220.0.0000.5274; Opinion number: 4,025,454; Date: May 13, 2020).

Patients of both genders, aged >20 years, with a confirmed histopathological diagnosis of advanced malignancy, regardless of tumor location, and who were hospitalized with SARS, with suspicion or confirmation of infection by COVID-19, were eligible. SARS is characterized by flu syndrome associated with dyspnea/increased respiratory rate or persistent pressure in the chest or saturation less than 95% in ambient air or cyanosis.[11]

As previously published by our research group, the criteria for suspected COVID-19 infection were being in contact with a suspected or confirmed case less than 14 days ago, having fever with no other defined focus, respiratory symptoms not explained by the oncological disease and / or suggestive radiological image. The preferred imaging test to help identify suspected infection was chest computed tomography. However, the computed tomography was only requested when the criteria based on the clinical evaluation were not sufficient to define or rule out the suspicion and when the patient's clinical condition allowed the imaging examination to be performed without increasing suffering. In case of doubt due to clinical aspects and impossibility of performing computed tomography, the patient was considered a suspect.[12]

Sociodemographic and Clinical Data

The following sociodemographic data were obtained: age (years) and gender (male vs. female). The clinical data evaluated were: diagnosis [breast vs. gastrointestinal tract (GIT) vs. head and neck (HN) vs. urological (URO) vs. gynecological vs. connective bone tissue (CBT) vs. lung vs. other types of cancer], disease progression (DP) (only local vs. only distant vs. local and distant simultaneously), most prevalent DP sites [lymph node (yes vs. no), lung (yes vs. no) and bones (yes vs. no)], time since the last surgery, chemotherapy (CT), radiation therapy (RxT) and hormone therapy (HT) until hospitalization [<30 days (yes vs. no) and <60 days (yes vs. no)], presence of more prevalent comorbidities [hypertension (SAH) (yes vs. no), diabetes mellitus (DM) (yes vs. no), cardiovascular disease (CVD) (yes vs. no), obesity (yes vs. no) and chronic obstructive pulmonary disease (COPD) (yes vs. no)] and Karnofsky Performance Status (KPS).[13]

Laboratory Exams

The following serum measurements were taken from medical records: complete blood count with hemoglobin (1st tertile vs. 2nd + 3 rd tertile), white blood cell count (3 rd tertile vs. 1st + 2nd tertile), neutrophils, lymphocytes, monocytes and platelets, albumin (1st tertile vs. 2nd + 3 rd tertile) and C-reactive protein (CRP; 3 rd tertile vs. 1st + 2nd tertile). The values were used to determine the neutrophil-lymphocyte ratio (NLR; 3 rd tertile vs. 1st + 2nd tertile), platelet-lymphocyte ratio (PLR; 3 rd tertile vs. 1st + 2nd tertile), lymphocyte-monocyte ratio (LMR; 1st tertile vs. 2nd + 3 rd tertile) and the CRP-albumin ratio (CAR; 3 rd tertile vs. 1st + 2nd tertile).

Furthermore, according to the graduation proposed by McMillan et al,[14] the modified Glasgow Prognostic Score (mGPS) was classified from 0 to 2, according to the concentrations of CRP and albumin (CRP ≤10 mg/L, mGPS = 0; CRP >10 mg/L and albumin >3.5 g/dL, mGPS = 1; CRP >10 mg/L and albumin <3.5 g/dL, mGPS = 2).

Outcomes

Two different outcomes were evaluated: diagnostic confirmation of COVID-19—all cases that met the suspicion criteria were submitted to nasal and oropharyngeal swab collection for COVID-19 research by Reverse Transcription Polymerase Chain Reaction (RT-PCR)—and death of hospitalized patients diagnosed with COVID-19 infection. Patients with inconclusive or indeterminate RT-PCR were excluded.

Statistical Analysis

The analyses were performed using the Stata Data Analysis and Statistical Software (STATA) program, version 13.1. To evaluate the distribution of data in the sample, the Kolmogorov Smirnof test was applied. The numerical variables were described as mean and standard deviation (SD) or as median and interquartile range (IQR), according to normal or non-
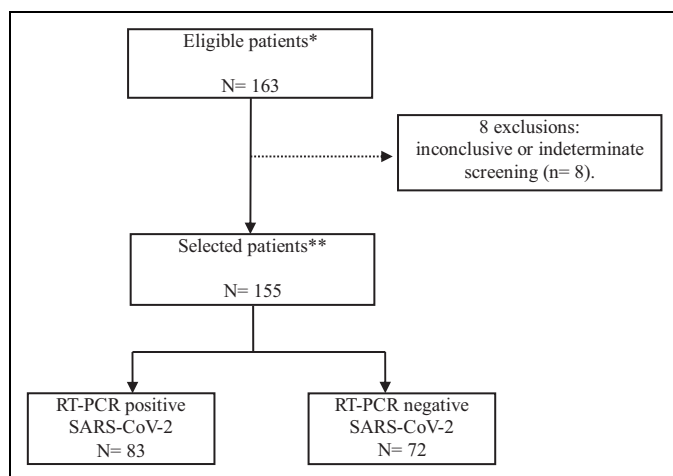
Figure 1. Flowchart of advanced cancer inpatients in the context of COVID-19 in an exclusive Palliative Care Unit, Brazil. N indicates number of observations; RT-PCR, Reverse Transcription Polymerase Chain Reaction. *Cases notified by the Hospital Infection Control Center of CH IV of hospitalized patients suspected of being infected with COVID-19 of March 19 to July 30, 2020. **Patients whose data were assessed in the survey.

normal distribution, respectively, while categorical variables were described in frequency (n) and percentage (%).The comparison between groups of variables was performed using Student's t-test for independent samples or by the corresponding non-parametric test, Mann-Whitney U, in case they have normal or non-normal distribution, respectively. The comparison between categorical variables was assessed using the Chi-square test. All variables with p-value < 0.200 in these statistical tests were selected for bivariate logistic regression, including the tumor type due to biological plausibility.

Regressions were performed for each outcome studied. All variables that in the bivariate regressions maintained a p-value < 0.200 were selected and launched simultaneously in the multiple analyses. A multiple regression was used for the diagnostic of COVID-19 on the entire 155 patient cohort (with the variables: gender, last CT in <30 and <60 days, last RxT in <60 days, DM, obesity, leukocytes, NLR and PLR) and one was used for the death outcomes only of patients with COVID-19 (with the variables: DP, DP to lung and bones, SAH, KPS, hemoglobin, CRP, mGPS and leukocytes). Through the backward selection method, the variables were excluded, one by one, in decreasing order of p-value. Only those that remained with a p-value < 0.050 were kept in the final multiple model.

Results

One hundred fifty-five advanced cancer patients who required hospitalization due to the condition of SARS were selected. After analyzing the RT-PCR, 83 (53.5%) of them were diagnosed as positive cases of infection by COVID-19 (Figure 1) and the first patient was hospitalized on April 1, 2020 (3 rd week of study's suspected cases). The peak of confirmed cases

occurred in the 14th epidemiological week (period from May 24th to 30th) (Figure 2).

Considering the total sample, the average age was 60.9 (±13.4) years, with a higher proportion of women (66.5%) and median KPS of 30% (20%-40%). The most prevalent tumor type was breast (30.3%), followed by GIT (18.7%). Patients with COVID-19 showed statistically significant differences in relation to the time of the last CT before hospitalization (p-value = 0.011) and in the prevalence of obesity (p-value = 0.020), when compared to others. The death rate in hospitalization and the median concentration of laboratory tests did not differ between the groups (Table 1). According to the multiple logistic regression analysis, having undergone CT in less than 30 days before hospitalization (OR: 3.8; 95% CI: 1.2-12.2) and having DM (OR: 2.2; 95% CI: 1.1-6.6) were considered independent associated factors the occurrence of COVID-19 infection in advanced cancer patients in palliative care (Table 2).

Among patients with COVID-19, 81.9% died, whose majority had bone metastasis (p-value = 0.009), KPS < 30% (p-value < 0.001) and CRP >21.6mg/L (p-value = 0.012) (Table 3). However, after multiple logistic regression analysis, only reduced KPS (OR: 14.8; 95% CI: 2.7-21.6) and elevated CRP (OR: 9.3; 95% CI: 1.1-27.8) at admission were considered independent risk factors for death in this group (Table 4).

Discussion

Given the current scenario, studies with cancer patients and COVID-19 are scarce, due to the heterogeneity of research, different types of neoplasm, comorbidities and treatment phases.[15] The present study allowed for the description of the profile of advanced cancer inpatients in a PCU with SARS and for the identification of factors associated with the diagnosis of infection by COVID-19 and the death rate in these cases. Therefore, we have 2 main results. First, we found that advanced cancer inpatients who underwent CT in less than 30 days before admission and who had DM were more likely to COVID-19 infection. Secondly, we were able to demonstrate that, among the confirmed cases, those who were hospitalized with worse KPS and bigger CRP were more likely to die.

From the perspective of the pandemic situation due to the new coronavirus, patients with malignant neoplasms are particularly more sensitive to pathogenic respiratory microorganisms and severe pneumonia, either due to the antitumor therapy or due to the malignancy itself.[6] Thus, the performance of CT for less than 30 days and the presence of DM were considered associated factors for the occurrence of COVID-19 infection. Regarding antitumor treatment, a cohort study of 1044 patients in the United Kingdom identified an increased risk of COVID-19 infection, in which 47.6% (108) of patients with hematological neoplasms received CT in the last 30 days.[16] The consequences of immune status can be numerous when performing CT, thus increasing the likelihood of serious outcomes related to the cytokine storm and leading to multiple organ failure.[17] It should be noted that due to their rapid anti-
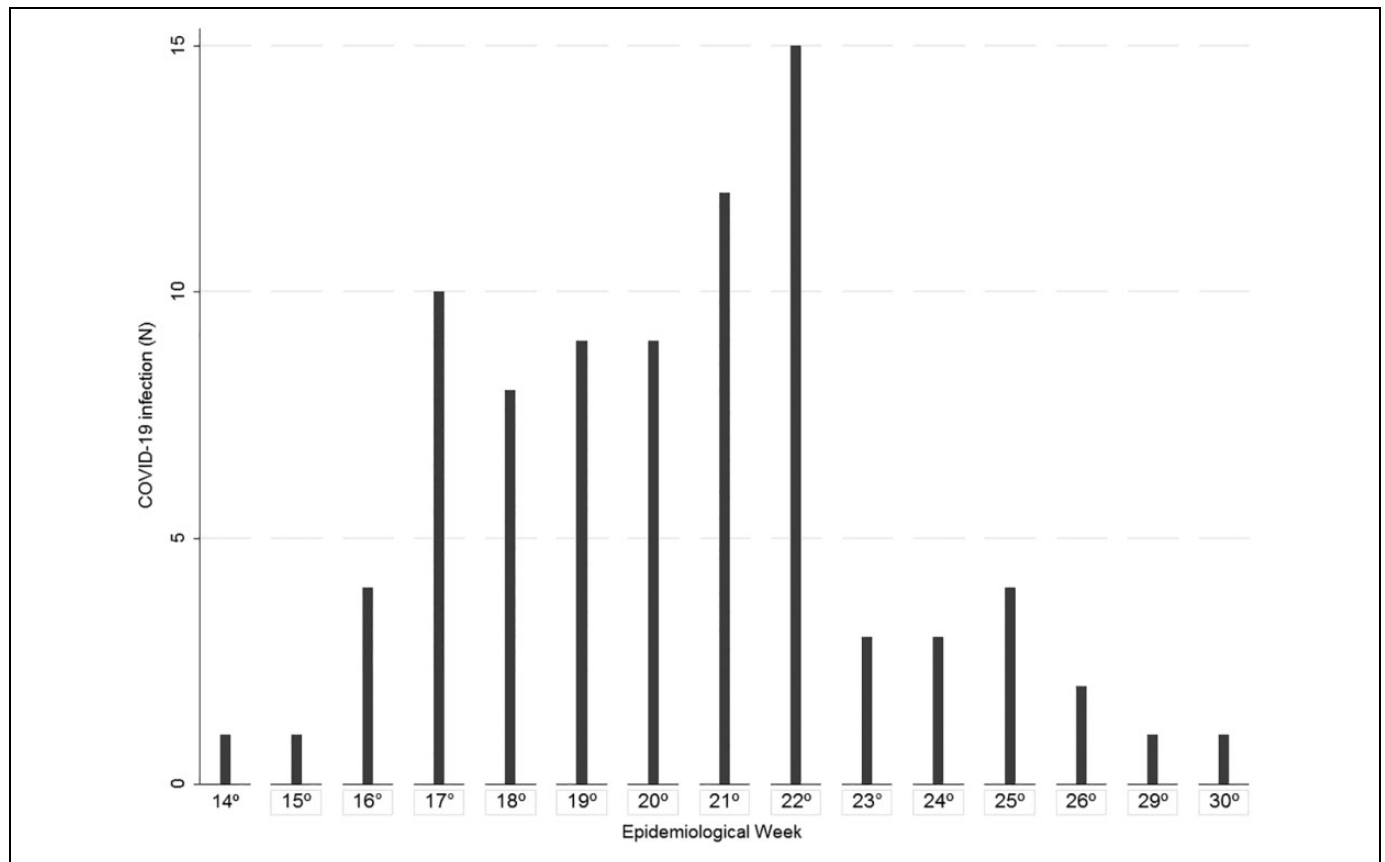
Figure 2. Advanced cancer patients with COVID-19 hospitalized per epidemiological week* in an exclusive Palliative Care Unit, Brazil. N indicates number of observations. *Cases notified by the Hospital Infection Control Center of CH IV of hospitalized patients suspected of being infected with COVID-19 of March 19 (12th epidemiological week) to July 30, 2020 (31st epidemiological week). The first confirmed case of COVID-19 was on April 1, 2020 (14th epidemiological week). The peak of confirmed cases occurred in the 22nd epidemiological week (period from 24th to 30th of May).

Table 1. Characteristics of Advanced Cancer Inpatients Suspected or Confirmed of COVID-19 Infection in an Exclusive Palliative Care Unit, Brazil.

		COVID-19		
Variables	Total (N = 155)	No, n = 72 (46.5%)	Yes, n = 83 (53.5%)	P value
Age (years)[a]	60.9 (±13.4)	60.4 (±14.3)	61.4 (±12.6)	0.653
Gender[b]				
Male	52 (33.5%)	30 (41.7%)	22 (26.5%)	0.066
Female	103 (66.5%)	42 (58.3%)	61 (73.5%)	
Diagnosis[b]				
Breast	47 (30.3%)	16 (22.2%)	31 (37.3%)	0.271
GI Tract	29 (18.7%)	13 (18.1%)	16 (19.3%)	
HN	20 (12.9%)	14 (19.4%)	6 (7.3%)	
Urological	16 (10.3%)	8 (11.1%)	8 (9.6%)	
Gynecological	15 (9.7%)	8 (11.1%)	7 (8.4%)	
CBT	10 (6.4%)	6 (8.3%)	4 (4.8%)	
Lung	8 (5.3%)	3 (4.3%)	5 (6.0%)	
Others	10 (6.4%)	4 (5.5%)	6 (7.3%)	
DP[b]				
Only local	20 (12.9%)	11 (15.3%)	9 (10.8%)	0.712
Only distance	18 (11.6%)	8 (11.1%)	10 (12.1%)	
Local +distance	117 (75.5%)	53 (73.6%)	64 (77.1%)	

Table I. (continued)

| | | COVID-19 | | |
Variables	Total (N = 155)	No, n = 72 (46.5%)	Yes, n = 83 (53.5%)	P value
Pumonar diease (diagnosis or DP)[b]				0.678
Yes	71 (45.8%)	34 (47.9%)	37 (52.1%)	
No	84 (54.2%)	48 (57.1%)	36 (42.9%)	
Local of DP[b]				
LFN	82 (52.9%)	39 (54.1%)	43 (51.8%)	0.397
Lung	63 (40.6%)	29 (40.3%)	34 (41.0%)	0.768
Bones	56 (36.1%)	27 (37.5%)	29 (34.9%)	0.257
Last time surgery before hospitalization (days)[b]				
≤30	1 (0.6%)	0	1 (1.2%)	0.350
≤60	3 (1.9%)	1 (1.4%)	2 (2.4%)	0.645
Last time QT before hospitalization(days)[b]				
≤30	7 (4.5%)	1 (1.4%)	6 (7.2%)	0.081
≤60	20 (12.9%)	4 (5.6%)	16 (19.3%)	**0.011**
Last time RxT before hospitalization (days)[b]				
≤30	9 (5.8%)	2 (2.8%)	7 (8.4%)	0.133
≤60	15 (9.7%)	6 (8.3%)	9 (10.8%)	0.598
Last time HT before hospitalization (days)[b]				
≤30	10 (6.4%)	5 (6.9%)	5 (6.0%)	0.816
≤60	17 (11.0%)	7 (9.7%)	10 (12.0%)	0.644
Co-morbities[b]				
DM	24 (15.5%)	7 (9.7%)	17 (20.5%)	0.065
SAH	68 (43.9%)	28 (38.9%)	40 (48.2%)	0.244
CD	15 (9.7%)	9 (12.5%)	6 (7.2%)	0.268
Obesity	6 (3.9%)	0	6 (7.2%)	**0.020**
COPD	5 (3.2%)	3 (4.2%)	2 (2.4%)	0.537
KPS (%)[c]	30 (20-40)	30 (30-40)	30 (20-40)	0.360
Death in hospital[b]	128 (82.6%)	60 (83.3%)	68 (81.9%)	0.818

| | | COVID-19 | | |
Variables	Total N = 155	No n = 72 (46.5%)	Yes n = 83 (53.5%)	p-value
mGPS 1+2[b]	73 (64.6%)	34 (63.0%)	39 (66.1%)	0.727
CAR[a]	3.8 (0.5-7.7)	3.8 (0.6-7.8)	3.9 (0.5-7.6)	0.908
CAR >6.5[be]	41 (33.9%)	22 (35.5%)	19 (32.2%)	0.703
Leukocytes[a]	11900 (8600-18200)	12100 (8900-18600)	11500 (7500-17900)	0.268
Leukocytes >16465[be]	49 (32.2%)	23 (32.4%)	26 (32.1%)	0.969
NLR[a]	10.5 (5.3-18.1)	11.6 (6.8-20.4)	8.3 (5.2-14.9)	0.137
NLR>14.8[be]	49 (32.7%)	27 (39.1%)	22 (27.2%)	0.119
PLR[a]	296.9 (167.7-462.4)	314.8 (172.4-552.2)	288.3 (171.0-413.0)	0.278
P LR>387[be]	50 (33.3%)	27 (39.1%)	23 (28.4%)	0.164
LMR[a]	2.0 (1.2-3.6)	1.6 (1.0-3.3)	2.0 (1.3-3.6)	0.210
LMR ≤1.34[bd]	48 (32.2%)	22 (31.9%)	26 (32.5%)	0.936

Abbreviations: COVID-19 = Coronavirus disease 2019; N = number of observations; GI = gastrintestinal; HN = head and neck; CBT = connective bone tissue; INCA = National Cancer Institute José Alencar Gomes da Silva; DP = disease progression; LFN = linphy node QT = chemotherapy; Rxt = radiotherapy; HT = hormone therapy; DM = diabetes mellitus; SAH = systemic arterial hipertension; CD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; KPS = Karnofsky Performance Status; CRP = C–reactive protein; mGPS = modified Glasgow Prognostic Score; CAR = C-reactive protein albumin ratio; NLR = neutrophil lymphocyte ratio; PLR = platelet lymphocyte ratio; LMR = lymphociye monocyte ratio.
[a]Mean (standard deviation)/Student's t test; [b]Absolute Number (frequency)/chi-square test; [c]Median (interquartile range)/Mann-Whitney U test; [d]1st tertile vs. 2nd + 3 rd tertiles; [e]3 rd tertile vs. 1st + 2nd tertiles.
Bold values signifies p-value <0.05.

inflammatory and immunosuppressive impact, corticosteroid drugs can be used to treat hyperinflammatory conditions, including COVID-19. However, its use is still controversial and more research is needed.[18-20]

Other studies have also found that the risk of syndrome severity and mortality is significantly high in patients with DM. In addition, individuals with impaired glucose tolerance or DM have been reported to have a 50–60% increased risk of lung infection.[21] Recent evidence suggests an increased risk of Respiratory Difficulty Syndrome in adults and complications of multiple organ failure in diabetic patients. Globally, during the COVID-19 pandemic, DM is present in up to 50% of confirmed cases.[22]

Table 2. Multiple Logistic Regressions of Factors Associated to Diagnosis of COVID-19 in Advanced Cancer Inpatients in an Exclusive Palliative Care Unit, Brazil.

Variables	COVID-19+ OR (CI 95%)	P value[a]
30 days from last QT before hospitalizatoin		
No	1.00	0.022
Yes	3.8 (1.2-12.2)	
DM		
No	1.00	
Yes	2.2 (1.1-6.6)	0.049

Abbreviations: COVID-19 = Coronavirus disease 2019; OR = odds ratio; CI = confidence interval; QT = chemotherapy; DM = diabetes melittus.
[a]p-value refers to multiple logistic regression.
Bold values signifies p-value <0.05.

It's important to highlight there was no significant difference in relation to the death rate between confirmed and unconfirmed cases of COVID-19. Pragmatically, the clinical manifestations of the infection, such as dyspnea and a decline in general condition[23] are common to the signs of imminent death in patients in palliative care.[24] We hypothesized that the active death process, which is frequent in advanced cancer inpatients, may have been a confounding factor for the classification of suspicion among those patients who were not infected with COVID-19.

Inpatients with COVID-19 and with KPS <30% and CRP >21.6 mg/L, were more likely to die. In a meta-analysis, there was a significant association between high CRP levels and mortality (HR: 1.9; CI 95%: 1.8-2.2; p < 0.001).[25] High levels of CRP are associated with poor prognosis in cancer patients,

Table 3. Characteristics of Advanced Cancer Patients With COVID-19 According to Outcome of Hospitalization in an Exclusive Palliative Care Unit, Brazil.

Variables	COVID-19 +		
	Hospital discharge, n = 15 (18.1%)	Death, n = 68 (81.9%)	P value
Age (Years)[a]	58.4 (15.5)	62.0 (11.9)	0.317
Gender[b]			
Male	3 (20.0%)	19 (27.9%)	0.528
Female	12 (80.0%)	49 (72.1%)	
Diagnosis[b]			
Breast	4 (26.7%)	27 (39.7%)	0.252
GI Tract	3 (20.0%)	13 (19.1%)	
HN	1 (6.7%)	5 (7.3%)	
Urological	1 (6.7%)	7 (10.3%)	
Gynecological	2 (13.3%)	5 (7.3%)	
CBT	1 (6.7%)	3 (4.4%)	
Lung	1 (6.7%)	4 (5.9%)	
Others	2 (13.3%)	4 (5.9%)	
DP[b]			
Only local	2 (13.3%)	7 (10.3%)	0.132
Only distance	4 (26.7%)	6 (8.8%)	
Local +distance	9 (60.0%)	55 (80.9%)	
Pumonar diease (diagnosis or DP)[b]			
Yes	5 (33.3%)	34 (50.0%)	0.242
No	10 (66.7%)	34 (50.0%)	
Local of DP[b]			
LFN	9 (69.2%)	34 (56.7%)	0.404
Lung	4 (37.8%)	30 (50.0%)	0.202
Bones	1 (7.7%)	28 (46.7%)	**0.009**
Last time surgery before hospitalization (days)[b]			
≤30	0	1 (1.5%)	0.637
≤60	0	2 (2.9%)	0.501
Last time QT before hospitalization(days)[b]			
≤30	1 (6.7%)	5 (7.3%)	0.926
≤60	4 (26.7%)	12 (17.6%)	
Last time RxT before hospitalization (days)[b]			
≤30	1 (6.7%)	6 (8.8%)	0.786
≤60	1 (6.7%)	8 (11.8%)	0.565
Last time HT before hospitalization (days)[b]			
≤30	2 (13.3%)	3 (4.4%)	0.212
≤60	2 (13.3%)	8 (11.8%)	0.866

Table 3. (continued)

	COVID-19 +		
Variables	Hospital discharge, n = 15 (18.1%)	Death, n = 68 (81.9%)	*P* value
Co-morbities[b]			
DM	2 (13.3%)	15 (22.1%)	0.448
SAH	5 (33.3%)	35 (51.5%)	0.200
CD	0	6 (8.8%)	0.232
Obesity	1 (6.7%)	5 (7.3%)	0.926
COPD	0	2 (2.9%)	0.501
KPS <30%[b]			
No	12 (80.0%)	19 (27.9%)	**<0.001**
Yes	3 (20.0%)	49 (72.1%)	

	COVID-19 +		
Variables	Hospital discharge n = 15 (18.1%)	Death n = 68 (81.9%)	p-value
Co-morbities[b]			
DM	2 (13.3%)	15 (22.1%)	0.448
SAH	5 (33.3%)	35 (51.5%)	0.200
CD	0	6 (8.8%)	0.232
Obesity	1 (6.7%)	5 (7.3%)	0.926
COPD	0	2 (2.9%)	0.501
KPS <30%[b]			
No	12 (80.0%)	19 (27.9%)	**<0.001**
Yes	3 (20.0%)	49 (72.1%)	
Hemoglobin $\leq$9.1g/dL[ac]	7 (46.7%)	16 (24.4%)	0.082
Albumin $\leq$2.7g/dL[ac]	2 (18.2%)	15 (31.2%)	0.388
CRP >21.6 mg/L[ad]	1 (7.7%)	21 (45.6%)	**0.012**
mGPS 1+2[b]	6 (46.1%)	33 (71.7%)	0.085
CAR >6.5[ad]	2 (18.2%)	17 (35.4%)	0.270
Leukocytes >16465[ad]	2 (13.3%)	24 (36.4%)	0.085
NLR >14.8[ad]	3 (20.0%)	19 (28.8%)	0.490
PLR >387[ad]	6 (40.0%)	17 (25.8%)	0.269
LMR $\leq$1.34[ac]	6 (42.8%)	20 (33.0%)	0.362

Abbreviations: COVID-19 = Coronavirus disease 2019; N = number of observations; GI = gastrintestinal; HN = head and neck; CBT = connective bone tissue; INCA = National Cancer Instituter José Alencar Gomes da Silva; DP = disease progression; LFN = linphy node QT = chemotherapy; Rxt = radiotherapy; HT = hormone therapy; DM = diabetes mellitus; SAH = systemic arterial hipertension; CD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; KPS = Karnofsky Performance Status.
CRP = C–reactive protein; mGPS = modified Glasgow Prognostic Score; CAR = C-reactive protein albumin ratio; NLR = neutrophil lymphocyte ratio; PLR = platelet lymphocyte ratio; LMR = lymphociye monocyte ratio.
[a]Mean (standard deviation)/Student's t test; [b] Absolute Number (frequency)/chi-square test; [c]1st tertile vs. 2nd + 3 rd tertiles; [d]3 rd tertile vs. 1st + 2nd tertiles.

Table 4. Multiple Logistic Regressions of Factors Associated to Death of Advanced Cancer Inpatients With COVID-19 in an Exclusive Palliative Care Unit, Brazil.

	COVID-19 +	
Variables	OR (CI 95%)	*P* value[a]
KPS $\leq$30%		
No	1.00	
Yes	14.8 (2.7-21.6)	0.002
CRP >21.6 mg/L		
No	1.00	
Yes	9.3 (1.1-27.8)	0.049

Abbreviations: COVID-19 = Coronavirus disease 2019; OR = odds ratio; CI = confidence interval; KPS = Karnofsky Performance Status; CRP = C-reactive protein.
[a]p-value refers to multiple logistic regression.

regardless of the tumor stage. Interleukin-6 (IL-6) and Tumor Necrosis Factor alpha (TNF-α) induce hepatic synthesis of this acute phase protein, its dosage being readily available as an important marker of systemic inflammation.[26]

In a retrospective study with patients with SARS COV-2, increased CRP levels were also an independent risk factor for death in a multivariate model (OR: 1.1; 95% CI: 1.1-1.2). Its high concentrations in patients with flu-like syndrome may come from excessive inflammatory stress and may contribute to serious diseases.[27] The cytokine storm is considered a major cause of SARS COV-2 and multiple organ failure. Such an event plays a fundamental role in the worsening of the disease.[28] The exact function and mechanism of CRP in patients with COVID-19 are still unclear. Therefore, it is essential to encourage more studies on the pathogenesis of the infection

and its relationship with laboratory markers of systemic inflammation, such as CRP.[27,29]

The reduced functionality is one of the early signs of the death process.[24] However, the condition of palliative care in advanced cancer represents, in itself, a high degree of fragility with regard to functional capacity.[30,31] Associated with the fact that the patients probably have complications responsible for the flu syndrome, it is not surprising that we verified it as a risk factor independent of the chance of death.

Knowing that the prognostic evaluation minimizes the risks of under treatment or disproportionate therapies in the advance of cancer,[24] our findings may be useful in elucidating indicators of a worse prognosis, so that elements such as recent CT (<30 days), DM, KPS <30% and CRP >21.6 mg/L can be guiding for decision making in the care plan for advanced cancer patients in palliative care infected by COVID-19. Furthermore, they are simple indicators that can be used by any health professional, previously trained in the case of KPS, expanding the practical utility of these findings. In addition, considering that Brazil was classified as one of the worst countries in relation to the growth of the spread of COVID-19 and in relation to the lethality resulting from the disease, these data are quite relevant and can assist in the foundation of clinics that provide the best clinical practices respecting the patient's condition.

To our knowledge, it is the first paper to analyze COVID-19 in a palliative care scenario in Brazil. We highlight the fact that the study involved the collection of numerous variables of explanatory potential, in relation to the selected outcomes, in a national referral center for palliative cancer care. In addition, it is important to note that the data were analyzed using robust statistical procedures, adding strength to the evidence found. However, some limitations need to be described. The study was carried out in a single institution and had a retrospective design. Therefore, more studies should be developed, so that multicenter research and prospective design should be performed and could reaffirm the role of these parameters in the context of advanced cancer inpatients with COVID-19.

We conclude that advanced cancer inpatients who underwent CT ≤30 days before admission and who had DM were more likely to develop COVID-19 infection. And, among the confirmed cases, those who were hospitalized with KPS <30% and CRP >21.6 mg/L at the time of admission were more likely to die.

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Declaration of Conflicting Interests

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