

Cancer and SARS-CoV-2 Infection: A Third-Level Hospital Experience

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Introduction: Madrid has been the epicenter of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in Spain. We analyzed our experience with SARS-CoV-2 infected and cancer patients.

Patients and Methods: We included patients from March 1 to April 30 2020 at Hospital Universitario Puerta de Hierro, Majadahonda, Madrid (Spain). The inclusion criteria were diagnosis of SARS-CoV-2 infection made by reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal specimens in cancer patients who were admitted to the hospital due to the need for respiratory support. The exclusion criteria were suspected cases not confirmed. The primary objective was to analyze the mortality rates of patients with cancer, especially those with lung cancer and COVID-19.

Results: Overall in-hospital mortality of cancer patients with coronavirus disease 2019 (COVID-19) was 15.2% similar to 12.7% of the global COVID-19 hospitalized population ($p=0.615$) and greater than that of patients admitted without SARS-CoV-2 infection during the same period 4.3% ($p<0.001$). Among 653 patients receiving active cancer therapy during the study period, 24 (3.7%) developed COVID-19 and required admission, 4.2% of those receiving chemotherapy, 9.5% immunotherapy and 2.1% targeted therapies. Lung and breast cancer were the most frequent cancer types (26.1%), followed by colorectal cancer (19.6%). Mortality in patients with lung cancer was 25%. The univariate analysis comparing patients who developed a serious event to those who did not showed that the higher Brescia index, CURB-65 scale, lactate dehydrogenase (LDH) or C-reactive protein (CRP) were the risk factors of developing severe complications.

Conclusion: Patients with cancer, especially lung cancer, and SARS-CoV-2 infection have a worse overall prognosis than the general population.

Keywords: cancer, COVID-19, lung cancer, severe clinical events

Introduction

Coronavirus disease 2019 (COVID-19) has led to an unprecedented pandemic situation all over the world; since it appeared in Wuhan, China, in December 2019,^{1,2} more than 2.5 million deaths have been reported. In the present moment, 124,871,140 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have been confirmed worldwide. Epidemiological data indicate that patients have a higher morbidity and mortality if they have at least one of the following characteristics: being older than 65 years old, or having either hypertension, cardiovascular disease, diabetes, chronic respiratory disease, renal disease, obesity or cancer.³⁻⁵

There are few studies with small cohorts describing cancer and COVID-19. Liang et al⁶ on a Chinese cohort describe a higher incidence than expected

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(0.29%) of patients with cancer history, with 18 (1%, 95% CI: 0.61–1.65) out of 1590 cases with COVID-19, having 5 of them (28%) lung cancer. Information about treatment was available for 16 patients. Four have received chemotherapy or surgery in the previous month and 12 developed SARS-CoV-2 during their follow-up after surgery resection, these 4 patients had a higher risk of severe events describing the older age as a risk factor (OR 1.43, 95% CI: 0.97–2.12; $p=0.072$). Even though it is difficult to obtain any conclusion with a small cohort of patients, other studies^{7,8} have supported the lack of information and the vulnerability of cancer patients according to age, gender and comorbidities as COVID-19 related deaths.

Madrid has been the epicenter of the SARS-CoV-2 pandemic in Spain. We analyzed our experience with SARS-CoV-2 infected and cancer patients during the period of highest incidence of the first wave.

Patients and Methods

We analyzed our experience with SARS-CoV-2 infected and cancer patients from March 1, 2020, to April 30, 2020 at the Hospital Universitario Puerta de Hierro of Madrid (Spain). This was the period of most incidence of the first wave of the pandemic in Madrid.

The inclusion criteria were diagnosis of SARS-CoV-2 infection made by reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal specimens in cancer patients who were admitted to the hospital due to the need for respiratory support. The exclusion criteria were suspected cases not confirmed.

The primary objective was to analyze the mortality rates of patients with cancer, especially those with lung cancer and COVID-19.

Acute respiratory distress syndrome (ARDS) was defined according to the interim guidance from the World Health Organization (WHO) for COVID-19.⁹

Clinical features and disease evolution have been described, focusing on the development of severe events during their admission. Severe event was defined as having severe respiratory distress, the need for mechanical ventilation, admission to an intensive care unit (ICU) or death. All information related to demographics features, patient comorbidities, medical history, laboratory tests, treatments received in the 30 days prior to admission, as well as all the tumor and oncological information, has also been collected.

Statistical Analysis

Descriptive analysis has been performed by means of absolute and relative frequencies for categorical variables and mean (standard deviation), or median (percentiles 25 and 75) for numerical variables. Univariable analysis was made with the chi-square or Fisher's exact tests for categorical variables and Mann–Whitney test for numerical. Significance level was established at 0.05. The software used was Stata/IC v.16. (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Ethics Approval

The study was evaluated by the Ethical Committee of Hospital Universitario Puerta de Hierro de Majadahonda, Madrid.

Our Institutional Ethics Review Board approved the study and waived the need for informed consent due to the characteristics of the study.

The study was carried out following the Declaration of Helsinki on Good Clinical Practices and Organic Law 3/2018, 5th December on Protection of Personal Data and digital rights that were guaranteed during the study.

Results

From March 1, 2020, to April 30, 2020, overall in-hospital mortality of cancer patients with COVID-19 was 15.2% (95% CI, 6.3; 5.2) (7/46).

Patients with COVID-19 and cancer had an average age of 65 years in men and 60 years in women, although the average age of the deceased was 68 and 63 years respectively.

Mortality in men was 12% in COVID-19 without cancer, 17% with COVID-19 and cancer and 5% without COVID-19 either cancer, while in women it was 13%, 15% and 4% respectively.

Table 1 shows the general characteristics of our series. Risk factors for COVID-19, such as hypertension or dyslipidemia, were prevalent among cancer patients.

After consulting the included patients, we know that a high proportion of cancer patients acquired their SARS-CoV-2 infection due to their contact with healthcare system (30.4% health-care related and 6.6% hospital-acquired).

Among the 653 patients who received active cancer therapy during the study period, 3.7% (24/653) developed COVID-19 and required admission, 4.2% (16/378) of those who received chemotherapy, 9.5% (6/63) of those receiving immunotherapy and 2.1% (2/97) of those treated

Table I General Characteristics of the Series

Variables	Other Cancer Patients, N=34 (%)	Lung Cancer Patients, N=12 (%)
Gender (male)	18 (52.9)	6 (50.0)
Age at hospitalization, years, mean (SD)	63.9 (10.2)	63.5 (15.5)
Active Smoking	0 (0.0)	2 (16.7)
Ex-smokers	12 (35.3)	6 (50.0)
Comorbidities		
Coronary heart disease	3 (8.8)	2 (16.7)
Hypertension	12 (35.3)	5 (41.7)
Hypothyroidism	3 (8.8)	0 (0.0)
COPD*	3 (8.8)	2 (16.7)
Obesity	2 (5.9)	0 (0.0)
Diabetes	6 (17.7)	0 (0.0)
Dyslipidemia	8 (23.5)	3 (25.0)
Stage		
I	6 (17.7)	0 (0.0)
II	5 (14.7)	0 (0.0)
III	5 (14.7)	6 (50.0)
IV	18 (52.9)	6 (50.0)
Lines of treatment		
First line	18 (52.9)	5 (41.7)
Other lines	8 (23.5)	5 (41.7)
Pending treatment	8 (23.5)	2 (16.7)
Recent cancer treatment <30d		
Active treatment	11 (32.3)	8 (66.7)
Last oncologic treatment		
Chemotherapy	14 (42.4)	2 (20.0)
Immunotherapy	1 (3.0)	5 (50.0)
Radiotherapy	3 (9.1)	0 (0.0)
Surgery	5 (15.2)	3 (30.0)
Others	10 (30.3)	0 (0.0)
Oncological situation		
Complete response	17 (50.0)	3 (25.0)
Partial response	1 (2.9)	4 (33.3)
Stable disease	1 (2.9)	2 (16.7)
Progression	10 (29.4)	1 (8.3)
Best supportive care	2 (5.9)	1 (8.3)
Others	3 (8.8)	1 (8.3)

Abbreviation: *COPD, chronic obstructive pulmonary disease.

with targeted therapies. The remaining cancer patients admitted with COVID-19 were receiving palliative care (6.6%) or were in complete response (43.5%).

Lung and breast cancer were the most frequent cancer types (26.1%), followed by colorectal cancer (19.6%). More than a half (52%) were stage IV. Although 19 (41.3%) had received cancer therapy during the last 30 days, only 2 (4.6%) had neutropenia below 1000 neutrophils/mL at COVID-19 presentation, and none of them received granulocyte colony-stimulating factor (G-CSF).

Of the 7 cancer patients who died from the infection, 3 patients had lung cancer and 4 patients other types of cancer.

Table 2 shows the main symptoms developed by the oncological patients as a result of the SARS-CoV-2, and the radiological and analytical findings that determine the prognosis. ARDS developed in 21.7%; however, only 1 case required noninvasive mechanical ventilation (NIMV) and 2 (4.3%) were admitted to ICU and required mechanical ventilation. None of our patients presented thrombotic events.

Different treatment options received during the SARS-CoV-2 infection are presented in Table 3.

Table 4 presents the results of the univariate analysis comparing patients who developed a serious event to those who did not, according to baseline characteristics at admission. Each increase in the Brescia, the CURB-65 scale, elevated lactate dehydrogenase (LDH) and elevated C-reactive protein (CRP) on admission were statistically associated with developing a serious event.

Other variables such as age, sex, type of cancer, recent therapy or active therapy were not independent predictors of serious events in the present study.

The median time from admission to discharge was 7 days (P25; P75: 4; 14 days) and 3 days from admission to death.

Discussion

In our series, the mortality among SARS-CoV-2 infected patients with or without cancer was not significantly different, overall in-hospital mortality of cancer patients with COVID-19 was 15.2% (95% CI, 6.3; 5.2) (7/46), similar to 12.7% (95% CI, 11.1; 4.4) (216/1700) of the global COVID-19 hospitalized population and greater than that of patients admitted without SARS-CoV-2 infection during the same period 4.3% (95% CI; 3.6; 5.2) (108/2520).

Table 2 Symptoms at Diagnosis and Prognostic Data

Symptoms	Other Cancer Patients (N=34)	Lung Cancer Patients (N=12)	P-value
Neutropenia	2 (6.1)	0 (0.0)	1.000
Cough	23 (67.6)	5 (41.7)	0.170
Fever	26 (76.5)	9 (75.0)	0.918
Temperature	37.1 (1.0)	37.3 (1.1)	0.360
Dyspnea	16 (47.0)	11 (91.7)	0.007
Diarrhea	3 (8.8)	1 (8.3)	1.000
Lymphopenia	22 (68.7)	4 (36.4)	0.080
Alteration liver function	3 (9.4)	2 (18.2)	0.589
Alteration kidney function	4 (12.5)	2 (18.2)	0.637
Radiological characteristics			0.726
Bilateral pneumonia	23 (71.9)	8 (72.7)	
Unilateral pneumonia	6 (18.7)	3 (27.3)	
Normal	3 (9.4)	0 (0.0)	
Prognostic criteria			
IL6			0.416
<4.4 pg/mL	28 (82.3)	8 (66.7)	
≥4.4 pg/mL	6 (17.7)	4 (33.3)	
D-DIMER	0.9 (0.6; 2.2)	0.9 (0.5; 2.7)	0.574
<0.5 ng/mL	5 (17.9)	3 (27.3)	0.761
0.5–7 ng/mL	22 (78.6)	8 (72.7)	
>7 ng/mL	1 (3.5)	0 (0.0)	
CRP		107.7	0.449
<10 mg/L	7 (21.9)	1 (9.1)	
10–150 mg/L	16 (50.0)	8 (72.7)	
>150 mg/L	9 (28.1)	2 (18.2)	
LDH	266 (207; 326)	290 (238; 352)	0.195
<246 U/L	14 (46.7)	3 (27.3)	0.309
≥246 U/L	16 (53.3)	8 (72.7)	
Ferritin	562 (358; 933)	1111 (392; 2672)	0.158
Charlson index*	8 (6; 9)	8 (6; 9)	0.800
CURB-65 scale**			0.314
0–1	21 (61.8)	5 (41.7)	
≥2	13 (38.2)	7 (58.3)	
Brescia scale***			0.178
0–1	30 (88.2)	8 (66.7)	
≥2	4 (11.8)	4 (33.3)	

Notes: *Charlson index (Comorbidities index), **CURB-65 scale (includes age, confusion, urea, breathing frequency, blood pressure), Brescia scale*** (depends on oxygen needs). p-values correspond to comparison between lung cancer patients and the other types of cancer.

Abbreviations: CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 3 Treatment Received During the COVID-19

Treatments	Other Cancer Patients (N=34)	Lung Cancer Patients (N=12)	p-value
Hydroxychloroquine	31 (91.2)	11 (100)	0.565
Lopinavir/ritonavir	18 (52.9)	6 (54.5)	1.000
Interferon	3 (8.8)	3 (27.3)	0.146
Systemic Corticosteroids	12 (35.3)	6 (54.5)	0.304
Tocilizumab	2 (5.9)	1 (9.1)	1.000
Anakinra	1 (2.9)	1 (8.33)	0.458

Table 4 Univariate Analysis Comparing Patients with Serious Event vs Non-Serious Event

Variable	N Valid (N=46)	Non Serious Event (N=38)	Serious Event (N=8)	p-value	OR (95% CI)
Gender (male)	46	20 (52.6)	4 (50.0)	0.892	0.9 (0.19; 4.14)
Age at hospitalization (years)	40	63.2 (11.6)	67 (11.4)	0.376	1.04 (0.96; 1.21)
Active Smoking	46	2 (5.3)	0 (0.0)	1	–
Ex-smokers	46	16 (42.1)	2 (25.0)	0.453	0.46 (0.08; 2.57)
Heart disease	46	4 (10.5)	1 (12.5)	0.871	1.21 (0.12; 15.57)
Hypertension	46	14 (36.8)	3 (37.5)	0.972	1.02 (0.21; 4.97)
Hypothyroidism	46	3 (7.9)	0 (0.0)	1	–
COPD*	46	4 (10.5)	1 (12.5)	0.871	1.21 (0.12; 12.57)
Obesity	46	2 (5.3)	0 (0.0)	1	–
Diabetes	46	6 (15.8)	0	0.571	–
Dyslipidemia	46	10 (26.3)	1 (12.5)	0.418	0.40 (0.04; 3.67)
First ferritin	27	562 (377; 1111)	903 (614; 1130)	0.757	1.00 (0.99; 1.00)
Higher ferritin	26	598 (382; 1111)	975 (903; 2403)	0.396	1.00 (0.99; 1.00)
First IL6 \geq 4.4 pg/mL	46	7 (18.4)	3 (37.5)	0.246	2.6 (0.51; 13.83)
Higher IL6 \geq 4.4 pg/mL	46	8 (21.1)	3 (37.5)	0.330	2.2 (0.44; 11.48)
First D-Dimer	39	0.8 (0.6; 1.9)	1.7 (0.6; 2.7)	0.133	1.38 (0.90; 2.11)
Higher D-Dimer	41	1.1 (0.7; 2.2)	2.6 (1.5; 5.6)	0.069	1.39 (0.97; 1.99)
First LDH**	41	254 (195; 316)	354 (266; 441)	0.020	1.01 (1.00; 1.03)
Higher LDH	40	271 (227; 332)	619 (354; 812)	0.007	1.01 (1.00; 1.03)
First CRP***	43	95 (11; 146)	169 (89; 228)	0.038	1.01 (1.00; 1.02)
Higher CRP	42	116 (43; 167)	202 (130; 249)	0.018	1.02 (1.00; 1.03)
Brescia	44	0.5 (0; 1)	2 (2; 5)	0.004	19.5 (2.54; 149.7)
CURB-65	42	1 (1; 2)	2 (1; 3)	0.060	2.41 (0.97; 6.03)

Abbreviations: *COPD, chronic obstructive pulmonary disease; **LDH, lactate dehydrogenase; ***CRP, C-Reactive protein.

No association was found between the oncological treatment and the development of a serious event linked SARS-CoV-2 infection. Nor were any objective analytical data easily identifiable in the clinic observed. In our opinion, the management of cancer patients with SARS-CoV-2 infection should not differ from those who do not have cancer.

The higher mortality in men compared to women and the apparent greater tendency to admission among patients undergoing immunotherapy remain to be investigated, but the small sample size does not allow more than hypothesis. In two independent cohorts of patients with heart failure, plasma concentrations of angiotensin-converting enzyme 2 (ACE2) were higher in men than in women, and these data might explain the higher incidence and fatality rate of COVID-19 in men.¹⁰

No significant differences have been found between lung cancer patients with SARS-CoV-2 infection admitted with the rest of the cancer patients and SARS-CoV-2 infection in any of the parameters studied, or in the treatments received. However, the highest mortality rate has been in patients with lung cancer, although no differences were found in the objective data at admission.

No clear association has been found between the severity of the infection and the specific cancer treatment received, paying special attention to immunotherapy. Other authors also do not find that immunotherapy has a clear impact on the severity of the infection.¹¹

Our mortality rate in patients with lung cancer (25%) is similar to what has been reported by the Memorial Sloan group in New York, which is 24%, with similar treatments for infection, even in ICU access. The mortality, in patients with thoracic cancer, reported in the Thoracic Cancers International COVID-19 Collaboration (TERAVOLT) registry, was 33%.¹² We know the role of Neuropilin-1 (NRP1), a member of a family of signaling proteins that facilitates SARS-CoV-2 cell entry and provides a possible pathway into the central nervous system. NRP1 is abundantly expressed in the respiratory and olfactory epithelium. NRP1 is highly expressed in lung cancer compared with normal lung.¹³ NRP1 is a cancer invasion and angiogenesis enhancer. NRP1 expression is an independent predictor of cancer relapse and poor survival in NSCLC patients.¹⁴

Even though it is difficult to have any conclusion with a small cohort of patients, other studies have supported the lack of information and the vulnerability of cancer patients in China⁷ as well as in Europe,¹⁵ including age, gender and comorbidities as COVID-19 related deaths. However, larger studies on cancer patients and SARS-COV-2 infected

patients have demonstrated that cancer types, cancer stage and cancer treatment contribute to severe event development.¹⁶

Our series has a clear selection bias since only patients with confirmed infection by PCR and who were admitted to the hospital due to the need for respiratory support and a serious situation have been studied. Those SARS-CoV-2 infected patients without admission are not represented, so the selection is among those with the worst prognosis. Mortality could not be higher since all cancer patients at the center have access to treatment and hospitalization without any limitation, beyond the medical one.

We could suspect COVID-19 if leukopenia or lymphopenia are present, as well as elevated transaminases, CRP, d-dimer, ferritin and LDH.¹⁷ In addition, an increase in interleukin 6 could be observed during the cytokine storm and could be considered a systemic disease indicator, including renal or cardiogenic failure.¹⁸

In our series, both the Brescia index and LDH, CPR, and to a lesser extent, CURB-65 are associated with a worse prognosis and a greater possibility of developing serious events. We believe that these clinical and analytical alterations have a greater prognostic value for a torpid evolution than the location of the tumor, taking into account that some of the symptoms may be associated with lung cancer and they force us to make a differential diagnosis with it.¹⁹

Other symptoms that do not normally appear in lung cancer patients could be helpful, as diarrhea, that appeared in a small percentage of our patients, or other digestive symptoms, such as headache, anosmia or ageusia, among others.²⁰

Reviewing the bibliography, we question the recommendation about using prophylactic G-CSF in some guidelines when, for example, pembrolizumab plus chemotherapy has around 5% of febrile neutropenia²¹ and no febrile neutropenia has been found among our patients.

On the contrary and according to the results obtained in our series, those patients with high LDH or CRP levels, high Brescia or CURB-65 should be considered as a population with a high risk of death or serious event in cancer patients and should be evaluated early for ICU admission.

Conclusions

Patients with cancer, especially lung cancer, and SARS-CoV-2 infection have a worse overall prognosis than the general population. Objective parameters such as LDH, CRP at admission, Brescia index or CURB-65 should alert us to a more

serious evolution and suggest an early admission to the intensive care unit.

Ethics Approval

The study was evaluated by the Ethical Committee of Hospital Universitario Puerta de Hierro de Majadahonda, Madrid.

Our Institutional Ethics Review Board approved the study and waived the need for informed consent.

The study was carried out following the Declaration of Helsinki on Good Clinical Practices and Organic Law 3/2018, 5th December on Protection of Personal Data and digital rights that were guaranteed during the study.

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Author Contributions

All authors made substantial contributions to the conception or design of the work and the acquisition, analysis and interpretation of data; drafted the work and revised it critically for important intellectual content; approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

Dr. Provencio has received personal fees from Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Roche, AstraZeneca and Takeda.

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The other authors have no conflicts of interest to declare.

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