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COVID-19 and cancer: an extensive review

COVID-19 e câncer: uma revisão extensa

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ABSTRACT

Emerging data postulates that cancer is an important risk factor for disease severity and higher in-hospital mortality amongst patients with COVID-19. From a pathophysiological perspective, COVID-19 induces an overproduction of inflammatory cytokines, causing systemic inflammation, hypercoagulability, and multiple organ dysfunction syndrome. The exact pathophysiological mechanisms associated with severe COVID-19 disease in patients with cancer is uncertain. Moreover, the challenge of implementing social distancing in patients requiring specific anticancer treatments urged international societies to issue recommendations regarding the adoption of safety measures to reduce transmission risk and optimize anticancer treatment during the COVID-19 pandemic. We provide an extensive review of the clinical outcomes, prognosis and management of patients with cancer and COVID-19 infection.

Keywords: COVID-19, Cancer, Pathophysiology, Clinical outcome, Management.

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RESUMO

Dados emergentes postulam que o câncer é um importante fator de risco para gravidade da doença e maior mortalidade hospitalar entre pacientes com COVID-19. Sob uma perspectiva fisiopatológica, a COVID-19 induz uma superprodução de citocinas inflamatórias, causando inflamação sistêmica, hipercoagulabilidade e disfunção de múltiplos órgãos. Os mecanismos fisiopatológicos exatos associados à COVID-19 grave em pacientes com câncer são incertos. Além disso, o desafio de implementar o distanciamento social em pacientes que requerem tratamentos anticâncer específicos instou as sociedades internacionais a emitir recomendações sobre a adoção de medidas de segurança para reduzir o risco de transmissão e otimizar o tratamento anticâncer durante a pandemia de COVID-19. Nós fornecemos uma extensa revisão dos resultados clínicos, prognóstico e tratamento de pacientes com câncer e infecção por COVID-19.

Descritores: Infecções por coronavírus; Sintomas de câncer; Evolução clínica.

INTRODUCTION

Currently, the world is facing the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]. In this century, two coronavirus epidemics occurred, the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 [1]. In late December 2019, several local health facilities reported clusters of patients with pneumonia of unknown cause that were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China [2]. In March 2020, due to its fast dissemination, COVID-19 was declared a pandemic by the World Health Organization (WHO) [3]. In early March of 2021, the world had already registered more than 116 million individuals infected, with more than 2.5 million deaths.

In 2018 cancer was responsible for an estimated 9.6 million deaths, making it the second highest cause of death worldwide [4]. Every year 18 million new cases are diagnosed [4]. Particular attention was immediately given to patients with cancer in the Chinese nationwide cohort, representing about 1% of the COVID19-infected population, who were particularly vulnerable, with a case fatality rate (CFR) of 5.6% compared to 2.3% in the general population [5]. This increased susceptibility is partially due to the cancer itself, exerting a chronic immunosuppressive state, and exacerbated by cytotoxic therapies. Therefore, it is expected that cancer patients are at higher risk, both of infection and complications, during the COVID-19 pandemic [6].

It is well established that early diagnosis and therapy are associated with better results in cancer morbidity and mortality. Due to COVID-19, many cancer diagnosis and treatments are being delayed which may result in worse outcomes for patients [7]. Maintaining cancer wards has been challenging in healthcare institutions currently focusing on the short-term emergency in response to COVID-19 [5].

In this review we will discuss the stages, pathophysiology, clinical evolution and management of COVID-19 of patients with cancer.

METHODOLOGY

We performed a critical literature review based on the PubMed electronic bibliographic database. The following descriptors were used in the search engines advanced tool: “COVID-19” or “SARS-CoV-2” and “cancer”, resulting in 4,376 articles. Utilizing article type filters to include retrospective studies, prospective studies, meta-analysis, and clinical guidelines regarding the association of Cancer and COVID-19, obtained 941 results. Articles with a central theme diverging, or not related to COVID-19, or the association between Cancer and SARS-CoV-2 infection were excluded from the revision. After title and abstract evaluation, 43 COVID-19 and Cancer articles were thoroughly reviewed, in addition to 25 articles on essential COVID-19 aspects used for contextualization, totaling 68 citations. Preprints articles were also included. A description of the methodology is depicted in Figure 1.

DISCUSSION

Clinical Evolution of COVID-19 patients

COVID-19´s clinical spectrum comprises three main phases that can range from asymptomatic carriers to individuals with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation [8]. To comprehend the pathophysiology of this disease and apply it to patients diagnosed with an active or previously treated cancer, the clinical and laboratorial evolution will be discussed and exemplified in detail. Different studies show that about 86% of patients do not present disease severity, only about 14% require oxygen therapy in a hospital unit, and less than 5% of this group require intensive care [9].

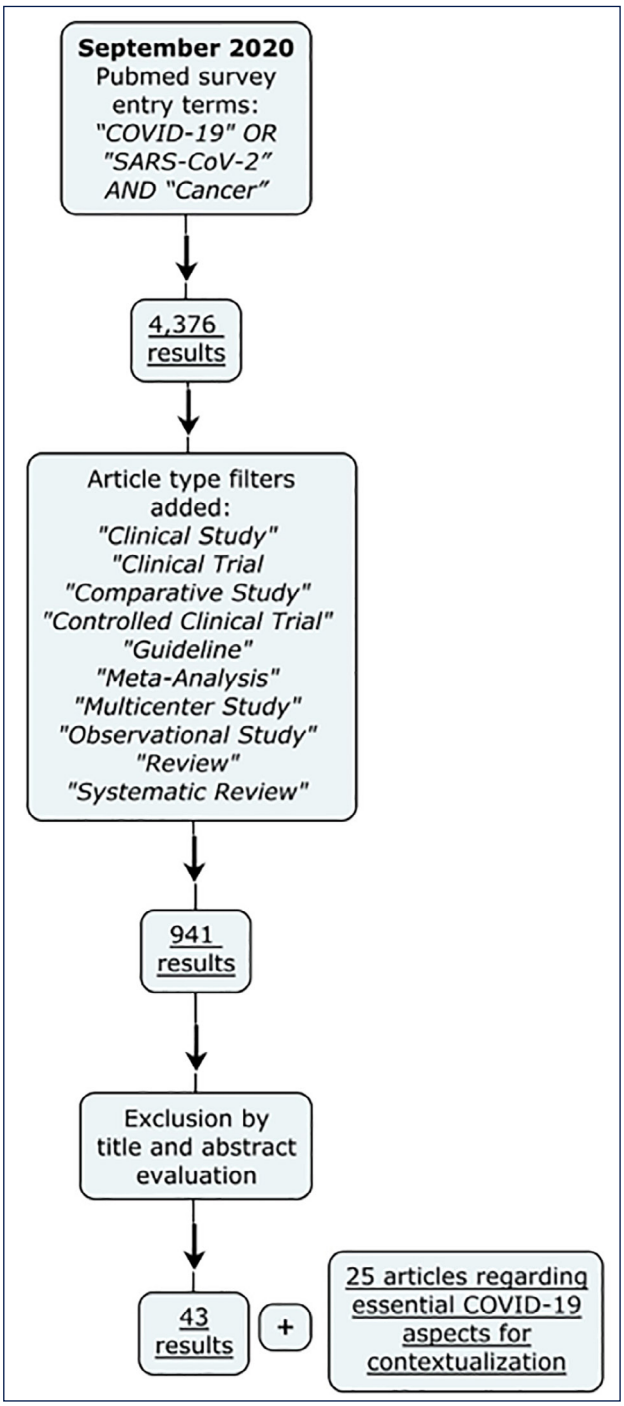

Figure 1. Flowchart of article selection.

The presentation of COVID-19 is predominantly mild and asymptomatic, which is exemplified as the first phase or nonpneumonia / mild pneumonia [10]. This stage occurs in the first 7 days containing a benign evolution, with symptoms characteristic of upper respiratory tract infection such as: dry cough, sore throat, rhinorrhea and respiratory secretion as well as headache, mild fever, fatigue, myalgia and malaise [11]. Nonspecific symptoms were also identified such as anosmia, ageusia and gastrointestinal manifestations: diarrhea, abdominal pain, nausea and vomiting. Early in the disease, chest computed tomographic (CT) imaging findings in approximately 15% of individuals and chest radiograph findings in approximately 40% of individuals can be normal [12]. In this phase, a complete blood count may reveal a lymphopenia and neutrophilia without other significant abnormalities and in dealing with these patients, approximately 80% of the cases are resolved [13].

The second phase occurs after the first week in which the disease progresses to a moderate pneumonia, revealing a pulmonary involvement which can be divided into two subgroups, patients with and without hypoxia [14]. This phase occurs in approximately 15% of the patients and usually from the tenth day on, when the symptoms begin to worsen, with dyspnea, cough, and oxygen saturation decrease suggesting a progression to lower respiratory tract infection [13]. This progression is associated with the extreme increase of inflammatory cytokines, including interleukins IL-2, IL-7, IL-10, granulocytes colony stimulating factor (G-CSF), interferon gamma-induced protein of 10 KDa (IP-10), monocyte chemoattractant protein (MCP-1), macrophage inflammatory protein 1α (MIP-1α), and transforming growth factor α (TGF-α) [15]. During this stage, patients develop a viral pneumonia, with cough, fever, and possibly hypoxia leading to dyspnea (defined as PaO2/FiO2 < 300 mm Hg). Imaging with chest roentgenogram or CT may reveal a bilateral peripheral pulmonary infiltrate in a ground-glass opacity pattern demonstrating the development of the viral pneumonia. Blood tests may reveal increasing lymphopenia along with transaminases. Laboratory evaluations also reveal an increase of inflammatory reagents such as C-reactive protein (CRP), ferritin, and D-dimer, evidencing an important systemic inflammatory and prothrombotic activity, also increasing the risk of bleeding by disseminated intravascular coagulation (DIC), in which both may be elevated, but not remarkably so [14].

The third and last phase occurs after the second week of clinical evolution, representing approximately 5% of the patients infected with COVID-19. These COVID-19 patients that transition into this third and most severe stage of the illness manifest a severe pneumonia, as well as hypercapnia which is associated with an advanced respiratory failure established by the COVID-19 ARDS. In chest CT, there is an exacerbation of the bilateral multifocal pulmonary ground-glass opacities, with possible concomitant foci of consolidation and pleural effusion, and an augmentation of the ventilatory ratio, which reflects an increase in pulmonary dead space and inadequacy of ventilation, demanding oxygen therapy and ventilatory support; in addition, extra pulmonary systemic hyper inflammation syndrome is also noted [16].

In this stage, markers of systemic inflammation are significantly elevated, and this systemic infection is characterized by a fulminant and fatal hypercytokinaemia (cytokine storm) with multiorgan failure [17]. Studies reveal that in this specific stage of the disease, inflammatory cytokines

and biomarkers such as IL-2, IL-6, IL-7, G-CSF, macrophage inflammatory protein 1-alpha, tumor necrosis factor-alpha, CRP, ferritin, and D-dimer are significantly elevated [18]. Also in this phase, procalcitonin (PCT) and erythrocyte sedimentation rate (ESR) increase gradually as the clinical status deteriorates, as does creatine kinase (CK), creatine kinase-MB fraction (CK-MB), Lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, and serum amyloid A protein (SAA) as well as prothrombin time in contrast with seric albumin which instead decreases [19]. When focusing in the immune response, other studies also show that in consequence to this state of hypercytokinaemia a decrease in CD4, CD8, suppressor, and regulatory T cell counts occur [20]. In this phase of the disease, these patients have critical manifestations such as septic shock, vasoplegia, unremitting fever, cytopenia and respiratory failure; cardiopulmonary collapse is also discernable, and/or multiple organ dysfunction syndrome [21]. Therefore, complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney and coagulation system, due to the endothelial damage possibly leading to disseminated intravascular coagulation. Concerning prognostic significance is the Sequential Organ Failure Assessment (SOFA) score, which predicts intensive care unit (ICU) mortality based on laboratory results and clinical data [22]. It is noteworthy that patients in this late stage of the disease have a dissociation between their relatively well-preserved lung mechanics and the severity of hypoxemia. This wide discrepancy is virtually never seen in most forms of ARDS [16].

Although most patients progress with a good prognosis, it is essential to highlight that in the case of the elderly or individuals with comorbidities, such as diabetes, chronic lung diseases, cardiovascular (CV) and kidney diseases and cancer, COVID-19 can progress more aggressively, leading to multiple organ dysfunction [23].

COVID-19 and Cancer- Pathophysiological Mechanisms

The SARS-CoV-2 infection is essentially initiated by the coupling of a host TMPRSS2 viral Spike-1 primed receptor with angiotensin-converting enzyme 2(ACE2), an anti-inflammatory receptor mostly present in the pulmonary alveolar epithelial type II cells [24]. Given that these cells produce surfactant and play a key role in pulmonary gas exchange, infection resulting in direct damage by pyroptosis and indirect lesion by inflammatory cell infiltration and secretion production, can result in lung injury [25,26] and cause dyspnea by hypoxemia, a cardinal symptom of COVID-19 [27].

SARS-CoV-2 also induces a decrease of ACE2 expression, thereby worsening lung injury [28] and increasing the already present pro-inflammatory host response, resulting in fever and fever-related symptoms (myalgia, chills, fatigue) and cough possibly due to the release of inflammatory mediators such as Histamine, Prostaglandin E2 and Prostaglandin F [29]. Interaction of SARS-CoV-2 with ACE2 in other tissues such as the heart, intestines, and blood vessels could account for other manifestations of the disease such as myocarditis, diarrhea and multi-organ failure in critical patients [25, 30]. SARS CoV-2 infection also provokes enhanced pro-thrombotic activity related to increased direct platelet activation and platelet-monocyte aggregates formation (thrombocytopathy) [31], coagulation abnormalities (coagulopathy) [32], complement activation with cytokine release (inflammation), and endothelial dysfunction (endotheliopathy).

Despite the mechanisms of thrombocytopathy and endotheliopathy in COVID-19 still being poorly understood, the clear clinical association is the presence of CV risk factors. The role of thromboinflammation is well known and highlights the crucial importance of endotheliopathy and thrombocytopathy to the morbimortality of this disease [33,34].

Compared to the general population, cancer patients will display a higher risk of thromboembolic complications due to a cancer related increase in general thromboinflammation [35], which could result in higher morbimortality in this group compared to the general population [36, 37].

However, this high risk of adverse outcomes of SARS-CoV-2 infection in cancer patients is also possibly explained through a series of immunologic mechanisms such as the immunosuppressive state caused by both the tumor itself and the cytotoxic therapies commonly used in this group. These therapies result in blunting of the immune response through lymphopenia and/or neutropenia and tumoral-induced exhaustion of antiviral lymphocytes [38]. This impaired immune response leads to the persistence of the virus ensuring continuous cytokine release probably by leukocytes other than T lymphocytes [39]. It causes and/or intensify the "cytokine storm" leading to severe lung damage. In addition, viral replication with consequent direct tissular lesion in other ACE2 rich biological sites such as the heart, intestine, and kidneys is also favored by this exacerbated immune response. Ultimately, it contributes to worsen the overall prognosis of the neoplasm patient when infected by SARS-CoV-2 [40].

COVID-19 and Cancer- Clinical Outcomes and Prognosis

Malignancy emerges as an important risk factor for disease severity and more adverse clinical outcomes amongst patients with SARS-CoV-2 infection. Impaired regulatory immune response observed in patients with cancer possibly enhances the cytokine storm and systemic inflammation observed in more severe forms of COVID-19. An initial report describing SARS-CoV-2 transmission in patients with cancer in a tertiary care hospital in Wuhan demonstrated a higher risk of COVID-19 infection. This example

portrayed the vulnerability of these patients amid the COVID-19 pandemic raising initial concerns for oncologists and frontline doctors, which has been confirmed by several more recent reports [41]. Thus, it is of utmost importance to clearly understand the clinical manifestations, evolution, prognosis, mortality rates, and risk factors for severity and in-hospital death in patients with COVID-19 and cancer

Clinical Manifestations, Laboratory and Radiographic alterations

In a retrospective study that included 28 hospitalized patients with COVID-19 and history of cancer, the most prevalent symptoms during hospital admission were fever (82.0%), dry cough (22.81%), and dyspnea (50.0%). Additionally, 4 patients (14.3%) presented significant baseline (>30 breaths per minute). In regard to laboratory findings, patients with SARS-CoV-2 infection and history of cancer presented a high incidence of lymphopenia (82.1%, $0.7x10^9$ [IQR 0.5-1.0]), anemia (75.0%, 118.5g/L [IQR 88.0-132.8]), and thrombocytopenia (46.4%, $134.5x10^9$ [IQR 100.0-202.5]). Furthermore, the retrospective analysis also demonstrated that cancer patients evolved with exacerbated inflammation and thrombotic biomarkers, presenting increased levels of CRP, ESR, IL-6, tumor necrosis factor (TNF) and D-dimer. Radiographic evaluation revealed that all cancer patients had abnormal findings on chest CT scan, where 22 of 28 patients (78.6%) developed bilateral lung alterations. The most prevalent CT imaging pattern was ground-glass opacity (21.4%) followed by patchy consolidation (46.3%), and interstitial abnormalities including reticular pattern, fibrous strips, and interlobular septal thickening (14.3%). Six of these patients (21.4%) received at least one kind anticancer therapy within 14 days of COVID-19 diagnosis. Multivariate adjusted Cox proportional hazards model analysis revealed that antitumor treatment within 14 days during hospital admission were significantly associated with an increased risk of severe disease among cancer patients with COVID-19 [42].

A multicenter retrospective cohort study evaluated the clinical characteristics and risk factors associated with COVID-19 disease severity in 232 cancer patients in Wuhan. It was evidenced that cancer predisposed patients to progress to severe COVID-19 when compared to non-cancer patients. Regarding clinical manifestations and symptomatology, SARS-CoV-2 infected cancer patients presented a higher prevalence of dyspnea (27.0% vs. 17.0%), dry cough (51.0% vs. 48.0%), and expectoration (22.0% vs. 16.0%) during hospital admission. Moreover, corroborating with Zhang et al.,pro-inflammatory cytokines including TNF (8.7 vs. 6.0 pg/ml, p=0.0040), IL-6 (12.8 vs. 4.9 pg/ml, p<0.0001) and IL-2R (615.0 vs. 535.0 U/ml, p=0.012), inflammation biomarkers such as CRP (46.4 vs. 40.7mg/L, p=0.047), and coagulation related indicators as thrombocytopenia (182.0 vs. 210.0 $x10^9$, p=0.0061), prolonged prothrombin time (13.6 vs. 13.2 s, p=0.036) and activated partial thromboplastin time (35.5 vs. 34.1], p=0.046), and D-dimer levels (1.2 vs. 0.8 g/ml, p=0.054) were increased in cancer patients when compared to patients without cancer. These findings have revealed a direct association between cancer and systemic inflammation, immune hyperactivity and prothrombotic state, more critical forms of SARS-CoV-2 infection related to hypercytokinemia. Additionally, CT scans demonstrated that ground-glass opacity (76.0% vs. 61.0%, p=0.00070) and patchy shadows (65.0% vs. 50.0%, p=0.0027) were more frequent in patients with cancer compared to non-cancer patients [43].

Cancer as a risk factor for severe COVID-19

Besides worse clinical features and a more adverse laboratory and radiographic profile, the retrospective analysis from Tian and colleagues also demonstrated that cancer is associated with a higher need of high-flow nasal cannula oxygen therapy (33.0% vs. 23.0%), and non-invasive mechanical ventilation (27.0% vs, 19.0%) or invasive mechanical ventilation (9.0% vs. 4.0%0) among patients with SARS-CoV-2 infection compared with non-cancer patients. Moreover, cancer was associated with severity increasing almost four-fold the risk of severe COVID-19 illness. The study also identified advanced tumor stage, elevated TNF, and increased NT-proBNP as novel predictors for poor prognosis among patients with cancer and SARS-CoV-2 infection. Multivariable logistic regression analysis revealed that target therapy and immunotherapy were correlated with 3 times increased risk of developing severe COVID-19, emphasizing that oncology teams must be attentive towards immunotherapy-related adverse events such as myocarditis and pneumonitis as they might contribute to worse prognosis in cancer patients with COVID-19 [43, 44].

Thus, cancer seems to be also associated with worse clinical outcomes among patients with COVID-19. An early nationwide analysis in China evaluating the clinical characteristics and outcomes of cancer patients in SARS-CoV-2 infection depicted that those patients were observed to have a higher risk of severe events (composite endpoint including the percentage of patients admitted to ICU, requiring mechanical ventilation or death) compared to non-cancer patients (39.0% vs. 8.0%, p=0.0003). Moreover, besides malignancy per se, the association between anticancer therapy status and impact on COVID-19 severity is also a concern for intensivists and oncologists during the pandemic. The nationwide analysis from Liang and colleagues showed that patients with history of chemotherapy or surgery in the past month had increased risk of clinically COVID-19 severe events (75.0% vs. 43.0%) than patients that did not receive these types of anticancer therapy. This indicates a fivefold i of severe COVID-19 infection after adjusting for age, smoking history and other comorbidities. Cox regression model to evaluate the time-dependent hazards of developing severe events demonstrated

that cancer patients evolved more rapidly to clinical deterioration (13 days [IQR 6-15] vs. 43 days [IQR 20-not reached], p<0.0001) than non-cancer patients after adjusting for age (HR 3.56 [CI95% 1.65-7.69, p<0.0001) [45].

A prospective cohort study describing the factors associated with hospital admission and critical illness among 5,279 hospitalized patients with COVID-19 in New York revealed that previous history of malignancy was an important predictor of hospitalization (OR 2.71 [CI95% 2.16-3.41) and critical illness (OR 1.68 [CI95% 1.31-2.14). Hence, history of cancer must be screened during patient triage and risk stratification of patients with confirmed or suspected COVID-19 [46]. Likewise, Liang et al. in another cohort study including 1,590 and a validation cohort of 710 patients for the development of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19, portrayed cancer history as an independent risk factor for severe disease as it increased in four-fold the risk of critical illness amongst COVID-19 patients [47].

Likewise, in a cohort study including 928 patients with active or previous malignancy and confirmed SARS-CoV-2 infection from the United States, Canada, and Spain from the COVID-19 and cancer consortium (CCC19) database identified potential prognostic factors for mortality and severe illness in patients with cancer and COVID-19. The primary endpoint was all-cause mortality within 30 days of diagnosis of COVID-19 and secondary outcomes were a composite of severe illness (death, severe illness requiring hospitalization, ICU admission, mechanical ventilation, and need for supplemental oxygen during the course of COVID-19). The most prevalent malignancies were breast (21.0%) and prostate (16.0%) cancer. Among 928 patients, 242 (26.0%) met the composite severe illness endpoint where 132 patients (14.0%) were admitted to the ICU, 405 patients (44.0%) required supplemental oxygen therapy, and 116 patients (12.0%) required mechanical ventilation. Moreover, the mortality rate for the composite secondary endpoint was 50.0% being 27.0% for patients who required supplemental oxygen, 38.0% among patients admitted to the ICU, and 43.0% for patients needing mechanical ventilation. Post-hoc analysis of the secondary outcome revealed that increasing age, hematological malignancy, progressing cancer or unknown cancer status, and Eastern Cooperative Oncology Group (ECOG) performance status ≥2 were associated with an increased rate of the composite outcome of severe illness [48].

In a multicenter, retrospective, cohort study including 205 patients with laboratory-confirmed severe SARS-CoV-2 infection evaluating the clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China, revealed that cancer was associated with high case-fatality rate and unfavorable prognosis. In the study the most prevalent types of cancer were breast, colorectal, and lung carcinomas, while lymphoma was the most frequent hematological malignancy. Among the 205 cancer patients included, 30 patients (15.0%) were referred to the ICU and invasive mechanical ventilation was applied to 21 (66.0%) of patients that required mechanical ventilation. Moreover, complications occurred in 126 (63.0%) of 199 cancer patients, and the most common complications identified in these patients were abnormal liver function (17.0%), secondary infection (13.0%), ARDS (12.0%), coagulopathy (9.0%), acute renal failure (7.0%) and septic shock (6.0%). The median duration of hospitalization observed for cancer patients was 19 (12-33) days for the total cohort of patients, 20 (13-33) days for survivors and 17 (6-29) days for non-survivors [49].

Another meta-analysis and systematic review including 32 studies and 1,776 cancer patients describing the effect of cancer on clinical outcomes of patients with COVID-19 evidenced that cancer was associated with higher ICU admission (RR 1.56 [CI95% 1.31-1.87], p<0.001) and increased all-cause mortality (RR 1.66 [CI95% 1.33-2.07], p<0.0001). Interestingly, in a subgroup analysis of patients >65 years of age, all-cause mortality was similar compared to patients without history of cancer (RR 1.06 [CI95% 0.79-1.41], p=0.71) and with no statistical significance obtained [50]. Authors postulate that the comparable mortality in-between patients with cancer and without cancer with advanced age implies that the presence of cancer may not affect the already more adverse prognosis of individuals > 65 years with COVID-19. Likewise, another meta-analysis and systematic review including 38 studies comprising7,094 patients with COVID-19 concluded that cancer associates with high risk and severe events of COVID-19. In this study the pooled prevalence of cancer in patients with COVID-19 was estimated at 2.3% and a fixed-effect meta-analysis demonstrated that cancer was significantly associated with severe COVID-19 (OR 2.20, [CI95% 1.53-3.17], p<0.001) [51].

A meta-analysis and systematic review of the literature including 22 articles assessing the risk and prognosis of COVID-19 infection in cancer patients indicated that these patients are at a higher risk of COVID-19 infection-related complications. The risk of critical disease in cancer patients with COVID-19 infection was remarkably 45.4%, where comparative analysis with logistic regression including four studies demonstrated that cancer was significantly associated with severe disease increasing in approximately four-fold the risk of critical disease compared to non-cancer patients. Moreover, the risk of ICU admission among cancer patients with COVID-19 was 14.5% with comparative analysis revealing a significantly higher risk of ICU (admission (OR 3.10 [CI95% 2.85-5.17], p<0.0001). Regarding the need of mechanical invasive ventilation, the risk amongst cancer patients was 11.7% and cancer patients had a significantly higher risk of requiring

mechanical invasive ventilation (OR 4.86 [CI95% 1.27-18.65], p=0.02) than non-cancer patients [52].

Robilotti et al. characterized the epidemiology and clinical characteristics of COVID-19 in 423 patients with cancer at the Memorial Sloan Kettering Cancer Center in New York to describe the determinants of COVID-19 disease severity in patients with cancer. In the total cohort of patients, 168 (40.0%) patients were hospitalized, and 87 patients (20.0%) evolved with ARDS being 47 (11.0%) who required high-flow oxygen and 40 (9.0%) who needed mechanical ventilation. Regarding clinical manifestations, shortness of breath and diarrhea were predictors of subsequent hospitalization and severe respiratory illness for patients with COVID-19 and cancer. Additionally, PCT (>0.5ng/ml), lymphopenia (<0.5K/mcL), interleukin-6 (>100pg/ml), D-dimer (>1mcg/ml), and LDH (250U/L) were laboratory biomarkers predictors of severe infection amongst cancer patients. Age (>65 years)], smoking status, cardiac disorder, history of hypertension/chronic kidney disease, and ICI were also independent predictors of severe COVID-19 in patients with cancer by Cox proportional hazard univariate analysis [53].

A multicenter study evaluating clinical outcomes and mortality among 105 patients with COVID-19 and cancer in Wuhan described poor clinical outcomes and heightened mortality, alerting clinicians and oncologists. Patients with cancer had higher observed death rates, higher rates of ICU admission, and higher chances of requiring mechanical ventilation. Lung cancer was the most prevalent cancer type (20.95%), followed by gastrointestinal cancer (12.38%), breast cancer (10.48%), thyroid cancer (10.48%), and hematological cancer (8.57%). Patients with hematological cancer had a relatively high death rate (33.33%), high ICU admission rate (44.44%), high risk of severe disease (66.67%), and high need of mechanical ventilation (22.0%0). Patients with lung cancer had the second-highest risk levels for critical COVID-19 disease. Concerning cancer stage, metastatic cancer was correlated with even higher risks of ICU admission (OR 6.59 [CI95% 2.32-18.72], p<0.01), critical disease (OR 5.97 [CI95% 2.24-15.91], p<0.01), and use of mechanical ventilation (OR 55.42 [IC95% 13.21-232.47], p<0.01). Nonetheless, patients without metastatic cancer did not demonstrate statistically significant different clinical outcomes compared with patients without cancer. From 105 COVID-19 patients with cancer, 12.26% had radiotherapy, 14.15% received chemotherapy, 7.62% received surgery, 3.81% had target therapy, and 5.71% received immunotherapy within 40 days before onset of COVID-19 infection. Patients who received immunotherapy had high chances of evolving with critical symptoms (66.67%). Furthermore, patients with COVID-19 and cancer had a higher hospital mean length of stay compared to non-cancer patients (27.01 vs. 17.75, p<0.01) [54].

Hence, cancer seems to be associated with a more severe SARS-CoV-2 infection with more adverse and unfavorable clinical outcomes. Intensivists and oncologists should screen for concomitant comorbidities, severe clinical manifestations and a laboratory profile denoting a more profound inflammatory and thrombotic profile in patients with COVID-19 and cancer, due to an augmented risk for severe illness and more adverse clinical outcomes during hospitalization.

Cancer as a risk factor for mortality in COVID-19

As already mentioned, cancer seems to be also associated with higher in-hospital mortality of patients with COVID-19. In a retrospective observational cohort study in Lombardy, including 3,988 critically ill patients with COVID-19 evaluating the risk factors associated with mortality among patients in ICUs, malignant neoplasm was associated with higher risk of death (HR 1.45 [CI95% 1.25-1.68], p<0.001) and the mortality rate per 100 patients-days was 17.3 [55]. Furthermore, Mehta et al. in an initial report describing the outcomes of 218 cancer patients with laboratory-confirmed COVID-19 in a New York hospital system revealed that COVID-19 in patients with cancer correlated with a significantly increased risk of case fatality. From 218 patients, a total of 61 (28.0%) patients died with a CFR of 37.0% for hematologic malignancies and 25.0% for solid tumors. Moreover, an age-and-sex matched cohort of 1,090 patients at a 5:1 ratio of non-cancer to cancer COVID-19 patients from the same hospital system and time period was also performed to compare and estimated the mortality risk among patients with cancer. The CFR was remarkably elevated in all age cohorts within cancer patients compared to non-cancer patients' control. Moreover, in a second comparison of cancer and COVID-19 mortality with official non-cancer case numbers from New York State, the CFR in cancer patients was significantly higher in 45-64 (64.0% vs. 4%; OR 4.65, p=0.0001), 65-74 (22.0% vs. 12.0%; OR 2.17, p=0.020), and >75 (46.0% vs. 26.0%; OR 2.44, p=0.0001) age groups. After logistic regression multivariate model analysis, ICU admission, D-dimer levels, lactate, LDH, and comorbidity score were significantly associated with mortality in cancer patients with COVID-19 [56]. Besides, findings from the retrospective analysis from Yang et al. also demonstrated that male sex and chemotherapy were factors associated with death during hospital admission [49, 57].

Meng et al. in a retrospective analysis including 3,232 hospitalized patients with pathogen-confirmed COVID-19 in Wuhan evaluated prognostic factors with epidemiological analysis and accentuated a higher risk of mortality for cancer patients with SARS-CoV-2 infection. Hospitalized patients with cancer and COVID-19 exhibited a significant increase in mortality rate (29.4% vs. 10.2%, p<0.0001). Interestingly, patients with hematological malignancies presented worse clinical outcomes with twice the risk of death than patients with solid

tumors (50.0% vs. 26.1%, p=0.06). In addition, the findings indicated a significantly increased risk of mortality in cancer patients which developed in-hospital complication. In univariate (OR 3.66 [CI95% 2.37-5.63], p<0.0001) and multivariate (OR 3.92 [CI95% 2.12-5.42], p<0.0001) analysis of risk factors for mortality in 2,665 included patients, cancer history was an independent risk factor for in-hospital mortality in patients with COVID-19 [58]. Likewise, in a prospective observational study analyzing 800 patients with a diagnosis of cancer and symptomatic COVID-19 risk of death was significantly associated with advanced age, male sex, and the presence of other preexisting comorbidities such as hypertension and CV disease, despite the latter not obtaining statistical significance. Also, patients received cytotoxic chemotherapy within 4 weeks before testing positive for SARS-CoV-2 infection. After adjusting for age, gender, and comorbidities, the study demonstrated that past chemotherapy had no significant impact on in-hospital mortality in cancer patients with COVID-19 compared with patients who had not received chemotherapy (OR 1.18 [CI95% 0.81-1.72], p=0.380).

Hence, these studies confirm cancer as an important risk factor for mortality in patents with COVID-19 [59]. A summary of the major studies describing the clinical characteristics and predictors associated with severe COVID-19 and mortality in patients with cancer can be found in Table 1.

Cancer Management during COVID-19 Pandemic

The COVID-19 pandemic had a considerable impact on the overall delivery of health care since health care workers and facilities have a high viral spreading

Table 1. Overview of oncologic patient management recommendations by ASCO and ESMO.

Situation description	ASCO Recommendation[63]	ESMO Recommendation[64]
Before patient arrival prevention	Screening for symptoms between 48 and 72 hours before the appointment. If present, rescheduling or telemedicine consultation should ensue.	Adaptation to pandemic scenario. + Telemedicine as a feasible option.
During patient arrival prevention	Establishment of COVID-19 triage stations in every point of entry of the respective facility. + Referral to isolated Ward if screening is positive with physician evaluation for the necessity of molecular testing for SARS- CoV2.	Patients with fever and upper respiratory tract symptoms OR suggestive radiographical findings should be tested if testing is available. + Patients should be referred to different areas (COVID positive, COVID under investigation OR COVID-19 negative) according to their status.
Clinical inpatient management	Infusion therapy and radiotherapy in COVID- 19 positive or suspected patients is conditioned to 2 negative tests done 24 hours apart. + Symptomatic inpatients have priority in case of scarce testing material for SARS-CoV2. + Providing surgical services for patients without immediately life- or limb-threatening conditions only after a local decrease of COVID-19 incidence for at least 14 days.	G-CSF criteria expansion to prevent febrile neutropenia during pandemic setting. + Prophylaxis with low molecular weight heparin or NOACs for all patients with cancer and COVID-19. + Constant individualization of therapy considering potential infection risk/ COVID-19 complication exacerbation and possible benefits.
Healthcare personnel prevention measures	WHO recommendations + Consider testing for COVID-19 positive patient exposed staff. + Immediate self-isolation for at least 14 days if HCP develops symptoms. + Facilities should consider screening for symptoms and fever in all HCP before the beginning of every work cycle	WHO recommendations + Testing intervals defined by local health authorities. + Swab testing should be offered to all symptomatic HCP. + Symptomatic healthcare workers should abstain from work/home quarantine until swab is negative.

ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; WHO: World Health Organization; NOACs: Novel oral anticoagulants; HCP: Health care personnel.

potential [60]. Cancer patients are often submitted to regular hospital admission and due to higher risk of severe disease in this group, oncological practice guidelines and recommendations be revisited [61,5]. The American Society of Clinical Oncology (ASCO) released a special report regarding the delivery of cancer care during the COVID-19 pandemic. The report addresses clinical consultations and cancer surgeries scheduling's. Oncologists are advised to ask patients about the presence of flu-like symptoms between 48 and 72 hours before the appointment. If these are present, telemedicine consultation or rescheduling after 14 days should be considered. If the symptoms persist for more than 14 days, the patient is directed to a primary care physician. In person consultation should only occur after the primary care physician determines that the patient is no longer infectious [62].

The European Society for Medical Oncology (ESMO) has a slightly different approach regarding in person medical consultation. ESMO highlights the importance of tailoring the intensity of care and social measures in cancer patients according to the local pandemic scenario. Telemedicine follow-up and triage may be a useful alternative to face-to-face appointments during the pandemic setting [63].

Upon patient arrival at the healthcare service, ASCO recommends the establishment of triage stations outside of the facility screening for COVID-19 symptoms and fever. The process should guarantee social distancing of a minimum of six feet between every person accessing the facility, with educational materials about infection prevention available and use of masks being obligatory. The suspected COVID-19 patients should receive a wristband before entry and be escorted to designated isolation areas. Testing for SARS-CoV-2 should be considered by the oncologist that would evaluate if a treatment delay is a necessity or whether patient is manifesting confounding symptoms (tumor fever) and further COVID-19 related action is not necessary [62].

ESMO conditions COVID-19 testing to the availability of laboratory resources in the respective healthcare facility. It also suggests dividing outpatients into three separate wards: COVID-19 positive, COVID-19 under investigation, and COVID-19 negative and suggests that patients COVID-19 positive or under investigation for COVID-19 should not be allowed to have access to the cancer center facilities [63].

ESMO also suggests expanding the criteria for the use of G-CSF (prevention and treatment of febrile neutropenia) during the pandemic setting especially in intermediate (10%-20%) risk, high risk (>20%), and elderly patients with comorbidities. Due to the increased risk of a thromboembolic event in COVID-19 cancer patients, ESMO also suggests prophylaxis with low molecular weight heparin or novel oral anticoagulants (NOACs) for all patients with these conditions. Constant evaluation of patient risk of infection and complications by COVID-19 infection and the benefits of specific therapies are heavily emphasized in the ESMO guidelines [63].

According to ASCO, infusion therapy and radiotherapy for COVID-19 positive patients or patients under investigation for COVID-19, should be conditioned to two negative COVID-19 tests performed at least 24 hours apart. In the case of scarce testing material, the priorities according to ASCO should be: (1) hospitalized symptomatic patients/symptomatic residents of congregated living settings; (2) symptomatic patients; (3) asymptomatic patients awaiting for immunosuppressive therapy/deemed a priority by public health departments or clinicians. Also, ASCO supports ACS measures about elective surgeries. ACS suggest resuming elective surgery only after at least a consecutive 14-day decline in local COVID-19 incidence rates [62, 64].

Furthermore, given that there is a considerable overlap between initial presentations of COVID-19 and febrile neutropenia in the oncologic patient, the Multinational Association of Supportive Care in Cancer (MASCC) released a position paper regarding clinical screening, evaluation and patients in the risk of febrile neutropenia with confounding symptoms, such as fever and dyspnea [65]. MASCC supports the notion that screening interviews that address responses indicative of at least one symptom including exposure risk, fever, and respiratory symptoms without other known causes are imperative to determine whether patients might be infected with COVID-19. If the interview reveals at least one symptom or exposure risks to SARS-CoV-2, the patient should be referred to a contact isolation room for blood collection, clinical examination by a physician wearing personal protective equipment, and COVID-19 testing. If the patient presents a high risk for febrile neutropenia (myeloablative therapy within the last 6 weeks), cultures of possible infection foci (blood, urine, sputum) should be performed, and a first dose of broad-spectrum antibiotics provided. After the results of the blood count, if signs of febrile neutropenia are present (single oral temperature of higher than 38.3 °C (101 °F), or greater than or equal to 38.0 °C over at least 1 hour and absolute neutrophil count less than 500/μL or less than 1000/μL with a predicted rapid decline to less than 500/μ), the patient should be stratified with the MASCC risk score for febrile neutropenia. If the MASCC score is less or equal to 21, the patient should be admitted to the hospital in the general wards/ICU if tested negative for COVID-19, to the shared COVID-19 inpatient facilities if positive for COVID-19 or to the individual COVID-19 inpatient facilities if tested negative for COVID-19 but presenting highly suggestive clinical symptoms (flu-like symptoms, bilateral lung infiltrates with peripheral distribution on CT, high-risk travel/exposure). In the latter cases, follow-up testing should be repeated in 24-48 hours. MASCC management recommendations for febrile neutropenia in the COVID19 pandemic are in line with ESMO guidelines [65].

It is remarkable the discordance between the numerous published articles in that matter due to

a multitude of factors, such as differences in the national healthcare systems and demographics of the publishing institutions. The scarcity of literature on cancer and COVID-19 at the time of publication and the need for a rapid response to the pandemic blunted the multicentric discussion during the formulations of these policies [66, 67].

Despite the absence of a consensus between the multiple published guidelines and recommendations, these share common ground in recognizing that a delay of unnecessary treatment, the reduction of toxicity, and the identification of priorities for surgery, radiotherapy, and systemic therapies as fundamental for cancer treatment during the pandemic setting. The notion of primum- non-nocere (first, do no harm) in conjunction with adequation of optimal care with demographic, structural, and organizational difficulties seem to be the main driving idea behind these ideals [66,67,68]. The main recommendations regarding oncologic patient management during the COVID-19 pandemic proposed by ASCO and ESMO are summarized in Table 2.

Table 2. Summary of the major findings regarding mortality and severe COVID-19 among patients with cancer.

Author	N	Design	Age (years)	Comorbities	Major findings
Tian et al. (2020)[51]	751	Prospective	64.0	HTN (39.0%) DM (26.0%) CAD (10.0%) CKD (3.0%)	1. Severe COVID-19: (Cancer vs. non-cancer): (64.0% vs. 32.0%; OR 3.61 [95%CI: 2.59-5.04], p<0.0001). 2. Risk factors for severity in patients with cancer: Advanced tumor stage (OR 2.60 [95%CI: 1.05-6.43], p=0.039), elevated TNF (OR 1.22 [95%CI: 1.01-1.47], p=0.037), elevated NTproBNP (OR 1.65 [95%CI: 1.03-2.78], p=0.032).
Kuderer et al. (2020)[48]	928	Cohort	66.0 (57.0-76.0)	0 (14.0%) 1 (22.0%) 2 (25.0%) 3 (13.0%) >4 (21.0%)	1. Severe COVID-19: -ICU admission (14.0%) -Supplemental oxygen therapy (44.0%) -Mechanical ventilation (43.0%)
Yang et al. (2020)[49]	205	Retrospective	63.0 (56-70)	HTN (33.0%) DM (11.0%) COPD (2.0%) CAD (8.0%)	1.Severe COVID-19: -ICU admission (15.0%) -Need for mechanical ventilation (66.0%) -Complications: (63.0%) -ARDS (12.0%) -Abnormal liver function (17.0%) -Secondary infection (13.0%) -Coagulopathy (9.0%) -AKI (7.0%) - Septic shock (6.0%)
Dai et al. (2020)[54]	105	Cohort	64.0	HTN (28.57%) CVD (7.28%) DM (5.41%) CLD (6.67%)	1.Severe COVID-19: -ICU admission (OR 2.84 [95%CI: 1.59-5.08]) 2. Mortality (OR 2.34 [95%CI: 1.15-4.77]).
Meng et al. (2020)[58]	2,665	Retrospective	-	-	1.Mortality: (Hospitalized patients with COVID-19 and cancer vs. non- cancer) -(29.4% vs. 10.2%, p<0.0001) (Increased risk of death after in- hospital complications) (OR 16.80 [95%CI: 3.81-74.19]).
Lee et al. (2020)[59]	800	Prospective	69 (59-76)	HTN (31.0%) DM (16.0%) CVD (14.0%) COPD (8.0%0	1.Risk factors for mortality in patients with cancer: Advanced age (OR 9.42 [CI95%: 6.56-10.02], p=0.003) -History of HTN (OR 1.95 [95%CI: 1.36-2.80], p<0.001) -History of CVD (OR 2.32 [95%CI: 1.47-3.64], p=0.281)

DM: Diabetes mellitus; HTN: Hypertension; CVD: Cardiovascular disease; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CLD: Chronic liver disease; CKD: Chronic kidney disease.

In contrast to the abundant number of publications about the management of cancer during the pandemic setting, no data on specific management of COVID-19 for cancer patients besides thromboembolic prophylaxis could be found while writing of this article. Given the complexity of oncologic patients and the high mortality that ensues for those infected with SARS-CoV-2, further studies addressing this particular issue are required.

CONCLUSION

Cancer seems to be associated with more adverse clinical outcomes, critical disease, higher mortality, and poorer prognosis amongst patients with SARS-CoV-2 infection. Moreover, history of cancer must be taken into consideration during the risk stratification of patients with confirmed or suspected COVID-19. Additionally, as cancer seems to be associated with an increased risk of severe disease and fatality, the implementation of preventive measures to reduce the probability of SARS-CoV-2 transmission and proactive strategies to guarantee a precocious diagnosis is vital to decrease the vulnerability of cancer patients during the COVID-19 pandemic. Further studies are still required to completely elucidate the clinical profile and prognosis of cancer patients with COVID-19.

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CONFLICTS OF INTEREST/DISCLOSURE STATEMENT

The authors declare that there is no conflict of interest.

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