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A snapshot of COVID-19 infection in patients with solid tumors

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Abstract

Coronavirus disease 2019 (COVID-19) pandemic is affecting a high percentage of the population at an unprecedented rate. Cancer patients comprise a subgroup especially vulnerable to this infection. Herein, we present a prospective analysis of epidemiological, clinical, radiological and laboratory data of consecutive adult cancer patients seen in the Clínico San Carlos University Hospital (Madrid, Spain), and admitted to hospital and tested for COVID-19 between 21 February 2020 and 8 May 2020 due to clinical suspicion of infection. Data from 73 patients with confirmed COVID-19 and active solid tumors or diagnosed within the previous 5 years were analyzed. The most frequent malignancy was lung cancer (19%) and 54 patients (74%) were on active cancer treatment. Most common findings on presentation included cough (55%), fever (52%) and dyspnea (45%), and 32 (44%) patients showed oxygen saturation levels below 95%. Radiologically, 54 (73%) patients presented an abnormal pattern, the most frequent being infiltrates (64%). 18 (24.7%) patients died in hospital and 55 (75.3%) were discharged with clinical resolution of the event. Multivariable logistic regression adjusted for age and tumor stage showed higher odds of in-hospital death associated with a history of cardiovascular disease, hospitalization in the previous 30 days, and several features on admission including dyspnea, higher qSOFA score, higher C-reactive protein levels and an abnormal neutrophil count. We present prospective, real-world evidence that can help articulate cancer care protocols for patients infected with SARS-CoV-2, with special focus on features on admission that can stratify patients with a higher risk of death from COVID-19.

1 | INTRODUCTION

In December 2019, a respiratory infectious process of unknown cause was reported in the Chinese Province of Wuhan.[1] A month later, a new coronavirus was identified as the causative pathogen of this condition and named as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), after the coronavirus responsible for the SARS

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ICU, intensive care unit; OR, odds ratio; PCR, polymerase chain reaction; qSOFA, Quick Sepsis-Related Organ Failure Assessment; REDCap, Research Electronic Data Capture; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

outbreak of 2003, to which it is genetically related.[2,3] In February 2020, the World Health Organization designated this disease as COVID-19. Although transmission appeared to start from animals, with bat as the candidate reservoir for the virus, person-to-person transmission was reported in a Wuhan seafood and wild animal trade market.[4,5] The clinical picture of COVID-19 encompasses different levels of severity, with most of those infected being asymptomatic or showing mild respiratory symptoms. However, the conjunction of a high transmissibility and a significant incidence of acute respiratory distress syndrome (ARDS) can ultimately lead to high hospitalization rates and nonnegligible mortality.[6-9] There are scarce data about how the virus behaves in the cancer population, who usually harbor dysfunctional immune systems, and particularly in those exposed to active chemotherapy or biological agents. Epidemiological research conducted in the Chinese population has indicated a higher incidence of infection (1% vs 0.29%) as well as a higher mortality rate (39% vs 8%).[10] Similarly, Zhang et al reported a retrospective cohort of 28 cancer patients, in which 28.6% experienced a composite endpoint including Intensive Care Unit (ICU) referral, use of mechanical ventilation or death.[11] The largest available cohort to date, composed of 928 individuals from United States, Canada and Spain, showed a mortality rate of 13% at study cutoff.[9] However, it remains unclear if cancer treatments could increase the risk of COVID-19.[12]

Here, we analyzed a prospective series of patients with solid tumors and infected with SARS-CoV-2 in a large urban area of Western Europe (Madrid, Spain).

What's new?

This report provides prospective data about cancer patients with COVID-19 in a situation of maximum pressure on the healthcare system of a large urban area in Western Europe. Despite a milder clinical profile on presentation, in-hospital mortality of COVID-19 was higher in cancer patients than in the general population. The mortality risk was associated with a history of cardiovascular disease and several variables on admission, but seemed not to be influenced by tumor type or anti-tumor therapy. The evidence could help articulate cancer care protocols for patients infected with SARS-CoV-2 and identify patients with a higher risk of in-hospital death.

2 | METHODS

2.1 | Study design and participants

This prospective study included consecutive cases of adult solid cancer patients diagnosed with SARS-CoV-2 infection at the Medical Oncology Department and/or Emergency Department of the Clínico San Carlos University Hospital (Madrid, Spain), between 21 February 2020 and 8 May 2020. Inclusion criteria for analysis were positive testing for COVID-19 and active cancer on treatment or cancer diagnosis in the previous 5 years regardless of cancer treatment.

A specific area in our outpatient facility was enabled in order to evaluate suspicious cases for COVID-19. Patients were actively interrogated for signs and symptoms of COVID-19 infection and contact history with positive patients before their scheduled appointment at the Medical Oncology Department. Particularly, patients were assessed for the following: (a) fever (37.5°C), cough, difficulty breathing, headache, sore throat/trouble swallowing, runny nose, loss of taste or smell, nausea/vomiting/diarrhea in the last 14 days; (b) close contact with someone who is sick or has confirmed COVID-19 in the previous 14 days; (c) travel to/from high-risk areas in the previous 14 days before symptom onset. Suspicious cases were referred to the Emergency Department for screening, and positive tested patients were admitted and/or treated according to the Internal Management Protocol for COVID-19 disease of our institution. Microbiological assessment of SARS-CoV-2 infection was performed using real-time PCR analysis of nasopharyngeal and/or pharyngeal swabs. The primary outcome was all-cause in-hospital mortality for both descriptive and analytical purposes. Mechanical ventilation or ICU referral were not explored as endpoints given the low number of cases occurring. This could be considerably attributed to the shortage of health resources at that time of the outbreak and would confound results. Clinical information and laboratory and radiological findings were prospectively collected from electronic medical records. All data were checked by at least two researchers, and a third researcher (AM) decided on conflicting information. This study was approved by the Ethics Committee of the Clínico San Carlos University Hospital. Written informed consent was not required given the emergency of the current pandemic.

2.2 | Study definitions

Fever was defined as the presence of a temperature equal to or greater than 37.5°C. Cut-off values in laboratory data for analytic purposes were based in those defined by the internal protocol of our institution and international clinical standards. Cardiovascular disease indicates a composite of ischemic heart disease, arrhythmia, cerebrovascular disease and thromboembolism. CURB65 is a widely used mortality prediction score in patients with community-acquired pneumonia.[13] Quick Sepsis-related Organ Failure Assessment (qSOFA) is the recommended score to assess high-risk patients for in-hospital mortality with suspected infection outside ICU units.[14] High-dose steroids were defined as a dose of more than 1.5 mg per kg of methylprednisolone daily or equivalent steroid dose.

2.3 | Statistical analysis

Clinical data and results from complementary tests were stored and managed using a Research Electronic Data Capture (REDCap)

TABLE 1 Demographic, baseline and oncological characteristics of cancer patients admitted with COVID-19

	Total (N = 73)	Survivor (N = 55)	Nonsurvivor (N = 18)	Unadjusted *P* value
Population demographic and base line clinical characteristics				
Age, years	72 (59–82)	72 (60-81)	72 (55-84)	.95
<50	9 (12%)	6 (11%)	3 (17%)	.50
50 to 75	33 (45%)	27 (49%)	6 (33%)	
>75	31 (43%)	22 (40%)	9 (50%)	
Male sex	41 (56%)	33 (60%)	8 (44%)	.37
Hospital admission in previous 30 days	24 (33%)	14 (25%)	10 (56%)	.038
Current tobacco use	7/70 (10%)	5/53 (9%)	2/17 (12%)	1
Comorbidity	53 (73%)	40 (72%)	13 (72%)	
Cardiovascular disease	20 (27%)	11 (20%)	9 (50%)	.029
Hypertension	32 (44%)	24 (44%)	8 (44%)	1
Diabetes mellitus	20 (27%)	15 (27%)	5 (28%)	1
Chronic liver disease	3 (4%)	2 (4%)	1 (6%)	1
Chronic kidney disease	5 (7%)	4 (7%)	1 (6%)	1
Chronic lung disease (COPD, asthma)	7 (10%)	5 (9%)	2 (11%)	1
Neuromuscular disease	2 (3%)	1 (2%)	1 (6%)	.43
Primary immunodeficiency	3 (4%)	1 (2%)	2 (11%)	.14
≤2	59 (80%)	47 (85%)	12 (67%)	.11
>2	13 (18%)	7 (13%)	6 (33%)	
Tumor diagnosis and treatment				
Tumor type				
Lung	14 (19%)	9 (16%)	5 (28%)	.29
Breast	10 (14%)	6 (11%)	4 (22%)	
Colorectal	9 (12%)	9 (16%)	0	
Urothelial	9 (12%)	7 (13%)	2 (11%)	
Head and neck	5 (7%)	3 (5%)	2 (11%)	
Other	26 (36%)	21 (38%)	5 (28%)	
Tumor stage				
I-III	28 (38%)	23 (41%)	5 (28%)	.41
IV	45 (63%)	32 (59%)	13 (72%)	
Cancer treatment				
On-treatment	54 (74%)	37 (67%)	17 (94%)	.029
Time from last treatment to admission, days	10 (1–33)	9 (6-42)	17 (1-21)	.11
Follow-up only	19 (26%)	18 (33%)	1 (6%)	
Time from last treatment to admission, days	413 (165-898)	427 (201-902)	75	.32
History of previous treatment				
Surgery	35 (48%)	28 (51%)	7 (39%)	.53
Chemotherapy	37 (51%)	28 (51%)	9 (50%)	.53
Radiotherapy	10 (14%)	8 (15%)	2 (11%)	1
Immunotherapy	12 (16%)	7 (13%)	5 (28%)	.15
Targeted therapy	9 (12%)	6 (11%)	3 (17%)	.68
Hormonotherapy	9 (12%)	5 (9%)	4 (22%)	.21
Number of treatment lines	1 (0)	1 (1–1)	1 (1–1)	.49
≤2	67 (91%)	51 (93%)	16 (89%)	.28
>2	6 (8%)	4 (7%)	2 (11%)	

(Continues)

TABLE 1 (Continued)

	Total (N = 73)	Survivor (N = 55)	Nonsurvivor (N = 18)	Unadjusted *P* value
Current treatment				
Chemotherapy	27 (37%)	18 (33%)	9 (50%)	.3
Last dose <14 days	14 (44%)	10 (42%)	4 (50%)	1
Immunotherapy	11 (15%)	6 (11%)	5 (28%)	.12
Last dose <14 days	3 (30%)	2 (40%)	1 (20%)	1
Radiotherapy	6 (8%)	3 (5%)	3 (17%)	.15
Targeted therapy	10 (14%)	7 (13%)	3 (17%)	.70
Hormonotherapy	10 (14%)	7 (13%)	3 (17%)	.70

Note: Data are median (IQR), n (%) or n/N (%). *P* values were calculated by using the chi-square test (or Fisher's exact test) or the Mann–Whitney *U* test, as appropriate.

database.[15,16] Continuous variables were presented as median (IQR) and n (%), respectively. We used the Mann-Whitney *U* test, chi-square test or Fisher's exact test to compare differences between survivors and nonsurvivors where appropriate. Due to the short-term evolution of the disease, we did not use the actuarial method to perform a survival analysis. To explore the risk factors associated with in-hospital death, univariable and multivariable logistic regression models were used. All variables that reported $P < .10$ in univariate logistic regression were included in the multivariate analysis adjusting for age and tumor stage (localized vs disseminated). Odd ratios with 95% confidence intervals were calculated to assess the relative risk of each variable. All statistical tests were two-tailed, and a *P* value of <.05 was considered statistically significant. Statistical analyses were performed using R v3.6.3 under R-Studio 1.1.383 (R Development Core Team Vienna, Austria; https://www.r-project.org).

3 | RESULTS

3.1 | Demographic and clinical characteristics

A total of 95 patients with solid tumors tested positive for COVID-19 infection during the study period. Of those, 73 (77%) were on cancer treatment or had had a tumor diagnosis within the last 5 years and composed the final cohort of the study.

The median age of the 73 patients was 72 years (IQR 59-82), and 41 (56%) were males (Table 1). Fifty-three (73%) patients had at least one comorbidity other than cancer, with 13 (18%) presenting more than two. The most frequent comorbidities were hypertension (44%), diabetes mellitus (27%) and cardiovascular disease (27%). The most common tumor type was lung cancer (19%), followed by breast (14%), colorectal (12%), urothelial (12%), and head and neck tumors (7%). Most patients had metastatic disease (63%), and 54 (74%) were under active treatment. In those, median time from last treatment administration to admission was 10 days (1-33). Twenty-four (33%) patients had been hospitalized for any reason within 30 days before the admission for COVID-19.

3.2 | Clinical features at admission and laboratory and radiological findings

The main clinical, laboratory and radiological findings at hospital admission are collected in Table 2. The median time from symptoms onset to admission was 3.5 days (IQR 1.3-7), and, similarly, time from symptoms onset to positive testing was 3 days (IQR 1-8). 40 (55%) patients presented with cough, 38 (52%) with fever and 33 (45%) with dyspnea. Asthenia was also a recurrent symptom in our cohort (37%). The median oxygen saturation was 95% (IQR 89-96), and 31 (42%) patients required oxygen supplementation at the time of admission, while only 1 patient was diagnosed with acute respiratory distress syndrome (ARDS) as initial presentation. The median CURB65 score was 1 (IQR 1-2) and the median qSOFA was 0 (IQR 0-1). Neutropenia and neutrophilia occurred in 5 (7%) and 13 (18%) patients, respectively, whereas lymphocytopenia was observed in 34 (46%) patients. Pulmonary infiltrates indicating pneumonia were evident in 47 (64%) patients, being bilateral infiltration the most common radiographic pattern on admission. Importantly, 19 (26%) patients displayed no imaging abnormalities.

3.3 | Treatments and outcomes

Treatment schemes were selected and administered according to the internal protocol of our institution. 59 (81%) patients received hydroxychloroquine and 44 (60%) patients received antibiotics, being the most frequent choices of therapy (Table 2, Figure S1). The median length of hospital stay was 7 days (IQR 4-11). Fifty-five (75%) patients were discharged and 18 (25%) died in hospital, 4 of them for causes other than COVID-19 infection, including tumor progression and sepsis secondary to malignant wound infection (Table S1). Only one patient was admitted in the ICU and could be successfully extubated and eventually discharged.

3.4 | Risk factors

A multivariate logistic regression analysis was performed adjusting for age and tumor stage (Table 3). Increased odds of in-hospital mortality

TABLE 2 Clinical, laboratory, radiological features and outcome of cancer patients admitted with COVID-19

	Total (N = 73)	Survivor (N = 55)	Nonsurvivor (N = 18)	Unadjusted *P* value
Clinical presentation on admission				
Symptoms				
Dyspnea	33 (45%)	18 (33%)	15 (83%)	.0003
Headache	3 (4%)	3 (5%)	0	1
Myalgia	11 (15%)	10 (18%)	1 (6%)	.44
Asthenia	27 (37%)	21 (38%)	6 (33%)	.65
Cough	40 (55%)	29 (53%)	11 (61%)	.73
Sputum	14 (19%)	12 (22%)	2 (11%)	1
Diarrhea	16 (22%)	11 (20%)	5 (28%)	,52
Nausea/vomiting	10 (14%)	7 (13%)	3 (17%)	.70
Signs				
Fever	38 (52%)	27 (49%)	11 (61%)	.54
Acute renal failure	4 (5%)	4 (7%)	0	.55
Oxygen saturation	95 (89.0-96.0)	95 (92-97)	89 (84-95)	.004
<95%	32 (44%)	21 (38%)	11 (61%)	.17
≥95%	40 (55%)	33 (61%)	7 (39%)	
Need for oxygen supply	31 (42%)	19 (35%)	12 (67%)	.52
Nasal cannula	18/31 (58%)	12/19 (63%)	6/19 (50%)	
Venturi mask	8/31 (11%)	5/19 (26%)	3/19 (25%)	
Reservoir mask	5/31 (7%)	2/19 (11%)	3/19 (25%)	
ARDS	1 (1%)	0	1 (6%)	.26
CURB65 score	1 (1–2)	1.5 (0.5-2)	1 (1–2)	.50
0	10/51 (19%)	10/39 (26%)	0	.23
1	20/51 (39%)	13/39 (33%)	6/12 (58%)	
2	18/51 (35%)	13/39 (33%)	5/12 (42%)	
3	2/51 (4%)	2/39 (5%)	0	
4	1/51 (2%)	1/39 (2%)	0	
5	0	0	0	
qSOFA score	0 (0–1)	0 (0–0)	1 (0–1)	.001
0	48 (66%)	42 (76%)	6 (33%)	.024
1	21 (29%)	11 (20%	10 (56%)	
2	4 (5%)	2 (4%)	2 (11%)	
3	0	0	0	
Imaging findings on admission				
Imaging technique				
X-ray	59 (81%)			
Computed tomography	14 (19%)			
Imaging findings				
Normal	19 (26%)	14 (26%)	5 (28%)	.48
Infiltrate	47 (64%)	36 (65%)	11 (61%)	
Unilobar infiltrate	13 (18%)	10 (18%)	3 (17%)	
Bilobar infiltrate	4 (5%)	4 (7%)	0 (0.0)	
Bilateral infiltrates	30 (41%)	22 (40%)	8 (44%)	
Interstitial pattern	1 (1%)	0 (0.0)	1 (6%)	
Other	6 (8%)	5 (9%)	1 (6%)	

(Continues)

TABLE 2 (Continued)

	Total (N = 73)	Survivor (N = 55)	Nonsurvivor (N = 18)	Unadjusted *P* value
Laboratory findings on admission				
Lymphocyte count, $\times 10^9$ per L	0.8 (0.5-1.2)	0.65 (0.35-1.05)	0.8 (0.6-1.2)	.21
≤0.8	34 (46%)	23 (42%)	11 (61%)	.27
>0.8	39 (54%)	32 (58%)	7 (39%)	
Neutrophil count, $\times 10^9$ per L	4.75 (2.9-6.4)	4.1 (2.75-5.77)	5.7 (4.8-7.9)	.08
<1.5	5 (7%)	2 (4%)	3 (17%)	
1.5-7	55 (75%)	45 (82%)	10 (56%)	.038
>7	13 (18%)	8 (14%)	5 (28%)	
Hemoglobin, g/L	12.6 (10.75-13.8)	13.05 (11.4-13.9)	11.2 (10.2-12.5)	.022
Platelet count, $\times 10^9$ per L	185.0 (120.0-256.0)	204.0 (126.0-269.0)	182.0 (108.2-198.2)	.15
≤150.0	26 (36%)	19 (35%)	7 (39%)	1
>150.0	47 (64%)	36 (65%)	11 (61%)	
C-reactive protein, mg/dL	5.08 (1.96-11.73)	3.65 (1.41-8.41)	11.3 (4.35-15.4)	.007
≤10	50/72 (69%)	43/54 (78%)	7/18 (39%)	.003
>10	22/72 (39%)	11/54 (20%)	11/18 (61%)	
Procalcitonin, ng/mL	0.11 (0.06-0.21)	0.09 (0.06-0.19)	0.21 (0.11-0.27)	.004
≤1	64/67 (95%)	51/51 (100)	13/16 (81%)	.012
>1	3/67 (5%)	0 (0.0)	3/16 (19%)	
Ferritin, μg/L	432 (237-1158)	412 (222-1108)	963 (436-1508)	.09
≤1000	40/57 (71%)	33/45 (73%)	7/12 (58%)	.48
>1000	17/57 (29%)	12/45 (26%)	5/12 (42%)	
D-dimer, μg/mL	1108 (703-2048)	1070 (594-2022)	1615 (1013-2111)	.095
≤1000	23/56 (41%)	20/43 (46)	3/13 (23)	.20
>1000	33/56 (58%)	23/43 (53)	10/13 (77)	
Lactate dehydrogenase, U/L	692 (519-900)	644 (498-802)	754 (599-984)	.069
≤500	13/68 (22%)	13/51 (26)	2/17 (12)	.32
>500	42/68 (72%)	38/51 (74)	15/17 (88)	
Troponin I, ng/mL	0.0 (0.0-0.02)	0 (0-0.018)	0.01 (0–0.02)	.45
ALT, U/L	29 (22-43)	27 (22-43)	35 (22-42)	.65
AST, U/L	23 (16-36)	23 (16-36)	25 (16-34)	.87
Clinical follow-up and in-hospital evolution				
Time from symptom onset to admission, days	3.5 (1.3-7)	4 (2-8)	3 (1-6)	.076
Time from symptom onset to positive test, days	3 (1-8)	4 (1-9)	2 (1-6)	.055
Hospital length of stay, days	7 (4–11)	8 (5-11)	6 (3-9)	.24
ICU referral	1 (1%)	1 (1%)	0	1
Treatments				
Hydroxychloroquine	59 (81)	47 (85)	12 (67)	.16
Lopinavir/ritonavir	24 (33%)	17 (31%)	7 (39%)	.74
High-dose steroids	14 (19%)	11 (20%)	3 (17%)	1
Interferon-beta	6 (8%)	2 (4%)	4 (22%)	.029
Antibiotics	44 (60%)	29 (53%)	15 (83%)	.026

Note: Data are median (IQR), n (%), or n/N (%). *P* values were calculated by using the chi-square test (or Fisher's exact test) or the Mann–Whitney *U* test, as appropriate. CURB65 score: confusion, blood urea nitrogen >19 mg/dL, respiratory rate ≥ 22, systolic blood pressure < 90 mmHg or diastolic ≤60 mmHg, age ≥ 65). qSOFA = Quick Sequential Organ Failure Assessment: Glasgow Coma Score < 15, systolic blood pressure ≤ 100 mmHg, respiratory rate ≥ 22. Abbreviations: ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; ICU, intensive care unit.

TABLE 3 Variables on admission associated with in-hospital death

	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Demographic and baseline clinical characteristics				
Cardiovascular disease	3.68 (1.21-11.48)	.022	4.44 (1.32-16.18)	.018
Hospitalization in previous 30 days	3.70 (1.28-11.11)	.017	3.45 (1.09-11.11)	.039
Active cancer treatment	8.33 (1.56-100)	.044	8.33 (1.25-100)	.065
Clinical presentation on admission				
Dyspnea	5.97 (1.81-23.82)	.006	6.3 (1.87–25.94)	.005
qSOFA score[a]	2.84 (1.18-7.34)	.023	2.87 (1.18–7.51)	.023
Laboratory findings on admission				
Procalcitonin, ng/mL				
≤1				
>1	10.93 (1.29-230.64)	.045	9.57 (1.07-208)	.064
C-reactive protein, mg/dL				
≤10				
>10	4.93 (1.65-15.57)	.005	4.54 (1.45–15.17)	.011
Neutrophil count, $\times 10^9$ per L				
<1.5				
1.5–7	6.25 (0.92-50)	.062	7.69 (1.04-100)	.049
>7				
Hemoglobin, g/L[b]	0.72 (0.52-0.94)	.025	0.73 (0.53-0.96)	.037

Abbreviations: OR, odds ratio; qSOFA, Quick Sequential Organ Failure Assessment.
[a]Per 1 unit decrease.
[b]Per 1 unit increase.

were associated with a previous history of cardiovascular disease (odds ratio [OR] 4.44, 1.32-16.18; *P* = .018), hospitalization in the previous 30 days (OR 3.45, 1.09-11.11; *P* = .039), and several variables on admission including dyspnea (OR 6.3, 1.87-25.94; *P* = .005), higher qSOFA score (OR 2.87, 1.18-7.51; *P* = .023), higher CRP levels (OR 4.54, 1.45-15.17; *P* = .011) and an abnormal neutrophil count (OR 7.69, 1.04-100; *P* = .049).

4 | DISCUSSION

This study shows the clinical characteristics and prognosis of 73 prospectively collected, confirmed COVID-19 patients with solid tumors, admitted during a short time frame in a tertiary university hospital and experienced a definite outcome. In sum, our observations depict a milder profile on presentation and yet a higher in-hospital mortality of COVID-19 compared to the general population. The risk of mortality was associated through logistic regression to a history of cardiovascular disease and to variables on admission including an abnormal neutrophil count, lower oxygen saturation levels, higher CRP levels and anemia, but seemed not to be influenced by any specific tumor type or antitumor therapy, nor by the time from its administration to the infection onset.

Clinical presentation typically consisted of fever, cough, dyspnea and/or asthenia, accompanied by oxygen saturation levels below 95%, and evidence of bilateral infiltrates in chest X-ray. However, cancer patients appeared less symptomatic on presentation than the general population (eg, fever 52% vs 83%-98.6%; cough 55% vs 59.4%-82%; pneumonia 73% vs 75%-100%), while showing similar laboratory findings with the exception of increased D-dimer levels.[6-8] Remarkably, most patients scored low (0-1) on both qSOFA and CURB65 scales on admission, suggesting that they were assessed at an early phase of the disease. This idea is reinforced by a median time from symptom onset to hospital admission of only 3.5 days (IQR 1.3-7.0).

We report an overall mortality rate of 24.7%, and COVID-19-related mortality of 19.2%, which clearly exceeds that of the general population (2%-3%), but is consistent with previous communications.[9,11,17] Although cancer patients are slightly older than the general population, the increased severity of the disease may rather rely on an impaired immune system.[10] Notably, the proportion of patients under active cancer treatment was higher among non-survivors (94% vs 67%, *P* = .029), which could be related to the debilitating and immunosuppressive effects of cytotoxic agents and the tumor itself. However, neither a specific type of therapy nor the time since the last administration were found associated with a poorer prognosis. Also, we consider our population to be at a higher risk group than the cohorts of Zhang et al and Kuderer et al, according to their older age (median age 72 years vs 65 and 66 years), frequency of comorbidities (at least one, 73% vs 39.2% and 78%) and disease stage (stage IV, 66% vs 35%).[9,11] Importantly, in the early stages of

the COVID-19 pandemic, the city of Madrid faced a pressing shortage of available intensive care beds, which narrowed admission criteria and likely affected patient mortality. Furthermore, treatment schemes were subjected to constant update, and while most patients received hydroxychloroquine, only 19% received high-dose steroids and almost none received immunosuppressive agents, which might be more incisive in alleviating the inflammatory state (Figure S1).

We identified a previous history of cardiovascular disease (a composite of ischemic heart disease, arrhythmia, cerebrovascular disease and thromboembolism), low oxygen saturation levels and an abnormal neutrophil count as risk factors on admission for in-hospital mortality. Cardiovascular disease has been previously linked to a poor prognosis in the general population by Zhou et al (24% vs 1%, $P < .0001$), which could be explained by a fragile response of cardiac output to inadequate oxygenation and to septic and hypercoagulable states.[18-20] Similar to the study by Zhou et al, D-dimer levels greater than 1000 μg per mL appeared more frequently in nonsurvivors, although this difference did not reach statistical significance in our series. In addition, no ischemic or thrombotic complications were observed during hospitalization, and necropsies might be required to elucidate their actual incidence and severity. An abnormal neutrophil count was also associated with an increased risk of death. Neutropenia is usually elicited by cytotoxic agents and reflects the greater vulnerability and impaired immune response of cancer patients. Conversely, neutrophilia could indicate the concurrence of a bacterial infection as an aggravating factor in COVID-19. In this regard, higher levels of procalcitonin (>1 ng per mL in 19% vs 0; $P = .012$) and the administration of antibiotics (83% vs 53%; $P = .026$) were also linked to a worse prognosis. Although positive bacterial cultures were observed in only three patients with fatal outcome, these data may encourage the early use of empiric antibiotic regimens in cancer patients.

The fact that the clinical presentation of COVID-19 in cancer patients may be more subtle in spite of the increased in-hospital mortality rate stresses the potential benefit of a comprehensive screening strategy in the outpatient setting interrogating for signs, symptoms and epidemiological status. Nasopharyngeal PCR testing should be performed without delay in all suspicious cases and repeated judiciously including bronchoscopy if initial results are negative. Also, cancer patients hospitalized for any reason could benefit from regular tests (eg, weekly). We believe that our screening effort contributed to mitigate lethality, which was similar to existing reports despite the exceptional situation endured in the city of Madrid during the early stages of the outbreak. Moreover, our experience leads us to advocate for the earlier treatment with high-dose steroids to manage the critical proinflammatory phase of COVID-19, which is consistent with the preliminary results of the RECOVERY trial.[21] As a next step, we encourage that patients with severe respiratory disease, at high risk of residual fibrotic changes, remain under tight follow-up by the pneumologist.

This study has some limitations. First, generalization of our results might be limited by a modest sample size. We might have considerably reduced our population by excluding false-negatives, since PCR tests were not systematically repeated or complemented with quantitative viral RNA or serologies in highly suspicious negative patients, and the test performance might have been compromised by the early assessment of patients after symptom onset. Second, patients were not homogeneously treated. Although most of them received hydroxychloroquine, only a few received interferon-beta during the first days of outbreak, and high-dose steroids were included in treatment protocols in the last weeks of our observation period (Figure S1).

To the best of our knowledge, we report herein one of the largest prospective series of patients with solid tumors diagnosed with COVID-19 in Western Europe. We described the main clinical features on presentation and found that a history of cardiovascular disease, higher CRP levels and an altered neutrophil count on admission are associated with a higher risk of in-hospital death. No specific tumor type or oncological therapy had a significant effect on mortality. Our finding of a high proportion of suspected nosocomial cases may encourage the development of care protocols that ensure patient safety without compromising the quality of cancer treatment. A joint effort is required to establish evidence-based strategies for the management of COVID-19-positive cancer patients.

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No founding sources. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available within the article and/or its supplementary materials. Raw data compliant with the institutional and home country confidentiality policies can be available upon request from the corresponding author.

ETHICS STATEMENT

This study was approved by the Ethics Committee of the Clínico San Carlos University Hospital and performed in accordance with the Declaration of Helsinki. Written informed consent was waived given the emergency of the current pandemic.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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