

## ORIGINAL ARTICLE

## COVID-19 IN CANCER PATIENTS: A SYSTEMATIC REVIEW

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## ABSTRACT

**Objective:** Development of severe disease and death from COVID-19 is more frequent in patients with comorbidities. Some studies report an increased frequency of severe COVID-19 in cancer patients. This review aims to describe the risk of infection and developing severe COVID-19 in cancer patients. **Materials and methods:** A systematic review was carried out through an exhaustive search of literature in PubMed and Scopus until May 2020. A secondary search was performed to include more studies. **Results:** The initial search identified 2,192 records, which included 17 publications with at least 10 infected cancer patients. Also, 5 articles were added from the additional search of the references cited by those 17 publications. Ten publications were from Chinese authors. Data analysis showed that COVID-19 infection is more frequent in cancer patients, and frequent therapeutic visits to the healthcare facility may be the cause. The presence of neoplasia predisposed patients to develop severe disease. Advanced age, associated comorbidities, advanced malignancy, and the presence of serum inflammatory markers increased the risk of developing severe disease. Initial studies indicate that the use of systemic treatment may also be a predisposing factor. **Conclusions:** The risk of becoming infected by COVID-19 and developing severe disease is higher in the oncological population.

**Keywords:** Coronavirus; Cancer; Risk Factors (Source: MeSH NLM).

## INTRODUCTION

COVID-19 is a public health emergency of international concern. Patients with severe forms of the disease constitute approximately 15% of the cases, which require specialized management due to high mortality rates<sup>(1,2)</sup>.

There are epidemiological, clinical, and prognostic differences between people with cancer and those without it. Cancer patients require continuous visits to health centers and hospitalizations to undergo surgical or medical procedures related to their disease. Also, this type of patients have several physiopathological characteristics that have previously been related to severe COVID-19 in the general population such as advanced age, smoking history, pre-existing cardiopulmonary, respiratory or renal disease and tumor lesions that predispose to respiratory infections<sup>(3-8)</sup>.

In addition, patients with advanced neoplasia are considered to be immunosuppressed because of the effect of premedication with steroids, chemotherapy, immunotherapy, or biological therapy (such as kinase inhibitors or PARP inhibitors) to which they are subjected<sup>(3-5)</sup>. Finally, the survival expectation is lower in patients with advanced cancer and may reduce their possibilities of access to hospitalization services or to the intensive care unit (ICU) in the event of developing a severe critical condition.

Despite the growing number of publications describing COVID-19 symptoms in different populations, only a few studies evaluate COVID-19 effects on cancer patients. This infor-

**Cite as:** Castañeda CA, Castillo M, Rojas JL, Fuentes H, Gómez HL. COVID-19 in cancer patients: a systematic review. Rev Peru Med Exp Salud Publica. 2020;37(4):611-9. doi: <https://doi.org/10.17843/rpmesp.2020.374.5976>.

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**Received:** 11/06/2020  
**Approved:** 12/08/2020  
**Online:** 12/10/2020

mation is needed to improve the approach and treatment of these patients during the pandemic. The goal of this systematic review is to describe the risk of infection and the development of severe forms of COVID-19 in cancer patients.

## MATERIALS AND METHODS

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to prepare the report of this systematic review. The study protocol was registered in PROSPERO with code CRD42020188164 ([https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=188164](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=188164)).

### Bibliographic search strategy

The literature search was conducted on PubMed and Scopus until May 20, 2020. Two authors developed the search strategies (CAC, MC) following to the recommendations of the Cochrane Manual of Systematic Reviews. Controlled vocabulary search terms were used for MEDLINE (MeSH), linked to free text terms for each of the selected concepts using Boolean operators. No date filters or document formatting restrictions were used in the search.

Demonstrations of the search strategies were made with the advanced search tool in each database before the final version of the search strategies was approved by consensus. The complete search strategy is available in the supplementary material. Duplicate articles were removed, using the EndNote program (version X7.3.1; Thomson Reuters, New York, USA).

### Eligibility criteria

In order to gather as much evidence as possible, cross-sectional, cohort, and case-series studies were included in this systematic review. The original articles, which included at least 10 cancer patients with COVID-19, were required to assess the following: a) risk of transmission and symptomatology; b) risk of severe disease; and c) factors associated with severe disease in cancer patients. Peer-reviewed publications were included. Given the urgency of the publication process, articles published in their final version and articles in the editing stage after the peer review (in press) were accepted. Articles that could not be accessed in full text were excluded. There were no publication date restrictions, and English language articles were included.

### Study selection and data extraction

We used Microsoft Excel to review the titles and abstracts identified in the electronic searches of the database for

## KEY MESSAGES

**Motivation for study:** The impact of SARS-CoV-2 infection on cancer patients needs to be evaluated to improve patient management during the pandemic.

**Main findings:** Cancer patients have a higher prevalence of contracting COVID-19 and an increased risk of developing severe disease. Clinical factors have been described to predict severe disease.

**Implications:** A greater understanding of the impact of SARS-CoV-2 infection on cancer patients will result in better approach and treatment of patients.

possible inclusion. The review was performed by two independent authors (CAC, MC). The full text was retrieved in cases where no decision could be made on possible exclusion or inclusion during the evaluation of the title and abstract.

We retrieved full texts of the articles, and two authors independently evaluated them to verify eligibility and complete the checklists of inclusion and exclusion criteria (CAC, MC). Disagreements were solved by discussing the issue, if this was not possible, a third author decided if the article was included (HLG).

Microsoft Excel was used to extract, store, and analyze data. We obtained means, ranges and percentages of the infection rate and the patients' clinical characteristics, such as age, sex, tumor location, mortality, severe events, and reported outcomes of interest. In the cases in which some researcher disagreed, the complete text of the article was reviewed again to verify the extracted data or to correct errors

### Synthesis of results

Infection prevalence, severe disease, and factors associated with severity were the main findings. This was a synthesis study without meta-analysis<sup>(9)</sup>. We conducted a formal narrative synthesis of the data collected. No formal statistical analysis was conducted.

The synthesis focused mainly on the qualitative analysis of the reported clinical manifestations, classified by country of origin. The limitations of the studies included were discussed. The results of certain included studies were prioritized in the conclusions only when they met criteria such as relevance of evidence and sample size. Also, this review did not require the approval of an ethics committee.

## Evaluation of the studies' quality

Two authors (CAC, MC) independently used the U.S. National Institutes of Health study quality assessment tools (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>), according to the design of each study. The tools contain a list of questions, with five possible answers in each one: "yes", "no", "cannot be determined", "not applicable" and "not determined". Disagreements were resolved through a consensus review.

## RESULTS

### Characteristics of the studies included

The initial search identified 2,192 results; 503 duplicate records were removed. After filtering by titles and abstracts, we evaluated 123 full-text articles. We found 23 records that included original articles with at least 10 cancer patients. We reviewed these articles in their entirety and selected 17 that provided specific information related to the objectives of this

review. In addition, a secondary search was conducted on the 302 papers cited in the 17 initially included studies, of which 5 additional studies were included. Finally, 22 articles were included, most of the studies were retrospective ( $n = 15$ ) (Figure 1). Eleven cohort studies, six cross-sectional and five case-control studies were included.

Overall, the quality of the studies was considered to be medium to low because of the following: small number of participants, unjustified sample size, poor information on participants, heterogeneous population, and the fact that several studies provided insufficient information on patient follow-up time.

Most of the articles were by authors from China (10/21), the United States (4/21) and Italy (3/21). One study included collaboration with centers from three countries: Canada, Spain, and the United States<sup>(10)</sup>. There were 1,933 patients with cancer and SARS-CoV-2 infection included in the series found; 53% were male (information obtained from 14 studies) and the mean age in the series with adults was 57.5 years (information obtained from 13 studies) (Table 1).

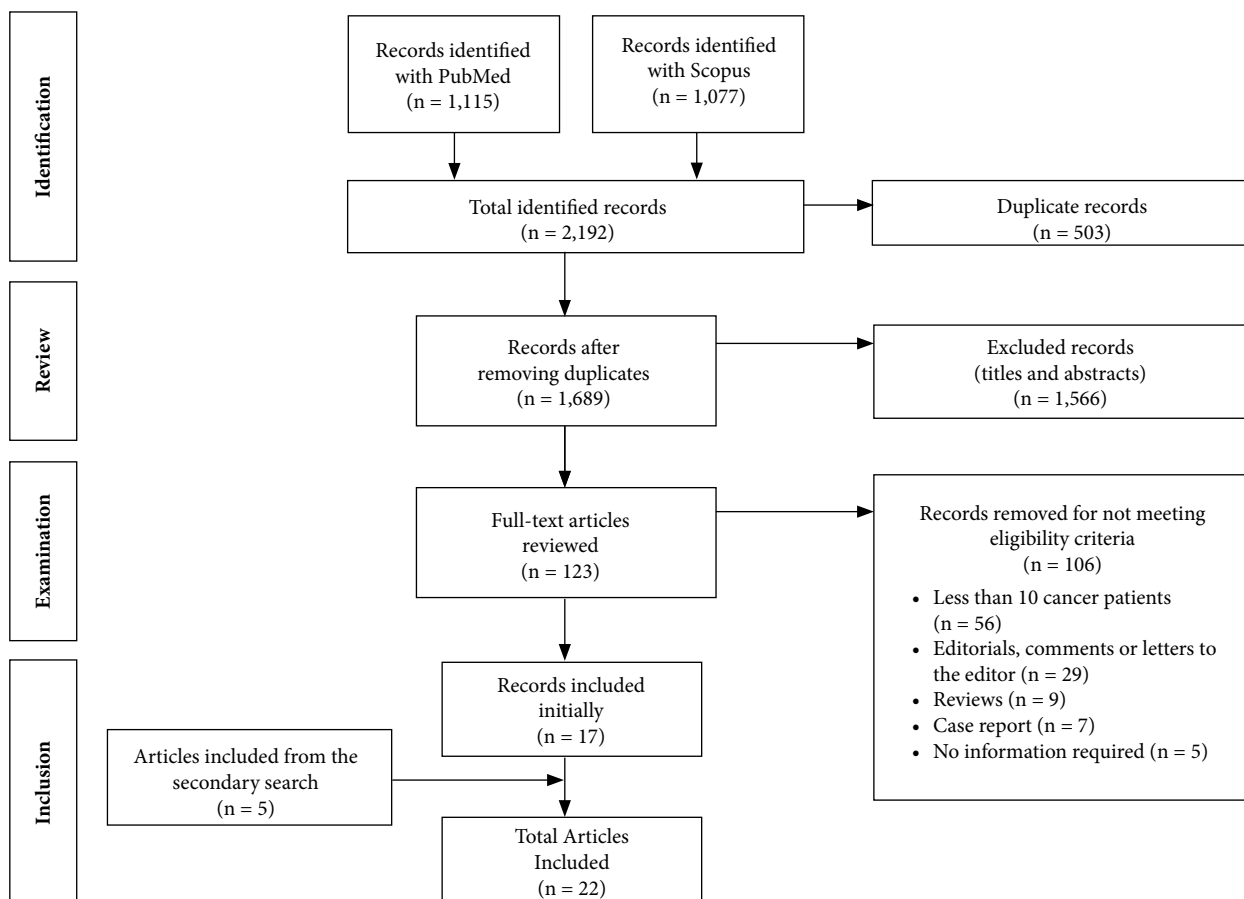


Figure 1. Article selection flowchart.

### Risk of infection and clinical findings

Yu *et al.* identified 12 cases (7 of them with lung cancer [LC]) with COVID-19 infection among the 1,524 cancer patients who attended the Department of Radiation and Medical Oncology at Zhongnan Hospital, with a higher prevalence than that reported for the general population of Wuhan City in the same period of time (0.79% vs. 0.37%). In the evaluation of the 228 patients with LC, it was estimated that patients over 60 years of age had higher incidence of COVID-19 than younger ones (4.3% vs. 1.8%)<sup>(11)</sup>. Four additional series in China<sup>(4,7,8,12)</sup> and one series in Italy also found that LC is the most frequent<sup>(6)</sup>. Similarly, De Rojas *et al.* identified that the infection rate in pediatric cancer patients (1.3%) is higher than that of children without cancer (0.8%) in Madrid<sup>(13)</sup>. Boulad *et al.* found an infection rate of 2.5% in the 120 pediatric cancer patients without symptoms of COVID-19 infection at the Memorial Sloan Kettering Cancer Center in New York<sup>(14)</sup>.

According to Zhang *et al.*, going to a Chinese health center was the probable cause of infection for 28.6 of cancer patients<sup>(12)</sup>. Similarly, Mehta *et al.* described that 61% of the 61 deaths in their hospital series from New York had attended health care settings in the last month<sup>(5)</sup>.

The most frequent findings associated with COVID-19 in cancer patients, as reported by Zhang *et al.*, were fever (82.1%), dry cough (81.0%), fatigue (64.3%), and dyspnea (50.0%), along with lymphopenia (82.1%), high C-reactive protein (82.1%), high lactate dehydrogenase (LDH) (50.0%), anemia (75.0%), hypoalbuminemia (89.3%), and leukopenia (32.1%). The most common tomographic findings were bilateral lung compromise (78.6%), frosted glass pattern (75.0%), irregular consolidation (46.3%), and interstitial abnormalities such as reticular appearance, fibrous strips, and interlobular septal thickness (14.3%)<sup>(12)</sup>. These findings were confirmed by other studies in solid<sup>(6,7,15-17)</sup> and hematological neoplasms<sup>(18)</sup>. Pan *et al.* evaluated the gastric symptoms of 13 cancer patients with COVID-19 (out of 204 patients with COVID-19) and found that 8 (61.5%) presented digestive symptoms (and 4 of them had critical symptoms). There was no difference in the frequency of gastrointestinal symptoms between oncological and non-oncological patients with comorbidities (38.5%;  $p = 0.410$ )<sup>(19)</sup>.

### Risk of severe disease

Liang *et al.* reported that the 18 cancer patients had more polypnea (47% vs. 23%), started with more severe COVID-19 lung lesions on CT (94% vs. 71%), and had a higher risk of

severe events (percentage of deceased patients or those in ICU that required invasive ventilation) compared to non-cancer patients (39% vs. 8%,  $p < 0.001$ ). In addition, patients with cancer deteriorated more rapidly than those without cancer (mean time to severe events 13 days vs. 43 days,  $p < 0.001$ )<sup>(8)</sup>. Two studies conducted in China with cancer patients confirm longer hospitalization times, faster deterioration, and high rates of severe disease and mortality<sup>(4,12)</sup>. The study by Dai *et al.* evaluated 105 cancer patients and 536 controls (by age) without cancer but with COVID-19 in 14 hospitals in China and reported that the predisposition to unfavorable evolution does not occur in cases without metastasis<sup>(4)</sup>.

Yang *et al.* found, in a series of 52 patients with cancer and COVID-19, that 55.8% of patients had complications, such as liver injury, respiratory distress syndrome, sepsis, myocardial injury, renal failure, and multiple organ dysfunction syndrome; 21.2% of the patients died<sup>(7)</sup>. He *et al.* found a higher frequency of having severe COVID-19 (69%) and dying (62%) in the 13 patients with hematological malignancy seen at the Institute of Hematology in Wuhan, compared to hospitalized patients without cancer<sup>(18)</sup>. The Chinese Center for Disease Control and Prevention report had information regarding comorbidities of 20,812 cases of COVID-19 (from a series with 44,672 total cases) and described that the death rate was 5.6% in cancer patients (higher than 2.3% of the general population rate)<sup>(1)</sup>.

Grasselli *et al.* reported a retrospective series of 1,591 patients with COVID-19 (out of a total of 17,713 positive cases of COVID-19 infection) who were admitted to the ICU in the Lombardy region (Italy) and indicated that 8% (81 out of 1,043 cases with information of comorbidities) had history of active cancer or in remission<sup>(20)</sup>. Additionally, Onder *et al.* showed in another Italian series that 20.3% of 355 patients who died from COVID-19 had cancer<sup>(21)</sup>, while Stroppa *et al.* reported that 9 of the 25 patients in their series in Italy died<sup>(6)</sup>.

Mehta *et al.* reported a series of 218 patients with cancer and SARS-CoV-2 infection evaluated at Montefiore Network Medical Centers in New York, and found that 28% died (37% of 54 cases of hematologic malignancy, 25% of 164 cases of solid malignancy, and 55% of 11 with LC). The mortality rate was higher in cancer patients than for non-cancer controls from health centers, and it was also higher than for the general population of New York (adjusted for age)<sup>(5)</sup>.

### Factors associated with severe COVID-19 in cancer

In China, different clinical, laboratory, and treatment factors associated with unfavorable outcomes were initially reported in different retrospective series (Table 2). Yang *et al.* in a series

**Table 1.** Clinical characteristics of patients with cancer and COVID-19

Study	City, Country	Type of study	Study design	Study population <sup>a</sup>	Patients with cancer and COVID 19 (%)	Men (%)	Age median (range)	Clinical stage or activity status	Diagnostic method	Severe COVID 19 (%)	Type of cancer (%)	Mortality
Chinese Center for Disease Control and Prevention <sup>(1)</sup>	Several, China	Retrospective	Cross-sectional	20,812 <sup>b</sup>	107 (0.5)	NA	NA	NA	RT-PCR	NA	NA	6 (5.6)
Liang <i>et al.</i> <sup>(8)</sup>	Several, China	Prospective	Cross-sectional	1,590 <sup>b</sup>	18 (1.1)	12 (66.7)	63 (47-87)	NA	RT-PCR	9 (50)	LC (27.8), colorectal (22.2), BC (16.7), bladder (11.1)	NA
Guan <i>et al.</i> <sup>(26)</sup>	Several, China	Prospective	Cross-sectional	1,099 <sup>b</sup>	10 (0.9)	NA	NA	NA	RT-PCR	3 (30)	NA	NA
Dai <i>et al.</i> <sup>(4)</sup>	Several, China	Prospective	Cohort	641 <sup>b</sup>	105 (16.4)	57 (54.3)	64	IV in 62%	RT-PCR	36 (34.3)	LC (20.1), gastrointestinal (12.4), BC (10.5), thyroid (10.5) and others	12 (11.4)
Pan <i>et al.</i> <sup>(19)</sup>	Several, China	Prospective	Cross-sectional	204 <sup>b</sup>	13 (6.4)	NA	NA	NA	RT-PCR	4/8 (50)	NA	NA
Wang <i>et al.</i> <sup>(27)</sup>	Wuhan, China	Retrospective	Cohort	138 <sup>b</sup>	10 (7.2)	NA	NA	NA	RT-PCR	4 (40)	NA	NA
Yang <i>et al.</i> <sup>(7)</sup>	Wuhan, China	Retrospective	Cohort	52 <sup>bc</sup>	52 (100.0)	28 (53.8)	63 (34-98)	NA	RT-PCR	19 (36.5)	LC (19.2), colorectal (25), BC (17.3) and others	11 (21.2)
Zhang <i>et al.</i> <sup>(12)</sup>	Wuhan, China	Retrospective	Cohort	28 <sup>bc</sup>	28 (100.0)	17 (60.7)	65 (56-70)	IV in 35.7 %	RT-PCR	15 (53.6)	LC (25.0), esophagus (14.3), BC (10.7) and others	8 (28.6)
Yu <i>et al.</i> <sup>(11)</sup>	Wuhan, China	Retrospective	Case series	1,524 <sup>c</sup>	12 (0.8)	10 (83.3)	66 (48-78)	NA	CT Scan and RT-PCR	3 (25)	LC (58.3), colon rectal (16.7) and others	3 (25.0)
He <i>et al.</i> <sup>(18)</sup>	Wuhan, China	Prospective	Cohort	128 <sup>c</sup>	13 (10.2)	7 (53.8)	35 (23-53)	Recently diagnosed	CT Scan and RT-PCR	9 (69.2)	Acute lymphoblastic leukemia (38.5), acute myeloid leukemia (30.8) and others	8 (61.5)
Grasselli <i>et al.</i> <sup>(20)</sup>	Several, Italy	Retrospective	Case series	1,043 <sup>b</sup>	81 (7.8)	NA	81.5% entre 60 y 80 años	NA	RT-PCR	NA	NA	NA
Onder <i>et al.</i> <sup>(21)</sup>	Several, Italy	Retrospective	Cross-sectional	355 <sup>b</sup>	72 (20.3)	NA	79.5 <sup>d</sup> (DE 8.1)	NA	RT-PCR	NA	NA	72 (20.3)
Stroppa <i>et al.</i> <sup>(6)</sup>	Piacenza, Italy	Prospective	Cohort	25 <sup>bc</sup>	25 (100.0)	20 (80)	71.6 <sup>d</sup> (10.1)	IV in 76%	RT-PCR	12 (48)	LC (32), gastrointestinal (24), genitourinary (24) and others	4 (16)
Vuagnat <i>et al.</i> <sup>(17)</sup>	Paris, France	Prospective	Case series	59 <sup>bc</sup>	59 (100.0)	NA	58 (48-68)	IV in 63%	CT Scan and RT-PCR	6 (10.2)	BC (100)	4 (6.8)
Martin-Moro <i>et al.</i> <sup>(22)</sup>	France	Retrospective	Cohort	34 <sup>bc</sup>	34 (100.0)	19 (55.9)	72.5 (35-94)	NA	CT Scan and RT-PCR	ND	Acute leukemia (20.6), plasma cell dyscrasia (20.6) and others	11 (32.4)
De Rojas <i>et al.</i> <sup>(13)</sup>	Madrid, Spain	Retrospective	Case series	15 <sup>bc</sup>	15 (100.0)	14 (93.3)	11 (0.6-18.6)	CR in 60%	RT-PCR	0 (0)	Acute lymphocytic leukemia (46.7), solid tumors (26.6) and others	0 (0)
Mehta <i>et al.</i> <sup>(5)</sup>	Madrid, Spain	Retrospective	Cohort	218 <sup>bc</sup>	218 (100.0)	127 (58)	69 (10-92)	IV in 19.7%	RT-PCR	68 (31.2)	Hematological (24.8), genitourinary (21.1), BC (12.8), colorectal (9.6) and other neoplasms	61 (28)
Luo <i>et al.</i> <sup>(16)</sup>	New York, USA	Retrospective	Cohort	69 <sup>bc</sup>	69 (100.0)	33 (48)	69 (31-91)	NA	RT-PCR	24/65 (36.9)	LC (100)	16/67 (23.8)
Kalinsky <i>et al.</i> <sup>(15)</sup>	New York, USA	Retrospective	Case series	27 <sup>bc</sup>	27 (100.0)	1 (3.7)	56 (32-87)	I-II in 63%, III in 18.5% and IV in 19%	RT-PCR	0 (0)	BC (100)	1 (3.7)
Kuderer <i>et al.</i> <sup>(10)</sup>	Several, USA, Canada, and Spain	Retrospective	Cohort	928 <sup>bc</sup>	928 (100.0)	468 (50.4)	66 (57-76)	Stable disease in 32%	RT-PCR	132 (14.2)	Hematological neoplasms (22), BC (20.6), prostate (16.4) and others	121 (13)
Boulad <i>et al.</i> <sup>(14)</sup>	New York, USA	Retrospective	Cross-sectional	178 <sup>c</sup>	20 (11.2)	17 (85)	11.1 <sup>d</sup> (SD: 8.5)	NA	RT-PCR	0 (0)	NA	0 (0)
Nikpouraghdam <i>et al.</i> <sup>(28)</sup>	Tehran, Iran	Retrospective	Cohort	2,964 <sup>b</sup>	17 (0.6)	NA	NA	NA	CT Scan and RT-PCR	NA	NA	1 (5.9)

<sup>a</sup> Obtained from cases with comorbidities information; <sup>b</sup> population with COVID-19; <sup>c</sup> population with cancer; <sup>d</sup> mean. NA: not available; SD: standard deviation; RT-PCR: reverse transcriptase polymerase chain reaction; CT: computed tomography, CR: complete remission; LC: lung cancer; BC: breast cancer.

of 52 cancer and COVID-19 patients found that severe disease was associated with the following factors: use of immunosuppressants such as steroids ( $p = 0.001$ ); hemodynamic decompensation patterns such as severe acute respiratory syndrome ( $p < 0.001$ ), myocardial injury ( $p = 0.04$ ), and shock ( $p = 0.02$ ); as well as serum markers of extensive inflammation, such as lymphopenia, and increased levels of IL-6, D-dimer, C-reactive protein (CRP), procalcitonin, and lactate dehydrogenase (LDH) ( $p < 0.05$ )<sup>(7)</sup>.

The multicenter work of Dai *et al.* indicated that hematologic neoplasms had high death rates (33.3%), followed by LC (18.2%). The presence of metastatic cancer (especially neoplasms with lung metastases) was associated with higher rates of severe disease and death (odds ratio [OR] = 5.58,

95% confidence interval [95% CI]: 1.71-18.23). The use of PD-1 immunotherapy (6 cases out of 105, 5.7%) and surgery (8 cases, 7.6%) within 40 days of infection were associated with severe disease or death. Immunosuppression levels did not predict an unfavorable evolution<sup>(4)</sup>.

Two retrospective series in China described that older cancer patients and those receiving antineoplastic treatment in the weeks surrounding SARS-CoV-2 infection were at higher risk for severe disease<sup>(8,12)</sup>. Liang *et al.* reported that patients who underwent chemotherapy or surgery in the month prior to diagnosis of infection had higher risk (3 out of 4 patients, 75%) of experiencing clinically severe events than those who did not receive chemotherapy or surgery (6 out of 14 patients, 43%) ( $p = 0.0026$ )<sup>(8)</sup>. Similarly, Zhan *et al.* found that the risk of

**Table 2.** Factors associated with the unfavorable evolution of patients with cancer and COVID-19.

Study	Factors associated with severe illness and death				
	Clinical factors	Type of cancer	Laboratory factors	Concurrent treatments	Antineoplastic treatment
Dai <i>et al.</i> <sup>(4)</sup>	Lung Metastasis <sup>a</sup>	LC <sup>a,b</sup>	NR	NR	PD-1 immunotherapy <sup>a,b</sup> and surgery within 40 days of infection <sup>a</sup>
Yang <i>et al.</i> <sup>(7)</sup>	Severe acute respiratory distress syndrome <sup>a</sup> , myocardial injury <sup>a</sup> and shock <sup>a</sup>	NR	Lymphopenia <sup>a</sup> , ↑IL-6 <sup>a</sup> , ↑D dimer <sup>a</sup> , ↑CRP <sup>a</sup> , ↑procalcitonin <sup>a</sup> and ↑LDH <sup>a</sup>	Corticosteroids <sup>a</sup> , immunoglobulin <sup>a</sup>	NR
Zhang <i>et al.</i> <sup>(12)</sup>	Older age <sup>a</sup> , male gender <sup>a</sup> , irregular consolidation in CT <sup>a</sup>	NR	NR	NR	Anti-tumor treatment (chemotherapy, targeted therapy and immunotherapy) within 14 days <sup>a</sup>
He <i>et al.</i> <sup>(18)</sup>	Acute Respiratory Distress Syndrome <sup>b</sup>	Hematological cancer <sup>a</sup>	↑D dimer <sup>b</sup>	NR	NR
Mehta <i>et al.</i> <sup>(5)</sup>	Older age <sup>b</sup> , heart disease <sup>b</sup> and concomitant chronic lung disease, need for ICU management <sup>b</sup> , active neoplasm <sup>b</sup> and metastasis (in solid tumors) <sup>b</sup>	NR	↑D dimer <sup>b</sup> , ↑LDH <sup>b</sup> and ↑lactate <sup>b</sup> , ↑neutrophil count <sup>b</sup> , ↑white blood cell count <sup>b</sup> , ↓hemoglobin <sup>b</sup>	NR	NR
Kuderer <i>et al.</i> <sup>(10)</sup>	Older age <sup>b</sup> , male gender <sup>b</sup> , history of smoking <sup>b</sup> , high number of comorbidities <sup>b</sup> and ↑ECOG <sup>b</sup> , active neoplasm <sup>b</sup>	NR	NR	NR	NR
Stroppa <i>et al.</i> <sup>(6)</sup>	Older age <sup>b</sup> and female gender <sup>b</sup>	BC <sup>b</sup> , genitourinary <sup>b</sup> and hematological <sup>b</sup>	↑CRP <sup>b</sup>	NR	NR
Moro <i>et al.</i> <sup>(22)</sup>	↑ECOG <sup>b</sup> and active neoplasm <sup>b</sup>	NR	↑Procalcitonin <sup>b</sup> , ↓platelet count <sup>b</sup>	NR	NR
Vuagnat <i>et al.</i> <sup>(17)</sup>	Older age <sup>a,b</sup> and High blood pressure <sup>a, b</sup>	NR	NR	NR	NR

<sup>a</sup> Factor associated with severe COVID-19; <sup>b</sup> factor associated with death; ↑: higher; ↓: lower.

BC: breast cancer; LC: lung cancer; ECOG: patient's quality of life scale; IL-6: interleukin-6; CRP: C-reactive protein; LDH: lactate dehydrogenase; CT: computed tomography; ICU: intensive care unit; NR: not reported.

developing severe disease was significantly increased if the last antitumor treatment (chemotherapy [3 cases], targeted therapy [2 cases], and immunotherapy [1 case]) was performed within 14 days ( $p = 0.037$ )<sup>(12)</sup>.

Two series in Europe confirmed that advanced age predicts higher mortality<sup>(6,17)</sup>. Stroppa *et al.* also found that female sex ( $p = 0.04$ ), some primary tumor locations such as genitourinary and hematological ( $p = 0.02$ ) and elevated CRP ( $p = 0.047$ ) were associated with higher mortality in a series of 25 cancer patients with COVID-19 in northern Italy (General Hospital of Plasencia)<sup>(6)</sup>. The series by Vuagnat *et al.* in Paris included 59 patients with breast cancer and found that also high blood pressure ( $p < 0.05$ ) was associated with severe infection. There was no relationship between the extent of pulmonary lesions from COVID-19 and the extent of the fields of previous radiation therapy or its pulmonary sequelae<sup>(17)</sup>. Martín-Moro *et al.* found that poor performance in the patient's quality of life scale (ECOG) ( $p = 0.016$ ), active neoplasia ( $p = 0.021$ ), platelet/anemia ( $p = 0.016$ ) and elevated procalcitonin ( $p = 0.016$ ) were associated with death in a series of 34 cases of hematological neoplasia in Madrid<sup>(22)</sup>.

Mehta *et al.* found, in 218 cases in New York, that the factors associated with an increased risk of death were older age ( $>65$  years) ( $p = 0.0006$ ), heart disease ( $p = 0.012$ ) and concomitant chronic lung disease ( $p = 0.0003$ ), need for ICU ( $p < 0.001$ ) and serum markers of extensive inflammation such as D-dimer ( $p = 0.002$ ), DHL ( $p = 0.01$ ) and lactate ( $p = 0.001$ ). Neither chemotherapy, immunotherapy nor radiotherapy were associated with an increased risk of death<sup>(5)</sup>. A series of 69 patients with LC and COVID-19 evaluated at Memorial Sloan Kettering Cancer Center in New York found no association between the use of immunotherapy and severe disease or death from COVID-19. It is suggested that the association found in other studies between immunotherapy and severe symptoms is due to the greater frequency of use of this therapy in patients with a history of smoking (which would be the cause of greater risk of severe infection)<sup>(16)</sup>.

Finally, the Cancer and COVID-19 Consortium published a series of 928 cases of adult patients from the United States, Canada, and Spain with active cancer or with previous neoplasia and with severe acute respiratory syndrome due to COVID-19. From the total of patients, 13% died, thus confirming the association described in the previous studies with advanced age (OR= 1.84, 95% CI: 1.53-2.21), cancer activity (OR= 5.2, 95% CI: 2.77-9.77), higher number of comorbidities (OR= 4.5, 95% CI: 1.33-15.28), poor ECOG performance (OR= 3.89; 95% CI: 2.11-7.18); and adds the following factors: being male (OR= 1.63; 95% CI: 1.07-2.48) and smoking status (OR= 1.6; 95% CI: 1.03-2.47). No association was found with race, obesity, type of cancer, or with treatment carried out in the 4 weeks prior to infection<sup>(10)</sup>.

## DISCUSSION

This systematic review identified 22 studies that assessed the prevalence and risk of complications from COVID-19 in cancer patients. Different retrospective series found that the risk of SARS-CoV-2 infection is higher in cancer patients. However, it must be emphasized that the infection tests were performed, in most cases, only in patients with suspected symptoms of infection (Table 1). This higher prevalence found is consistent with the results of the meta-analyses carried out by Tian *et al.* (2.3%)<sup>(23)</sup>, Elgohary *et al.* (2.1%)<sup>(24)</sup> and Desai *et al.* (2%)<sup>(25)</sup>.

Frequent visits to healthcare facilities (with less protection than that used by health personnel) may explain the higher prevalence of infection in the cancer patient. In addition, there is a higher number of patients with LC in the oncological series, and this could be due to the bias caused by the superposition of respiratory symptoms of both conditions, which increases the number of screening tests in this population<sup>(3,12)</sup>. The symptoms described in the retrospective series evaluated are similar to those described in the non-neoplastic population<sup>(1,2)</sup>.

Different series evaluating the effect of COVID-19 on cancer patients report that complications and deaths are more frequent in this population (Table 1)<sup>(8,11)</sup>. However, three series conducted in general eastern population infected with COVID-19, including a small oncological population, did not find cancer as a comorbidity to be associated with worse disease progression<sup>(26-28)</sup>. Similarly, the meta-analyses conducted by Tian *et al.* and the one conducted by Elgohary *et al.* reveal that cancer patients are at greater risk of developing severe/critical illness. This effect may be due to an altered immune system that produces an unregulated immune response with extensive inflammation and elevated cytokines<sup>(23,24)</sup>.

Various clinical factors have been associated with the development of severe disease. Studies in China have identified the following factors: age, comorbidities, and advanced malignancy, as well as close administration of cytotoxic treatment and immunotherapy. As a result, and despite the small size of the series in these studies, most of the healthcare institutions worldwide limited the administration of systemic therapy. It is likely that selecting patients according to prioritization criteria and the scaling up of the use of immunosuppressive systemic therapy (suspension of palliative therapies, dose reductions, and wide use of colony-stimulating factors) resulted in subsequent series from Europe and the United States presenting differences regarding the effect of systemic treatment on unfavorable evolution<sup>(3)</sup> (Table 2).

The main strength of this study is the fact that we carried out an exhaustive literature review of two scientific databases and the description of the findings are consistent with the objectives. Although no other databases were used, the review was expanded with a secondary search, shortening the search time and allowing studies from other databases to be included, given the progressive state of the COVID-19 pandemic and the need for timely evidence. One of the limitations of the study is the small number of articles found and the short follow-up of studies due to the need of knowledge generation. Another limitation of the study was the quality of the studies, which were biased regarding sample size. Several studies did not report data such as age, types of cancer and clinical stage. The in-press versions, included in this review, may present modifications in the final version of the article. Series with larger sample sizes, more homogeneous populations, and designs that produce more robust conclusions are likely to be published in the coming months, but the results of this review provide information that healthcare providers can apply to the current management of cancer patients.

This review provides evidence that the risk of infection and the risk of developing severe diseases from COVID-19 are higher in the cancer population, based on information gathered from published studies. Advancing age, associated comorbidities, poor general condition, advanced (or active) malignancy, and serum inflammatory markers have been associated with increased mortality in cancer patients. Case series from China report that receiving systemic therapy in the weeks following SARS-CoV-2 infection is also associated with severe disease.

**Authors' contributions:** CAC and MC conceived and designed the article. CAC, MC, and HLG collected and evaluated the data. All authors analyzed and interpreted the data, wrote the article, and approved the final version.

**Funding:** Self-funded.

**Conflicts of interest:** The authors declare no conflict of interest.

**Supplementary material:** Available in the electronic version of the RPMESSP.

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