SARS-CoV-2 Virus in Cancer Patients: A New Unknown in an Unsolved Equation

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Keywords
SARS-CoV-2 · Cancer · Oncologic treatments

Abstract
Introduction: Cancer patients are more susceptible to infections, and infection can be more severe than in patients without cancer diagnosis. We conducted this retrospective study in patients admitted for SARS-CoV-2 infection in order to find differences in inflammatory markers and mortality in cancer patients compared to others. Methods: We reviewed the electronic records of patients admitted for SARS-CoV-2 infection confirmed by PCR from March to September 2020. Data on socio-demographics, comorbidities, inflammatory makers, and cancer-related features were analyzed. Results: 2,772 patients were admitted for SARS-CoV-2, to the Hospital Universitario Ramón y Cajal in Madrid during this period. Of these, 2,527 (91%) had no history of neoplastic disease, 164 (5.9%) patients had a prior history of cancer but were not undergoing oncological treatment at the time of infection, and 81 (2.9%) were in active treatment. Mortality in patients without a history of cancer was 19.5%, 28.6% for patients with a prior history of cancer, and 34% in patients with active cancer treatment. Patients in active oncology treatment with the highest mortality rate were those diagnosed with lung cancer (OR 5.6 95% CI: 2.2–14.1). In the multivariate study, active oncological treatment (OR 2.259 95% CI: 1.35–3.77) and chemotherapy treatment (OR 3.624 95% CI: 1.17–11.17), were statistically significant factors for the risk of death for the whole group and for the group with active oncological treatment, respectively. Conclusion: Cancer patients on active systemic treatment have an increased risk of mortality after SARS-CoV-2 infection, especially with lung cancer or chemotherapy treatment.

Introduction
The emergence of a new betacoronavirus called SARS-CoV-2 since December 2019 and its rapid spread, causing the COVID-19 pandemic, has resulted in more than 700,000 deaths in Europe [1]. In some individuals, the vi-
rus triggers an exaggerated immune response through the expression of proinflammatory factors, such as increased synthesis of interferon I and stimulation of signaling pathways that activate phagocytosis, dendritic cell maturation, and immune cell chemotaxis, which contribute to virus control but also to tissue damage especially at the pulmonary level, leading to severe respiratory distress [2]. Given the damage that the uncontrolled immune reaction causes in patients, immunosuppressive agents such as tocilizumab have been added to the therapeutic arsenal against SARS-CoV-2 infection. In cancer patients, the immunosuppressed state caused by the disease itself and cancer treatments makes them more susceptible to infection and the prognosis is worse. Paradoxically, cancer patients in active treatment may be protected from the uncontrolled immune reaction caused by SARS-CoV-2, which causes severe respiratory distress. Thus, although several retrospective studies have shown a worse prognosis in patients diagnosed with cancer under active cancer treatment [3–9], other studies find a similar mortality rate [10], or even a lower percentage of hospital admissions in patients treated with targeted therapies [11].

In order to minimize the risk of infection and its severity, during the first months of the pandemic when vaccines were not yet available, different strategies were proposed in cancer patients. These strategies included modifications of cancer treatments that could affect their effectiveness, such as delaying adjuvant treatments. Elucidating which cancer patients have the highest morbidity and mortality from SARS-CoV-2 infection is important because these measures could be applied more selectively in case of a return to situations like the first months of the pandemic with no vaccine available due to new variants or new viruses. In this study, we analyzed the inflammatory profile and evolution of SARS-CoV-2 infection in patients admitted while undergoing active cancer treatment or prior history of cancer without oncologic treatment at the time of infection, compared to patients without a pre-existing history of neoplastic disease.

Table 1. Characteristic of patients

|                          | Nonhistory of cancer (n = 2,527) | Cancer survival (n = 164) | Active oncologic treatment (n = 81) | p value |
|--------------------------|---------------------------------|---------------------------|--------------------------------------|---------|
| Sex, n (%)               |                                 |                           |                                      |         |
| Male                     | 1,487 (58.8)                    | 115 (70)                  | 49 (60.5)                            | 0.01    |
| Female                   | 1,040 (41.2)                    | 49 (30)                   | 32 (39.5)                            |         |
| Age, median (IQR), years | 69 (55; 81)                     | 80 (70; 85)               | 71 (62; 79)                          | ns      |
| Age, median for death patients (IQR), years | 82 (73; 87) | 84 (79; 88)               | 71 (67; 83)                          | ns      |
| Comorbidities            |                                 |                           |                                      |         |
| Obesity, n (%)           |                                 |                           |                                      |         |
| No                       | 2,148 (85)                      | 136 (83)                  | 74 (91.4)                            | ns      |
| Yes                      | 379 (15)                        | 28 (17)                   | 7 (8.6)                              |         |
| Hypertension, n (%)      |                                 |                           |                                      |         |
| No                       | 1,434 (55.3)                    | 56 (34.1)                 | 42 (51.9)                            | 0.01    |
| Yes                      | 1,093 (43.3)                    | 108 (65.9)                | 39 (48.1)                            |         |
| Diabetes, n (%)          |                                 |                           |                                      |         |
| No                       | 2,061 (81.5)                    | 115 (70.1)                | 60 (74.1)                            | 0.04    |
| Yes                      | 466 (18.5)                      | 49 (29.9)                 | 21 (25.9)                            |         |
| Chronic kidney disease, n (%) |                        |                           |                                      |         |
| No                       | 2,330 (92.2)                    | 137 (83.5)                | 77 (95.1)                            | 0.01    |
| Yes                      | 197 (7.8)                       | 27 (16.5)                 | 4 (4.9)                              |         |
| Chronic cardiovascular disease, n (%) |                     |                           |                                      |         |
| No                       | 2,069 (81.9)                    | 100 (61)                  | 67 (82.7)                            | 0.01    |
| Yes                      | 458 (18.1)                      | 64 (39)                   | 14 (17.3)                            |         |
| Chronic pulmonary disease, n (%) |                      |                           |                                      |         |
| No                       | 2,245 (88.8)                    | 130 (79.3)                | 71 (87.7)                            | 0.01    |
| Yes                      | 282 (11.2)                      | 34 (20.7)                 | 10 (12.3)                            |         |
| Clinical outcomes        |                                 |                           |                                      |         |
| Discharge from hospital  | 2,034                           | 120                       | 54                                    | 0.01    |
| Death, n (%)             | 493 (19.5)                      | 44 (26.8)                 | 27 (33.3)                            |         |
| Site             | Patients in active treatment, N (%) | Cancer survival, N (%) |
|------------------|-------------------------------------|------------------------|
|                  | **N** (%), **Stage IV**, **N**      | **Death**, **OR (95% CI)** |
| Breast           | 19 (23)                             | 16 (9.7)               |
| Pegylated liposomal doxorubicin | 2 (5.8)                           |                        |
| Capecitabine     | 2 (5.8)                             |                        |
| Carboplatin; gemcitabine | 1 (2.9)                           |                        |
| Trastuzumab      | 1 (2.9)                             |                        |
| Exemestan palbociclib | 1 (2.9)                           |                        |
| Letrozole        | 8 (22.9)                            |                        |
| Tamoxifen        | 2 (5.7)                             |                        |
| Exemestan        | 1 (2.9)                             |                        |
| Surgery          | 1 (2.9)                             |                        |
| Death            | 3 (15.7) OR 0.7 (95% CI: 0.2; 2.6)  | 2 (12.5)               |
| Prostate         | 16 (19.3)                           | 32 (19.5)              |
| LHRH             | 10 (42)                             |                        |
| LHRH; docetaxel  | 1 (2.1)                             |                        |
| LH; RH; cabazitaxel | 1 (2.1)                           |                        |
| Darolutamide     | 1 (2.1)                             |                        |
| Surgery          | 1 (2.1)                             |                        |
| Death            | 6 (37.5) OR 2.4 (95% CI: 0.8; 6.8)  | 10 (31.2)              |
| Lung             | 10 (13.4)                           | 10 (6)                 |
| Carboptatin pemetrexed | 2                                  |                        |
| Carboplatin paclitaxel | 1                                  |                        |
| Durvalumab       | 2                                   |                        |
| Nivolumab        | 1                                   |                        |
| Pembrozipumab    | 2                                   |                        |
| Alectinib        | 1                                   |                        |
| Surgery          | 1                                   |                        |
| Death            | 7 (70) OR 9.6 (95% CI: 2.4; 37.3)   | 4 (40)                 |
| Colorectal       | 9 (10.8)                            | 35 (20.9)              |
| FOLFOX           | 2                                   |                        |
| FOLFOX; bevacizumab | 4                                   |                        |
| Capecitabine     | 1                                   |                        |
| Regorafenib      | 1                                   |                        |
| Surgery          | 1                                   |                        |
| Death            | 4 (44.4) OR 3.3 (95% CI: 0.8; 12.3) | 7 (20.6)               |
| Hematologic      | 8 (9.6)                             | 14 (8.6)               |
| Lenalidomide     | 3                                   |                        |
| Cyclophosphamide | 1                                   |                        |
| Cytarabine, idarubicin, IT | 1                                   |                        |
| Pomalidomide bortezomib | 1                                 |                        |
| Brentuximab      | 1                                   |                        |
| Cytarabine       | 1                                   |                        |
| Death            | 3 (37.5) OR 2.4 (95% CI: 0.5; 10.3) | 4 (28.5)               |
| Head and neck    | 4 (4.8)                             | 5 (3.1)                |
| Stage IV         | 2                                   |                        |
| CDPP radiotherapy | 1                                  |                        |
| Nivolumab        | 2                                   |                        |
| Surgery          | 1                                   |                        |
| Death            | 0                                   | 3 (60)                 |
| Kidney           | 3 (3.6)                             | 12 (7.4)               |
| Stage IV         | 3                                   |                        |
| Nivolumab        | 1                                   |                        |
Material and Methods

We retrospectively analyzed the cohort of patients admitted for SARS-CoV-2 infection at the Hospital Universitario Ramón y Cajal in Madrid, Spain, between March 2020 and September 2020. No vaccines were available at that time. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at IRYCIS [12]. REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for

| Site                        | Patients in active treatment, N (%) | Cancer survival, N (%) |
|-----------------------------|------------------------------------|------------------------|
| Axitinib                    | 1                                  | 0                      |
| Sunitinib                   | 1                                  | 0                      |
| Death                       | 0                                  | 4 (33.3)               |
| Bladder                     | 3 (3.6)                            | 15 (9.2)               |
| Stage IV                    | 1                                  |                        |
| BCG instillation            | 2                                  |                        |
| Durvalumab                  | 1                                  |                        |
| Death                       | 0                                  | 3 (20)                 |
| Pancreatic                  | 2 (2.4)                            |                        |
| Stage IV                    | 1                                  |                        |
| FOLFIRI                     | 1                                  |                        |
| Gemcitabine; paclitaxel     | 1                                  |                        |
| Death                       | 1 (50)                             |                        |
| Endometrial                 | 1 (1.2)                            | 2 (1.2)                |
| Stage IV                    | 1                                  |                        |
| Surgery                     | 1                                  |                        |
| Death                       | 0                                  | 0                      |
| Ovarian                     | 1 (1.2)                            | 1 (0.6)                |
| Stage IV                    | 1                                  |                        |
| Rituximab                   | 1                                  |                        |
| Death                       | 0                                  | 0                      |
| Sarcoma                     | 2 (1.2)                            | 3 (1.8)                |
| Stage IV                    | 1                                  |                        |
| Doxorubicin                 | 1                                  |                        |
| Radiotherapy                | 1                                  |                        |
| Death                       | 1                                  | 1 (33.3)               |
| CNS                         | 1 (1.2)                            |                        |
| Temozolamide                | 1                                  |                        |
| Death                       | 0                                  |                        |
| Melanoma                    | 1 (1.2)                            | 3 (1.8)                |
| Stage IV                    | 1                                  |                        |
| Pembrolizumab               | 1                                  |                        |
| Death                       | 1 (100)                            | 1 (33.3)               |
| Thyroid                     | 1 (1.2)                            |                        |
| Stage IV                    | 1                                  |                        |
| Tremelimumab                | 1                                  |                        |
| Death                       | 0                                  |                        |
| Seminoma                    | 2 (1.2)                            |                        |
| Death                       | 0                                  |                        |
| Skin                        | 8 (4.3)                            |                        |
| Death                       | 3 (42)                             |                        |
| Stomach                     | 3 (1.8)                            |                        |
| Death                       | 1 (33)                             |                        |
| Hepatocarcinoma             | 3 (1.8)                            |                        |
| Death                       | 0                                  |                        |

CDDP, cisplatin; BCG, bacillus Calmette-Guerin.
seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. We reviewed the electronic health records of patients with a history of solid neoplastic or hematological neoplastic disease. Only patients with a diagnosis of SARS-CoV-2 infection confirmed by PCR in nasopharyngeal exudate and with available data for status, current oncological treatment, and follow-up of the oncological disease were included. The cohort of patients was divided into three groups: no history of cancer disease, history of prior cancer without active treatment at the time of infection, and patients with active cancer treatment for neoplastic disease, in any setting, curative, adjuvant, or neoadjuvant and including systemic, surgical, or radiotherapy treatment. The values of lymphocytes, neutrophils, D-dimer, procalcitonin, and C-reactive protein are those obtained in the analysis of the day of admission or the following day when they were not requested in the emergency department. For the analysis of interleukins (ILs), ferritin, and lactate dehydrogenase (LDH), the first available determination during admission was used.

**Statistical Study**

Categorical variables are presented as absolute and relative frequencies and percentages. Continuous data are presented as mean and standard deviation (±) or as median with interquartile range (IQR). Pearson’s χ² test was used to compare categorical variables. The one-factor ANOVA test was used to compare continuous data from three groups, and Student’s t test was used to compare continuous values of two variables. When the criteria of normality and homogeneity of variances were not met, the nonparametric Kruskal-Wallis test was used. Binary logistic regression was used for the multivariate study. The significance level was set at 0.05.

**Results**

**General Characteristics**

Between 1 March and 4 September 2020, 2,772 patients were admitted to the Hospital Universitario Ramón y Cajal for SARS-CoV-2 infection. Of these, 2,527 (91.1%) had no history of cancer, 164 (5.9%) had history of prior cancer, and 81 (2.9%) had received active cancer treatment in the 12 weeks prior to admission. Among the patients without active treatment, cancer diagnosis had been made between 44 years, and shortly before infection, this group also included 9 patients who were pending treatment or who were diagnosed during SARS-CoV-2 infection, 8 patients who were decided not to receive any cancer treatment and were on surveillance and 1 patient on supportive care. Of the 81 patients on active cancer treatment, 41 (50.6%) were in stage IV cancer disease. The general characteristics of the 3 groups of patients can be seen in Table 1. The median age of patients who died relative to the overall group was higher for patients with no history of cancer and patients without treatment (82 and 84 years, respectively), but was the same for patients in active cancer treatment, 71 years. Oncologic patients without active treatment had higher comorbidity with statistically significant differences for diabetes, hypertension, chronic kidney disease, cardio-

| Marker (units)            | No history of cancer (n) mean | Cancer survival (n) mean | Active oncologic treatment (n) mean | p value |
|--------------------------|--------------------------------|--------------------------|------------------------------------|---------|
| Ferritin, ng/mL          | (780) 1,337                   | (53) 986                 | (25) 2,002                         | ns      |
| LDH, U/L                 | (2,107) 350                   | (136) 337               | (68) 498                           | 0.01    |
| Procalcitonin, ng/mL     | (885) 0.99                    | (48) 1.2                | (35) 1.2                           | ns      |
| C-reactive protein, mg/L | (2,168) 105.9                 | (140) 97.49            | (68) 110.46                        | ns      |
| D-dimer, ng/mL           | (1,250) 2,531.8               | (79) 2,746.7            | (40) 1,680.1                       | ns      |
| Lymphocytes, 10³/μL      | (2,255) 1,235                 | (149) 1,101             | (71) 1,000                         | ns      |
| Neutrophils, 10³/μL      | (2,256) 6,181                 | (149) 5,692             | (71) 5,097                         | ns      |
| IL-6, pg/mL              | (754) 133.2                   | (39) 117.2              | (14) 45.6                          | ns      |
| IL-12, pg/mL             | (728) 0.48                    | (38) 0.73               | (14) 0.53                          | ns      |
| IL-10, pg/mL             | (744) 7.2                     | (39) 5.1                | (14) 10.2                          | ns      |
| IL-17, pg/mL             | (479) 1.3                     | (25) 0.82               | (9) 0.69                           | ns      |
| IL-18, pg/mL             | (416) 0.45                    | (15) 0.26               | (12) 0.53                          | ns      |
| IL-8, pg/mL              | (745) 37.6                    | (36) 37.74              | (14) 25                            | ns      |
| TNF, pg/mL               | (610) 6.8                     | (30) 7                  | (14) 8.3                           | ns      |
| INFg, pg/mL              | (478) 4.1                     | (25) 1.7                | (9) 8.1                            | ns      |

LDH, lactate dehydrogenase; IL, interleukin; TNF, tumor necrosis factor; INFg, interferon gamma.

Table 3. Inflammatory markers
vascular disease, and chronic lung disease than nononcologic patients.

The most frequent site of neoplasia in patients with history of prior cancer was colorectal (20.7%) followed by prostate (19.5%) and breast (9.8%). Among patients on active cancer treatment, the most frequent location was breast (23.5%), prostate (19.8%), lung (12.3%), and colorectal (11.1%) (Table 2). Twenty-five patients were receiving hormonal treatment when they contracted SARS-CoV-2 infection, 27 chemotherapy treatment (2 of them also received hormone therapy, and 2 others received chemotherapy treatment combined with bevacizumab), 11 immunotherapy, 7 targeted therapies, 2 bladder instillations with BCG, 6 treated with major surgery in the month prior to infection. Only 3 patients were receiving radiotherapy, one of them palliative radiotherapy for spinal cord compression secondary to bone metastases from lung cancer, another one radiotherapy concurrent with chemotherapy for tongue cancer, and the third one RT on surgical site of subcutaneous leiomyosarcoma at scapular level.

### Laboratory Findings

Anemia, hemoglobin (HGB) below 12 g/dL, was present in 18% of patients without a history of cancer, while in patients on cancer treatment the rate of anemia was 50% (mean HGB for patients on active cancer treatment 11.4 and for patients without a history of cancer 13; p < 0.001). The rate of lymphopenia (less than 1,000 cells per mm³) was 69% and 55%, respectively. Albumin levels <3 g/dL were found in 57% of patients without a history of cancer and 83.9% in patients on active cancer treatment (mean albumin in patients on active cancer treatment 2.5 and in patients without a history of cancer 2.8; p < 0.001). There were no differences in inflammatory parameters between the 3 groups of patients (Table 3), except for LDH which was higher in patients on active oncology treatment and a trend toward lower IL-6 values, although not statistically significant, probably due to the low number of patients on active oncology treatment in whom IL-6 levels were available.

There were also no statistically significant differences compared to the population without a history of cancer. Although IL-6 levels were lower in patients treated with chemotherapy than with other types of cancer treatment, these differences were not statistically significant (Table 4).

| Table 4. Clinical characteristics and outcomes by cancer treatment type |
|---------------------------------------------------------------|
| **Chemotherapy**                  | **Hormonotherapy**                  | **Targeted therapies**                | **Immunotherapy**                | **Surgery**                  | **Nononcologic patients** |
|-----------------------------------|-------------------------------------|--------------------------------------|----------------------------------|------------------------------|----------------------------|
| **Age, years (IQR)**              | 69 (56; 74)                         | 79 (70; 85)* (p 0.004)               | 63 (57; 76)                      | 67 (61; 71)                  | 71 (57; 85)                 |
| **Sex, n (%)**                    |                                     |                                      |                                  |                              |                            |
| Male                              | 22 (68.8)                           | 14 (56)                              | 2 (28.6)                         | 9 (81.8)                     | 2 (40)                     |
| Female                            | 10 (31.2)                           | 11 (44)                              | 5 (71.4)                         | 2 (18.2)                     | 3 (60)                     |
| **Ferritin, ng/mL (mean)**        | 2,663* (p 0.4)                      | 548                                  | 1,227                            | 1,493                        | 4,691                      |
| **LDH, U/L (mean)**               | 384                                 | 338                                  | 391                              | 507                          | 295                        |
| **Procalcitonin, ng/mL (mean)**   | 1.3                                 | 0.76                                 | 0.12                             | 2.59                         | 0.04                        |
| **C-reactive protein, mg/L (mean)** | 126.96                        | 93                                   | 95.9                             | 114.99                       | 106.8                      |
| **D-dimer, ng/mL (mean)**         | 2,583                               | 1,457                                | 761                              | 700                          | 561                        |
| **Lymphocytes, 10⁹/μL (mean)**    | 1,092                               | 1,032                                | 999                              | 797                          | 1,133                      |
| **Neutrophils, 10⁹/μL (mean)**    | 4,428* (p 0.49)                     | 5,488                                | 6,620                            | 5,420                        | 4,652                      |
| **IL-6, pg/mL (mean)**            | 19                                  | 126                                  | 51.7                             | 44                           | 6.9                        |
| **IL-12, pg/mL (mean)**           | 0.13                                | 0                                    | 1.8                              | 1.41                         | 0.24                       |
| **IL-10, pg/mL (mean)**           | 3.6                                 | 3.09                                 | 56.7                             | 16.9                         | 0.97                       |
| **IL-17, pg/mL (mean)**           | 0.28                                | 0                                    | 2.99                             | 0.43                         | 0.26                       |
| **IL-18, pg/mL (mean)**           | 0.73                                | 0.09                                 | 0                                | 0.37                         | 0.21                       |
| **IL-8, pg/mL (mean)**            | 16.9                                | 41.17                                | 79.3                             | 36                           | 0.2                        |
| **TNF, pg/mL (mean)**             | 4.6                                 | 0.4                                  | 62.66                            | 1.53                         | 5.7                        |
| **INFg, pg/mL (mean)**            | 1.33                                | 0                                    | 59.77                            | 0.744                        | 0.99                       |
| **Discharge from hospital, mean days** | 18                              | 10                                   | 3                                | 7                            | 16                        |
| **Death, n (%)**                  | 14 (45,2)                           | 8 (32)                               | 0                                | 4 (36,4)                     | 1 (16,7)                   |

* Statistically significant differences from nononcologic patients.
Survival

SARS-CoV-2 mortality in noncancer patients was 19.5%, for patients with prior history of cancer without treatment 26.8% and for patients on active cancer treatment 34% (p < 0.005). Among patients on active cancer treatment, the highest mortality was found in patients with lung cancer 70%, and odds ratio (OR) with respect to nononcologic patients was 9.6 (95% CI: 2.4; 37.3) followed by patients with colorectal carcinoma, 44.4% OR 3.3 (95% CI: 0.8; 12.3), prostate cancer, 37.5% OR 2.4 (95% CI: 0.8; 6.8), hematological tumors 37.5% OR 2.4 (95% CI: 0.5; 10.3), and breast cancer 15.7% OR 0.7 (95% CI: 0.2; 2.6). In terms of mortality by type of treatment, 43% of patients treated with chemotherapy died (OR 3.15 95% CI: 1.52–6.53), 32% of those treated with hormone therapy (OR 1.9 95% CI: 0.83–4.52), 36.4% treated with immunotherapy (2.35 95% CI: 0.6–8.08), and there were no deaths in patients being treated with targeted therapies.

In the multivariate study, adjusted for age, sex, obesity, hypertension, and diabetes, active cancer treatment was statistically significant risk factor for mortality (OR 2.25 95% CI: 1.35–3.77) (Table 5). For patients on active oncologic treatment, chemotherapy versus other treatments (OR 3.6 95% CI: 1.17–11.17) was statistically significantly associated with the risk of death, adjusted by age, sex, hypertension, and diabetes (Table 6).

Discussion

In this study, we analyzed the inflammatory profile and mortality of patients with SARS-CoV-2 infection, on active cancer treatment and with a history of cancer compared to infected patients without a history of cancer. This is a patient population series selected from a register of patients admitted to a tertiary hospital, covering a health area with an aging population and a medium-low socioeconomic level. No vaccines were available in the study timeframe. All patients were admitted due to the need for oxygen support and therefore with severe SARS-CoV-2 infection. We found a higher mortality rate in cancer patients under active treatment, especially in patients with lung cancer and undergoing chemotherapy. Oncology patients who did not require admission due to infection were not represented.

The incidence of a history of neoplastic disease in patients admitted for SARS-CoV-2 infection was 8.8% (246 patients out of 2,772). Of these, 81 patients were receiving some form of treatment for oncological disease, representing 2.9% of admissions, which is very similar to the 2.6% (1.7% in China and 5.6% for Western countries) described in the meta-analysis by Zarifkar et al. [13]. Since we only analyzed patients who required admission, we cannot state that the incidence of this infection is higher in cancer patients, although Liang et al. found a percentage of patients with a history of cancer among those infected with SARS-CoV-2 of 1%, while in the general population it is 0.29% [3] any case, our data do show a higher mortality in hospitalized patients than in the general population.

### Table 5. Uni- and multivariate analysis of risk of death in patients under active oncological treatment

|                     | Univariate | Multivariate |
|---------------------|------------|--------------|
|                     | OR (95% CI) | p value      | OR (95% CI)   | p value     |
| Oncologic active treatment | 2.06       | 0.003        | 2.259 (1.35; 3.77)* | 0.002       |

* Adjusted for age, sex, obesity, hypertension, and diabetes.

### Table 6. Uni- and multivariate analysis of risk of death in patients under active oncological treatment by treatment type

|                     | Univariate | Multivariate |
|---------------------|------------|--------------|
|                     | OR (95% CI) | p value      | OR (95% CI)   | p value     |
| Chemotherapy treatment versus other treatments | 3.15 (1.52; 6.53) | 0.002 | 3.624 (1.17; 11.17)* | 0.025 |

* Adjusted for age, sex, obesity, hypertension, diabetes, and site of the neoplasm.
The sociodemographic characteristics are similar to other studies, with a higher percentage of men among cancer patients and a lower percentage of hypertension and obesity, but the mean age of our cancer patients is slightly higher than in other studies [5, 8, 10, 14], similar to that reported by Lee et al. [15] who found a greater association between COVID-19 and cancer in male patients and those over 65 years of age. Regarding the analytical profile, in our study oncology patients have lower HGB and albumin levels, as in the series of Zhang et al. [6], probably related to the nutritional deterioration of oncology patients that may contribute to the morbidity and mortality associated with the infection.

In relation to the immune system, most cancer treatments are immunosuppressive. High levels of IL-6 have been linked to an increased risk of death from SARS-CoV-2 infection due to cytokine storming [16, 17]. IL-6 inhibitors such as tocilizumab have been added to the therapeutic arsenal for SARS-CoV-2 patients. Retrospective studies have found a decrease in mortality in patients with severe pneumonia treated with tocilizumab, especially if they have high levels of C-reactive protein [18, 19]. In the two randomized studies published to date, no survival benefit is found with tocilizumab treatment, but while the COVACTA study found no improvement in clinical status, the EMPACTA study found a reduced likelihood of worsening pneumonia and need for mechanical ventilation when tocilizumab was used [20, 21]. Neither study selects patients according to inflammatory markers such as IL-6 or C-reactive protein. In oncology patients, IL-6 hyperactivation has also been reported, so it is unknown whether immunosuppressive oncology treatments could lead to a decreased risk of cytokine storm and thus death from SARS-CoV-2. Except for neutrophil levels, which were significantly lower in patients treated with chemotherapy, we found no statistically significant differences in the levels of IL-6 or other cytokines involved in cytokine release syndrome [22] between patients who did and did not die, between oncology and nononcology patients, or between the different oncology treatments, probably due to the small number of patients in whom these factors were available.

Our data suggest that the state of immunosuppression prevents a correct reaction against the virus, given the excess mortality from SARS-CoV-2 in oncology patients under active treatment (34%) compared to patients without a history of cancer (19.5%). Other retrospective studies [4, 8, 23–25] and two meta-analyses [6, 26] also find higher mortality in these patients, although there is no clear consensus in the literature, as different studies find similar mortality rates when adjusted for patient morbidities [10, 27–29]. In general, patients with cancer under active treatment who are admitted for SARS-CoV-2 infection have an advanced tumor stage, in our case 50.6% stage IV, older age, and a higher percentage of males. We did not find a higher rate of associated morbidities in cancer patients on active treatment. However, patients with history of prior cancer without active treatment had higher comorbidity rates, not only hypertension, diabetes, and obesity, but also other chronic pathologies such as heart, lung, and kidney disease, which justifies the higher mortality in this group compared to patients without a history of cancer. In the multivariate study, for patients undergoing active cancer treatment, age was not statistically significantly related to mortality in our cohort. Other studies find higher mortality in cancer patients with COVID infection in relation to age [30, 31], but these studies also include outpatients. In our work, with cancer patients with severe COVID infection, the stage of neoplasia, location, and treatments received had a greater influence on the risk of mortality than age. However, in the case of prostate carcinoma, the second site of mortality after lung cancer, patients had a median age of 81 years (IQR 74–81) higher than patients with breast cancer, patients had a median age of 68 years (IQR 55–83), lung 71 (IQR 67–76), or colorectal cancer 69 (IQR 58–72), and age was probably a determining factor in these prostate cancer patients. The 6 patients who died were on hormone treatment. It has been described in the Montopoli study that patients on androgen deprivation treatment may have a lower risk of infection [32] although there are no data on the influence of these treatments on mortality caused by SARS-CoV-2. By location, the lung cancer represents the tumor with the highest mortality risk with an OR of 6.4 (95% CI 1.38–29.98), findings consistent with those reported in other studies such as the meta-analysis by Zhang et al. [6], the TERAVOLT thoracic tumor registry [11], and the studies by Dai et al. [8] and Calvo et al. [10] which found a higher risk of death in patients with lung carcinoma. A greater severity of pneumonia has not been described at the time of admission, but lung damage due to previous pulmonary pathologies or the tumor may trigger a rapid worsening and hinder recovery [3]. In our study, only 1 patient with lung cancer was admitted to the ICU. In addition, 2 deceased patients diagnosed with lung cancer had received at least two therapeutic modalities, radiotherapy, and chemotherapy in one case, chemotherapy and surgery in another, and two others had previously required pleural drainage and draining for pleural effusion, so that although the number of patients is very
small, the use of several therapeutic modalities and locally advanced disease could have influenced the evolution of the infection. Regarding the type of cancer treatment, chemotherapy is statistically significantly associated with the risk of death independently of the primary tumor. Two meta-analyses and retrospective studies also find an increased risk of death in patients treated with chemotherapy, when adjusted for risk factors [3, 33, 34]. In general, this is attributed to possible complications inherent to chemotherapy treatment or advanced stage disease. Treatment with immunotherapy also poses an increased risk of mortality in our work. In Liu’s meta-analysis, they describe immunotherapy as the systemic treatment with the highest risk [34] and attribute this to the activation of T cells by the immune therapy, which can lead to an aberrant and uncontrolled inflammatory response [35]. However, it has been described as a safe treatment in studies with larger numbers of patients and including outpatients [36]. In this study, we found no differences in IL-6 levels between patients treated with immunotherapy and those without [36]. Other systemic treatments, such as targeted therapies, do not appear to increase the risk of death in patients with SARS-CoV-2 infection in our series, in agreement with the works of Garassino and Liu [11, 34].

Our study has limitations inherent to retrospective studies. The number of cancer patients with inflammatory parameters measured is small, which, together with the severity of the patients at the time of hospital admission, probably prevented us from finding statistically significant differences in IL-6 levels between the different subgroups of patients analyzed. The population of patients with cancer under active treatment is low, we were not able to study the influence of treatments such as surgery or radiotherapy, and only 3 patients were receiving radiotherapy treatment. The systemic treatments received are diverse, which prevents us from drawing accurate conclusions about the influence of each of them on the evolution of the infection. Likewise, we have not been able to analyze the type of complications of infection with or without death in oncology patients.

**Conclusions**

Our data confirm a high mortality of SARS-CoV-2 infection in cancer patients under active treatment, especially if they have been diagnosed with lung carcinoma or were receiving chemotherapy treatment. It is therefore necessary to make an effort to protect these patients from infection, to give them priority access to vaccination and in case of infection to closely monitor the clinical situation in order not to delay effective treatment against the virus if necessary. Given the impact of infection in these patients and the recommendation to administer suboptimal oncology treatments, in some cases, to reduce the risk of infection, prospective studies or joint efforts to collect data from multiple centers are needed to clarify questions about the management of oncology patients during a pandemic such as the current one.

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**Statements of Ethics**

This study protocol was reviewed and approved by Comité de Ética para la Investigación con Medicamentos del Hospital Universitario Ramón y Cajal, approval number 098/20. This is a retrospective study with no clinical implications for the patients, and always we work with coded data files, so informed consent was not necessary. The consent protocol was reviewed, and the need for written informed consent was waived by Comité de Ética para la Investigación con Medicamentos del Hospital Universitario Ramón y Cajal.

**Conflict of Interest Statement**

The authors have no competing interests to declare that are relevant to the content of this article.
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Author Contributions

Margarita Martín, Carmen Vallejo, Fernando López-Campos, and Sonsoles Sancho conceived, designed the study, and wrote the paper. Alfonso Muriel carried out the statistical analysis. Teresa Muñoz, Jose Antonio Domínguez, Pilar Garrido, Mercedes Martín, Carolina de la Pinta, Raúl Hernández, Eva Fernandez, Marina Alarza, and Asunción Hervás contributed to manuscript revisions. Carmen Quereda, Matilde Sánchez-Conde, Cruz Soriano, Cecilia Suárez-Carantoña, Julio Acero, Ana Alvarez-Díaz, and Laura Martínez-García contributed to the design and development of the database, as well as to the collection and review of data.

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.
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