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Review

Review

Health influence of SARS-CoV-2 (COVID-19) on cancer: a review

Rachel Parise[1], Yiran E. Li[2], Rishi M. Nadar[1], Sindhu Ramesh[1], Jun Ren[3,4], Manoj Yogish Govindarajulu[1], Timothy Moore[1], and Muralikrishnan Dhanasekaran[1,*]

[1]Department of Drug Discovery and Development, Auburn University Harrison School of Pharmacy, Walker Building, Auburn, AL 36849, USA, [2]Queen Mary College of Nanchang University, Nanchang 330006, China, [3]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, WA 98195, USA, and [4]Department of Cardiology, Zhongshan Hospital Fudan University, Shanghai Institute of Cardiovascular Diseases, Shanghai 200032, China

*Correspondence address. Tel: +1-334-750-0193; E-mail: dhanamu@auburn.edu

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Abstract

The novel coronavirus, namely, SARS-CoV-2 (COVID-19), broke out two years ago and has caused major global health issues. Adequate treatment options are still lacking for the management of COVID-19 viral infections. Many patients afflicted with COVID-19 may range from asymptomatic to severe symptomatic, triggering poor clinical outcomes, morbidity, and mortality. Cancer is one of the leading causes of death worldwide. It is pertinent to re-examine cancer prevalence during the COVID-19 pandemic to prevent mortality and complications. Understanding the impact of SARS-CoV-2 on cancer is key to appropriate healthcare measures for the treatment and prevention of this vulnerable population. Data was acquired from PubMed using key search terms. Additional databases were utilized, such as the Centers for Disease Prevention and Control, American Cancer Society (ACS), and National Cancer Institute (NCI). Cancer patients are more prone to SARS-CoV-2 infection and exhibit poor health outcomes, possibly due to a chronic immunosuppressive state and anticancer therapies. Male sex, older age, and active cancer disease or previous cancer are risk factors for COVID-19 infection, leading to possible severe complications, including morbidity or mortality. The speculated mechanism for potentially higher mortality or COVID-19 complications is through reduced immune system function and inflammatory processes through cancer disease, anticancer therapy, and active COVID-19 infection. This review includes prostate, breast, ovarian, hematologic, lung, colorectal, esophageal, bladder, pancreatic, cervical, and head and neck cancers. This review should help better maintain the health of cancer patients and direct clinicians for COVID-19 prevention to improve the overall health outcomes.

Key words SARS-CoV-2, COVID-19, pathology, cancer, tumor

Introduction

Since its first inception in Wuhan, China, in late 2019, the novel coronavirus infectious disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has claimed over 200 million confirmed cases with 5 million mortalities over the past two years. Currently, limited therapeutic options are readily available. COVID-19 exhibits vast variation in subpopulations of individuals, making clinical management extremely challenging. Our main goal here is to determine the impact of SARS-CoV-2 (COVID-19) on adult cancer patients during the current COVID-19 pandemic. The National Cancer Institute (NCI) reported that cancer is a leading cause of death worldwide, with 18.1 million new cases in 2018 and 9.5 million cancer-related deaths worldwide. The number of annual new cancer cases is estimated to increase to 29.5 million, and the number of cancer-related deaths is estimated to increase to 16.4 million by 2040. The Centers for Disease Prevention and Control (CDC) stated that both cancer patients and survivors of cancer are more prone to COVID-19 infection than the general healthy population. Cancer patients are more vulnerable to infections because of the presence of comorbidities, poor health

status, and immunosuppression caused by both cancer disease and anticancer treatment [1,2]. Our study focused on analysing the clinical health outcomes, risk factors, and potential pathologies of prediagnosed cancer patients with SARS-CoV-2 infection. Data was acquired from PubMed and other databases using key search terms (Supplementary Data, a, b, and c). Cancer patients may also be at an increased risk for contracting COVID-19 through nosocomial transmission among patients in healthcare settings because of more frequent visits to hospitals for anticancer therapy [3]. Dai and colleagues [1] reported patients with cancer and COVID-19 infection display a 3-fold increase in the death rate compared with COVID-19 patients without cancer, with a more severe complication. The CDC's list of medical conditions putting an individual at higher risk for severe COVID-19 illness are cancer, chronic kidney disease, chronic liver disease, chronic lung disease, dementia, diabetes, Down syndrome, cardiac conditions, HIV infection, immunocompromised state, mental health conditions, overweight or obese, pregnancy, sickle cell disease, current or former tobacco smokers, organ or blood stem cell transplant, stroke, substance use disorder, and tuberculosis.

Development of Cancer

Cancer is a genetic disease where gene mutations cause the development of abnormal uncontrollable dividing cells capable of invading and destroying normal body tissues and cells, leading to disruption of normal organ and cellular function. Normal cells undergo abnormal alterations named hyperplasia and dysplasia that progress into cancer cells. A healthy body system is capable of eliminating damaged DNA prior to the onset of carcinogenesis. Nonetheless, this function declines with age to evoke an increased prevalence of cancer later in life. A tumor develops when a cluster of uncontrolled cancer cells grows in solid tissues such as muscle and bone. Tumors may be benign or malignant. Benign tumors do not grow rapidly or spread like malignant tumors, which grow rapidly, invade, and destroy normal tissues while spreading throughout the body.

There are over 100 forms of cancer, and each type is named after organs or tissues where the cancer originates or by cell type that forms the cancer. The more prevalent types of cancers listed by the NCI include carcinomas, sarcomas, leukemia, lymphoma, multiple myeloma, melanoma, brain and spinal cord tumors, germ cell tumors, neuroendocrine tumors, and carcinoid tumors. Three types of genes, proto-oncogenes, tumor suppressor genes, and DNA repair genes, are responsible for genetic changes leading to cancer. Many cancer types have similar mutations, and treatments are now designed and available to target gene mutations associated with different cancer types.

Impact of COVID-19 and Cancer on Immune System Function

The normal function of the immune system is designed to recognize and eliminate foreign cells, including potential tumorigenic cells [4]. Cancer cells must bypass normal immune system control by evading eradication. Tumor-associated inflammation also contributes to tumorigenesis by providing growth factors, proangiogenic factors, and extracellular matrix-modifying proteins that favor tumor cell proliferation and metastases [4,5]. This mechanism supports cancer development in immunocompromised states, placing cancer patients at elevated risk for infections. Cytotoxic CD8 + T cells associated with the adaptive immune system are important regulators in the anticancer immune response [6]. T lymphocytes are responsible for identifying unwanted and foreign material in the body that is essential for normal immune function. Cytotoxic CD8 + T cells are prominent killers of pathogens and neoplastic cells. CD4 + T cells aid in the maintenance of the CD8 + T-cell response and prevent exhaustion and senescence. These T cells are a viable option for targeted therapy in COVID-19 because they are less susceptible to viral escape than antibodies [7]. Immune checkpoint inhibitors are specifically designed to increase the adaptive immune response through CD8 + T-cell checkpoints and regenerate exhausted CD8 + T cells to restore normal function. The dysregulation of both innate and adaptive immune function is a key sign of SARS-CoV-2 and cancer. CD8 + T-cell function in the lungs of COVID-19 patients and within the tumor microenvironment will alter their functionality, contributing to an exhaustive state and inducing apoptosis [8]. This reduced immune response will cause cancer patients to be at higher risk for COVID-19 disease, COVID-19-related complications, and mortality. Immunological stress caused by SARS-CoV-2 infection or a tumor microenvironment could mimic aging status and result in increased T-cell senescence [9]. In those of advanced age, the stimulation of antigens caused CD8 + T cells to present senescent features that contribute to low-grade inflammation, a major contributor to several age-related diseases. Immune checkpoints act as gatekeepers for immune responses and maintain immune homeostasis by balancing stimulatory and inhibitory immune checkpoints [10]. Immunity homeostasis fails with tumor growth because of an imbalance between the stimulatory and inhibitory immune checkpoints on the surface of tumor cells. Increased inhibitory immune checkpoints result in tumor immune escape and are major targets in cancer immunotherapy.

Innate immunity is the defense system developed from birth protecting against all antigens. Adaptive immunity develops when a person's immune system induces a response to a foreign particle or substance. SARS-CoV-2 has the ability to evade innate immune system pathways, such as innate recognition, signaling, IFN induction, and IFN-stimulated genes, through the expression of a number of viral proteins responsible for inhibiting these mechanisms [11]. Antibodies can neutralize SARS-CoV-2 by inhibiting spike protein binding to the angiotensin converting enzyme-2 (ACE2) receptor. The antibody response is poor in immunosuppressed patients, contributing to the chronic persistence of the virus and its variants [11,12]. The CD4 + and CD8 + T cells induced by SARS-CoV-2 target many antigens and are associated with mild disease [11,13]. Antibody-mediated depletion of CD8 + T cells partially reduces protection against rechallenge with SARS-CoV-2 [11,14]. The major immune mechanism of COVID-19 leading to serious complications is increased cytokine production causing cytokine release syndrome or cytokine storm. Cytokine storm occurs when COVID-19 triggers the immune system to release excess proinflammatory proteins or cytokines, which have detrimental consequences on various tissues and organ systems. Interestingly, CD8 + T cells from COVID-19 patients produced granzyme B, CD107a, IL-17A, IL-2, TNF-alpha, and IFN-gamma, which fueled a cytokine storm in severe COVID-19 [9,15,16]. Inflammation is also a serious consequence caused by SARS-CoV-2 that is responsible for COVID-19 complications in hospitalized and nonhospitalized patients causing mild to severe symptoms. In elderly individuals, it is possible that a low-grade inflammatory state characterized by increased levels of IL-6,

IL-1RA, TNF-alpha, IL-1 and C-reactive protein (CRP) may contribute to impaired defense of the SARS-CoV-2 virus and detrimental inflammatory responses contributing to lung injury or other infection-induced complications [9]. Additionally, this response may also correlate with uncoordinated adaptive responses of COVID-19 CD4+ and CD8+ T cells in elderly individuals, leading to an unsuccessful response to new viral antigens [9,13]. During COVID-19, a storm of soluble immune checkpoints occurs in peripheral circulation and correlates with disease severity [10]. The circulating levels upon hospital admission could be better predictors of mortality versus inflammatory markers, such as cytokines and chemokines. Similar to their role in cancer therapy, soluble immune checkpoints could also serve as drug targets for COVID-19 treatment [10,17].

B.1.1.529, the SARS-CoV-2 variant, commonly known as Omicron, has more than 30 mutations in the spike protein, allowing for its ability to overcome immune responses from infection and vaccine-induced immunity [7]. Tarke *et al.* [18] stated there was limited impact of mutations on T-cell reactivity within the spike after natural SARS-CoV-2 infection and mRNA vaccination against the concerning variants at the time of study, which included B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.427/429 (Epsilon); however, in a minority, there was a 2-3-fold decrease in the CD8+ T-cell response against beta and epsilon variants [7].

Moreover, anticancer treatments, such as cytotoxic chemotherapy and radiation, cause immunosuppression by reducing white blood cell counts. Therefore, cancer disease and anticancer therapy may predispose a patient to viral infections, such as COVID-19. Cancer patients receiving oral anticancer agents, such as tyrosine kinase inhibitors, targeted therapy, and hormonal treatment, and those receiving monoclonal antibodies have less impact on the immune system compared to cytotoxic chemotherapy. Cancer patients taking immunotherapy may be at the greatest risk for serious COVID-19 infection [4]. Chemotherapy, targeted therapy, immunotherapy, radiation therapy, and surgery are more likely to enhance infection risk due to the possibility of injuring skin cells or causing damage to mucous membranes, which allows easier transmission of bacteria or viruses to enter the body, causing immune dysfunction and infection. Immune checkpoint inhibitors are immunotherapy drugs that block checkpoint proteins from binding with their respective partners, allowing CD8+ T cells to target and kill cancer cells. Mortezaee and Majidpoor [8] reported PD(L)-1 blockade is safe for use in cancer patients with COVID-19, and the use of this pathway reduces the risk of attack from the virus. Minkove *et al.* [19] found that prior use of immune checkpoint inhibitors before COVID-19 infection did not alter outcomes, such as survival, severe events, or hospitalizations, significantly.

Cancer Is Related to COVID-19 Risk

The cancer patient population has an elevated risk of becoming infected with SARS-CoV-2 (COVID-19), leading to severe complications, including mortality. Cancer patients are a vulnerable population because of cancer disease, anticancer therapy, and surgery-induced immunosuppression [20,21]. Kong *et al.* [22] reviewed the epidemiology and clinical characteristics of cancer patients with COVID-19 and determined that Europe presented higher cancer and COVID-19 prevalence rates and incidences of COVID-19 severe illness in cancer patients than North America and Asia-Pacific. The study also concluded prevalence rates increase with increasing age. The prevalence rate for severe illness and mortality in COVID-19 patients with cancer was higher than the incidence rate for severe illness in COVID-19 patients without cancer. However, it is important to note the small sample sizes depicted in the study, which could negatively influence the reported prevalence rates. Liang *et al.* [23] studied COVID-19 patients with cancer in China and concluded that cancer patients represented a 3.5-fold increased risk for COVID-19-related serious events, characterized by intensive care admission, requirement for mechanical ventilation, or mortality due to the immunocompromised condition related to both their malignancy and anticancer therapy management.

The information listed in Table 1 characterizes the potential mechanisms COVID-19 utilizes to cause infection in the cancer patient population. The most common and well-studied mechanism of COVID-19 pathology for causing severe disease is the activation of cytokine storm. Cytokine storm occurs through the excess production of proinflammatory cytokines, leading to a common COVID-19 complication known as acute respiratory distress syndrome (ARDS) [24]. ARDS can lead to further tissue damage, causing multiorgan destruction and death. Hyperinflammatory processes can occur in conjunction with cytokine storm to cause tissue damage, ARDS, or multiorgan failure [25]. COVID-19 uses angiotensin-converting enzyme-2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) to enter pneumocytes, the cells lining the alveoli of the lungs [26]. This mechanism is active when a person inhales the aerosolized particles, and the infection enters the lungs. As the coronavirus binds to ACE2 with the aid of TMPRSS2 for entry into human host cells, the virus can then spread to other organs and tissues throughout the body. Airway damage from former or current smokers could increase the risk of COVID-19 since the body's airways no longer function as a barrier and could allow viral particles to pass through and spread to other tissues. In cancer, IFN-1 plays a role in inhibiting tumor proliferation and promoting tumor cell death [21]. However, impaired IFN-1 signaling allows tumor progression. Studies have shown that IFN-1 signaling is reduced in COVID-19 infection, which allows tumors to proliferate and grow [21]. Androgen receptor signaling is another pathway that increases TMPRSS2 expression, an aid for COVID-19 entry and a potential aid in tumor formation [21]. Immune checkpoint signaling plays a key role in immune tolerance, but many viral pathogens use

Table 1. Potential SARS-CoV-2 infection pathology in cancer patients

Pathology	Reference
Cytokine storm	Chakravarty *et al.* [27]
Hyperinflammatory mechanisms	Chaudhari *et al.* [28]
COVID-19 entry mechanism through ACE2/TMPRSS2	Gallo *et al.* [26]
Airway damage of former/current smokers (lung)	Zong *et al.* [21]
Androgen receptor signaling	Ragab *et al.* [24]
Immune checkpoint signaling	Tan *et al.* [25]

this signaling pathway to escape immunity by upregulating checkpoint molecules [21].

The information provided in Figure 1 represents the relationship between cancer and COVID-19. Cancer patients are more prone to COVID-19 infection due to various risk factors and different pathologic mechanisms. After infection, COVID-19 can lead to severe, symptomatic disease and complications causing morbidity and/or mortality.

The information provided in Table 2 displays the common patient parameters identified in COVID-19 patients with cancer. Overall, COVID-19 patients with cancer were older (≥60 years old) and male. Advanced age and male sex are common risk factors seen in COVID-19 patients without cancer. The common risk factors for both COVID-19 and cancer are males, increased age, ethnicity (minorities), comorbidities, obesity, and tobacco smoking [21,27,29]. Men and women have similar susceptibility to COVID-19, but men

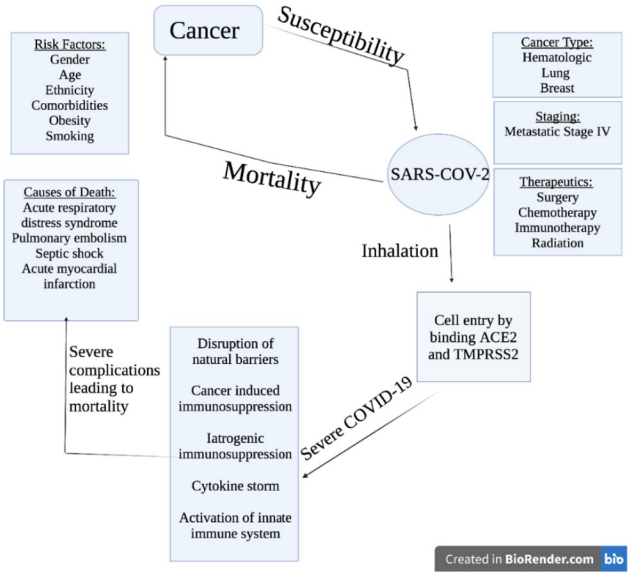

Figure 1. Mode of SARS-CoV-2 transmission in cancer patients

Table 2. Cancer patient parameters with increased risk for cancer and COVID-19

Cancer type	Age	Sex	Genetics*	Reference
No differentiation	≥ 60	Male	–	Dai *et al.* [1] Kong *et al.* [22] Zhang *et al.* [29]
Prostate cancer	≥ 60	Male	ACE2 TMPRSS2	Bhowmick *et al.* [30] Chakravarty *et al.* [27] Rodriguez *et al.* [35] Mou *et al.* [55] Liang *et al.* [23]
Breast cancer	≥ 50	Female	–	Chakravarty *et al.* [27] Shakartalla *et al.* [36]
Ovarian cancer	50–60	Female	–	Chaudhari *et al.* [28]
Hematologic cancer	≥ 60	–	–	Chakravarty *et al.* [27]
Lung cancer	≥ 60	Male	ACE2 TMPRSS2	Wang *et al.* [37] Chakravarty *et al.* [27] Gallo *et al.* [26]
Colorectal	≥ 60	Male	ACE2 TMPRSS2	Wang *et al.* [37] Chakravarty *et al.* [27]
Esophagus	≥ 60	Male	ACE2 TMPRSS2	Wang *et al.* [37]
Bladder	≥ 60	Male	ACE2	Wang *et al.* [37] Chakravarty *et al.* [27]
Pancreatic	≥ 60	Male	ACE2	Wang *et al.* [37]
Cervical	≥ 60	Female	–	Wang *et al.* [37]
Head and neck cancer	≥ 70	–	–	Sharma *et al.* [38]

*More research is needed to study cancer genetics directly with the SARS-CoV-2 virus to determine the impact on susceptibility rates in the cancer patient population.

appear to have greater disease severity and mortality regardless of age [30,31]. Park *et al.* [32] studied sex differences in COVID-19 illness in cancer patients. This study revealed males with cancer were at higher risk of severe illness and death due to COVID-19. Zhang *et al.* [29] confirmed COVID-19 patients with cancer have an increased risk of fatality and severe illness, and the occurrence of severe events or mortality is attributed to age, sex, and coexisting comorbidities. Cheng *et al.* [33] discussed the role of ferritin in COVID-19 patients with one or more existing comorbidities, including diabetes mellitus, thrombosis, and cancer. The results indicated significantly higher levels of ferritin were present in these comorbidities versus patients without. Elevated ferritin could be a poor prognostic factor since levels were significantly increased in severe patients and in nonsurvivors versus nonsevere patients. Hyperferritinemia can occur in COVID-19 infection, which can promote the production of several proinflammatory and anti-inflammatory cytokines, including IL-1β and IL-10 [34].

ACE2 and TMPRSS2 are known genes that aid in COVID-19 entry into host cells. Cells with ACE2 and TMPRSS2 expression may act as targets, increasing susceptibility to COVID-19 infection [27,37]. COVID-19 has been shown to be dependent on TMPRSS2 activity for the entrance and infection of human host cells [39]. Wang *et al.* [37] reported the mRNA expression levels of ACE2 and TMPRSS2 were higher in lung and colorectal cancers, and these two cancer types contained the highest prevalence rates (24.7% and 20.5%, respectively) among breast (13.0%), esophageal (7.6%), bladder (7.3%), pancreatic (6.1%), and cervical (6.0%) cancers. However, it is important to note the study was limited by a small sample size and could alter accurate prevalence rates.

COVID-19 cases with a confirmed time since cancer diagnosis of 1-5 years vs < 1 year were significantly associated with nonsevere disease outcomes, suggesting that the more active the tumor is, the more serious the COVID-19 infection (HR 0.227, 95% 0.116–0.446, $P < 0.0001$) [40,41]. Cancer type was not differentiated for this statistic. Tagliamento *et al.* [42] and Lunski *et al.* [43] reported cancer patients with active or progressive disease during COVID-19 infection had an increased likelihood of mortality ($P < 0.001$). This was determined by analysing the death rate of 312 patients who had cancer and 4,833 patients without cancer in the USA who were diagnosed with COVID-19. Additionally, Liu *et al.* [3] analysed lab findings in cancer patients with COVID-19, showing a higher percentage of bilateral lung involvement versus noncancer patients. There was also a higher percentage of anemia in COVID-19 patients with cancer, which could explain nutritional deficiencies, suppressed immunity, and increased susceptibility to respiratory pathogens leading to further complications. COVID-19 patients with prediagnosed cancer were more likely to progress to fatal outcomes across 96 articles with 6,518,992 patients [44]. This identified prediagnosed cancer as an independent risk factor for mortality in COVID-19.

Data on post-COVID syndrome is limited, especially in the cancer patient population, but Iqbal *et al.* [45] emphasized the importance of surveillance programs for COVID-19 patients, similar to the National Cancer Survivorship Initiative, in cancer survivorship to improve patient outcomes with follow-up care. The most common symptoms in acute post-COVID-19 were fatigue and dyspnea, while the most common symptoms in chronic post-COVID-19 were fatigue and sleep disturbances. Ernst *et al.* [46] studied potential differences in mental health outcomes of cancer patients versus the general population during the first wave of COVID-19 in Germany. Those with cancer were more likely to report anxiety symptoms, loneliness, and suicidal ideation. Cancer patients reported higher rates of anxiety than control participants. Other studies have also reported higher rates of loneliness in cancer survivors. This data emphasizes the need for psychological support in these populations. Carreira *et al.* [47] studied cancer survivors and their risk of COVID-19 complications. The cohort showed cancer survivors were more likely to have diabetes, asthma, respiratory, cardiac, neurological, renal, and liver diseases and less likely to be obese. There were 205 influenza hospitalizations and deaths, with cancer survivors at higher risk. Overall, the study concluded the risks of severe COVID-19 outcomes were elevated in cancer survivors compared to the general population.

Hematologic cancer and COVID-19

Hematologic cancers are blood cancers that develop in the bone marrow, where blood is formed. Abnormal cancer cells begin to grow rapidly and interfere with normal blood cells, which usually aids in fighting infections and producing new blood cells. Numerous studies have labeled hematologic cancers as having a higher prevalence rate with COVID-19 infection. Dai *et al.* [1] stated hematologic cancers were one of the cancers with the highest frequency of severe events. The study reported the prevalence rate for hematologic cancer and COVID-19 was 8.57% (9/105 patients), the death rate was 33.33% (3/9 patients), the ICU admission rate was 44.44% (4/9 patients), the risk of severe or critical symptoms was 66.67% (6/9 patients), and the chance of utilizing invasive mechanical ventilation was 22.22% (2/9 patients). Based on this study, hematologic cancers, including leukemia, lymphoma, and myeloma, had the highest severity and death rates compared to other cancers. This is likely attributed to malignant plasma cells, lymphocytes, or white blood cells in hematologic cancer having a reduced immune function. Chakravarty *et al.* [27] reported hematological cancers (leukemia, lymphoma, myeloma) had an incidence rate of 8.57% and a mortality rate of 37.0%. Additionally, Tagliamento *et al.* [42] reported patients with solid or hematological malignancies and COVID-19 infection had a higher probability of mortality with a case fatality rate of 25.4%. This percentage is slightly lower than the other mortality predictions previously mentioned, but the value still represents an elevated risk for hematologic cancers over other cancer types.

Finally, Pagano and coworkers [48] studied hematologic malignancies across 3,801 cases and reported that severe or critical COVID-19 was seen in 63.8% (2425 patients). A total of 73.1% (2778 patients) were hospitalized, 18.1% (689 patients) were admitted to the ICU, and 31.25% (1185 patients) died. The primary cause of death was COVID-19 in 58.1% (688 patients), hematologic malignancies in 14.6% (173 patients), and a combination of both COVID-19 and progressing hematologic cancer in 13.1% (155 patients). The highest mortality in hematologic cancer was in acute myeloid leukemia (40% or 199/497 patients) and myelodysplastic syndromes (42.3% or 118/279 patients). Interestingly, the mortality rate was significantly decreased between the first COVID-19 wave (40.7%, March–May 2020) and the second wave (24.8%, October–December 2020), $P < 0.0001$. This difference might be explained by COVID-19 mutations forming new variants containing different infective characteristics. The risk factors identified for mortality in these patients are age, active malignancy, chronic cardiac disease,

liver disease, renal impairment, smoking history, and ICU stay.

Lung cancer and COVID-19

Lung cancer most commonly develops in smokers. Two major types are non-small cell lung cancer and small cell lung cancer. The most common causes of lung cancer are smoking, secondhand smoke, toxin exposure, and family history. Lung cancer is most prevalent in older age (> 60 years) and males, as represented in Table 2. Patients with lung cancer and COVID-19 had higher mortality rates than those without lung cancer [49]. The risk of severe symptoms of COVID-19 in tobacco smokers was 1.4 × higher and the risk of ICU admission, mechanical ventilation, or death was 2.4 × higher than in nonsmokers [26,50].

Dai *et al.* [1] reported lung cancer as the most frequent cancer type out of 105 hospitalized patients with cancer and COVID-19, containing an incidence rate of 20.95% (22/105 patients). The study included results for lung, gastrointestinal, breast, thyroid, and hematologic cancers. Lung cancer patients had the second highest rates of death (18.18%, 4/22 patients), ICU admission (27.27%, 6/22 patients), risk of severe or critical symptoms (50.00%, 11/22 patients), and chance of utilizing invasive mechanical ventilation (18.18%, 4/22 patients). It was noted metastatic (stage IV) compared to nonmetastatic cancer had higher risks of death, ICU admission, severe conditions, and use of invasive mechanical ventilation. The nonmetastatic cancer groups did not demonstrate significant differences versus noncancerous COVID-19 patients. Chakravarty *et al.* [27] reported the highest incidence rates versus mortality rates in lung cancer (20.95% vs 55%) compared to breast, hematologic, prostate, urothelial, and colorectal cancers. Tagliamento *et al.* [42] compared hematologic, lung, and breast cancer, showing that lung cancer has higher case fatality rates (32.4%).

Studies have shown that ACE2 is highly expressed in comorbidities associated with severe COVID-19 infection, suggesting a higher susceptibility to COVID-19 [51]. ACE2 expression was significantly elevated in lung adenocarcinoma and lung squamous cell carcinoma versus normal tissues, and DNA methylation might be a pathologic mechanism for ACE2 upregulation [52]. ACE2 plays protective role in the lung. Since SARS-CoV-2 uses ACE2 for entry into host cells, the coronavirus causes downregulation of ACE2 in the lung, causing acute respiratory failure [53,54]. Additionally, tobacco smoking increases ACE2 expression in the lungs, a risk factor for lung cancer and susceptibility to COVID-19 [55].

Traditional COVID-19 and cancer risk factors for severe clinical disease are advanced age, comorbidities, and iatrogenic immune impairment; however, cancer of both the upper and lower airways share more risk factors, including tobacco smoke exposure, male sex, airway epithelial damage, chronic obstructive pulmonary disease (COPD), and cerebrovascular disease [26]. Gallo *et al.* [26] explained replication and shedding of COVID-19 occurs in nasal and bronchial epithelial respiratory cells through interactions with ACE2 and TMPRSS2 receptors, both overexpressed in smokers and former smokers. Tobacco smoke airway exposure causes chronic inflammation because of inflammatory cell activation and cytokine release, including IL-6. IL-6 is prevalent in cytokine storm or cytokine release syndrome, leading to severe complications and adverse effects, such as multiorgan damage. This pathway is presented in Table 1, placing patients with cancer of the upper and lower airways at elevated risk for COVID-19 infection, morbidity, and mortality due to tobacco exposure, immunosuppression, cancer disease, and anticancer therapy.

Colorectal cancer and COVID-19

Colorectal cancer is a cancer that starts either in the colon or the rectum. It is the most frequent type of abdominal cancer, and gastrointestinal cancer patients have a greater risk of contracting COVID-19 infection [56]. The CDC's list of common risk factors for colorectal cancer are family history, lack of physical activity, a diet low in fruits and vegetables, a low fiber or high fat diet, a diet high in processed meats, overweight and obesity, alcohol consumption, and tobacco use. Table 2 represents the individual parameters of patients with colorectal cancer having increased susceptibility to COVID-19 infection. Older age (> 60 years) and males are at greater risk. The Mayo Clinic states that the ages for colon cancer are mostly > 50 years.

Chakravarty *et al.* [27] compared the incidence and mortality rates of lung, breast, hematologic, prostate, urothelial, and colorectal cancers in COVID-19. Colorectal cancer had the lowest incidence rate (4.79%) and one of the second highest mortality rates (38%) behind lung cancer and was equal to urothelial cancer mortality. A report from China analysed 1590 cases of COVID-19; 18 cases (1%) had a history of cancer, of which 3 cases (16.7%) had colorectal cancer [56,57]. In this analysis, COVID-19 patients who had an active or previous history of cancer were observed to have greater adverse effects.

ACE2 and TMPRSS2 are expressed in the ileum, colon, and intestinal epithelial cells, allowing COVID-19 entry into colon cells [58]. Anticancer therapy, cancer disease, and immunosuppression could be possible mechanisms contributing to increased COVID-19 susceptibility in colorectal cancer. Other potential pathologies related to COVID-19 infection in cancer are listed in Table 1. Severe complications, morbidity, and mortality are predicted in coexisting cancer and COVID-19 since there is a weakened immune response due to the cancer disease and anticancer therapy. Immunosuppression allows COVID-19 to continue spreading throughout the body with the potential to cause multiorgan damage.

Prostate cancer and COVID-19

Prostate cancer affects the gland that produces seminal fluid and is one of the most common cancers in men. Typical risk factors from the American Cancer Society (ACS) for prostate cancer are older age (> 50 years), African American/Caribbean men of African ancestry, family history, genetics, diets high in dairy and calcium, obesity, smoking, chemical exposures, prostatitis, sexually transmitted infections, and vasectomy. The individual parameters putting prostatic cancer patients at risk for COVID-19 are older age (> 60 years), males and genetics, as represented in Table 2. Liang *et al.* [23] reported males with cancer were more likely to be infected with COVID-19 and have a worse prognosis than other patient populations.

Chakravarty *et al.* [27] reported an incidence rate of prostate cancer patients with COVID-19 of 16.76% and a mortality rate of 20.0%. The incidence rate was the second highest cancer type behind lung cancer, and the mortality rate was the second lowest after breast cancer. In a male study, 9.5% (430/4532 patients) had cancer and COVID-19, and prostate cancer accounted for 2.6% (118/4532 patients) [59,60]. These data represent elevated infection rates for prostatic cancer patients. Mou *et al.* [59] concluded prostate cancer patients were more likely to be susceptible to

COVID-19 than healthy people because of the immunocompromised state, but no evidence indicates prostate cancer is a risk factor for COVID-19. Lundon *et al.* [61] conducted a retrospective study showing out of 38,324 patients tested for SARS-CoV-2, 880 (2.3%) had a documented genitourinary malignancy, and 10,362 (27%) tested positive. Of these cancers, prostate cancer was the most common, representing 315 patients, of whom 34.3% tested positive. Based on this cohort, those with prostate cancer tested positive more frequently than those with other genitourinary cancers, such as bladder, kidney, and testicular cancer.

As previously stated, COVID-19 utilizes ACE2 and TMPRSS2 for viral entry and fusion into human host cells. TMPRSS2 is highly expressed in prostate secretory epithelial cells and is dependent on androgen signaling [39]. TMPRSS2 is upregulated in prostate cancer, supporting tumor growth and progression [35]. Therefore, these patients would most likely be more susceptible to COVID-19 infection. TMPRSS2 could possibly be a drug target for COVID-19 therapy and prevention in prostate cancer [39,35]. Systemic immunosuppression in prostate cancer may be due to the disease and anticancer therapies. However, cancer patients are more prone to infection than noncancer patients and have a higher risk for detrimental COVID-19 infection.

Breast cancer and COVID-19

Breast cancer is the second most common cancer among women in the USA, with a higher death rate among African American women versus white women, as reported by the CDC. Risk factors for breast cancer are older age (> 50 years), genetic mutations (BRCA1, BRCA2), reproductive history, dense breasts, family history, diethylstilbestrol, low physical activity, overweight or obese after menopause, hormone replacement therapy, reproductive history, and alcohol consumption. The individual patient parameters increasing the infection risk of COVID-19 in breast cancer are > 50 years and females, as listed in Table 2.

Chakravarty *et al.* [27] reported an incidence rate of breast cancer and COVID-19 of 10.48%, and the mortality rate in these patients was 14.0%. This was the second highest incidence rate and lowest mortality rate compared to lung, hematologic, prostate, urothelial, and colorectal cancers. Tagliamento *et al.* [42] also reported breast cancer as having a lower case fatality rate of 14.2% than lung and hematologic cancer. Dai *et al.* [1] reported an incidence rate of 10.48% (11/105 patients) in breast cancer patients with COVID-19. Shakartalla *et al.* [36] and Fillmore *et al.* [62] reported breast cancer was associated with the highest rate of COVID-19-related death in a study containing 1,794 COVID-19 with cancer patients. In this study, dyslipidemia was associated with an increased risk of COVID-19. COVID-19 utilizes lipids by ACE2 receptor binding, entry, fusion, and replication. Elevated lipid levels, such as phospholipids, cholesterol, sphingolipids, and eicosanoids, were identified in the serum of breast cancer patients and were relocalized to the alveolar spaces, increasing the susceptibility and possible severity of COVID-19 infection [36]. With this evidence, dyslipidemia management in breast cancer could have potential benefits for COVID-19 therapy and prevention. A retrospective study in China focused on early breast cancer patients who received treatment during the first quarter of the COVID-19 pandemic in 2020 [63]. The results showed that early breast cancer in high-risk regions had a comparative rate of COVID-19 infection, and after COVID-19 quarantine restrictions, fewer diagnoses and surgeries with significant delays were observed when compared with treatment before the restrictions.

Ovarian cancer and COVID-19

Ovarian cancer is a female cancer located in the ovaries. The ovarian cancer types are epithelial ovarian cancer, stromal tumors, and germ cell tumors. Risk factors listed by the Mayo Clinic for ovarian cancer are older age, genetics, family history, overweight or obese, postmenopausal hormone replacement therapy, endometriosis, age at the start and end of menstruation, and never being pregnant. The typical patients with ovarian cancer who become infected with COVID-19 are older age (50-60 years) and females, as shown in Table 2. Chaudhari *et al.* [28] stated hospitalization and death in COVID-19 patients are lower in women than men, but the comorbidities present in ovarian cancer female patients may increase their COVID-19 risk. Common conditions observed in ovarian cancer patients and COVID-19 infection are increased gonadotropin and androgen levels, a dysregulated renin-angiotensin-aldosterone system (RAAS), hypercoagulation, and chronic inflammation [28]. Additionally, the upregulation of proinflammatory cytokines and chemokines, such as TNF-alpha, IL-1beta, IL-2, IL-6, IL-10, IP-10, G-CSF, MCP-1, and M-CSF, in the sera of COVID-19 and ovarian cancer patients suggests similar mechanisms of hyperinflammatory processes seen in both diseases. Circulatory inflammatory markers, such as IL-2, IL-4, IL-6, IL-12, and IL-13, are associated with the risk of epithelial ovarian cancer [28]. Overall, ovarian cancer has a similar pathology to COVID-19. This may cause ovarian cancer patients to be more at risk for COVID-19 infection, hospitalization, or death.

Esophageal cancer and COVID-19

Esophageal cancer develops when cancer cells form in the tissues of the esophagus. Smoking, heavy alcohol use, older age, and Barrett's esophagus are common risk factors [64]. The risk factors identified in esophageal cancer and COVID-19 are older age (> 60 years) and males, as shown in Table 2. COVID-19 likely infects esophageal cells through ACE2 and TMPRSS2 expression [65], similar to the other cancers described in this study. There are minimal studies available in PubMed concerning esophageal cancer patients with COVID-19; however, most studies conclude that having general cancer increases susceptibility/risk for severe complications in COVID-19. It is important to consider the mortality rates of esophageal cancer, alone, when applying the cancer to the risk of severe COVID-19. The 5-year survival rate of esophageal cancer locally in the esophagus is 47% (Cancer.net). The 5-year survival rate for those with disease that has spread to surrounding organs, lymph nodes, or tissues is 25%. The 5-year survival rate for esophageal cancer that has spread to distant parts of the body is 5%. It is likely that COVID-19 mortality in esophageal cancer patients may depend on the severity of the cancer disease, immunosuppression, and anticancer therapy.

Bladder cancer and COVID-19

Bladder cancer is common and involves bladder cells that grow uncontrollably. This cancer type is typically diagnosed in older adults (> 55 years). Common risk factors, listed on the ACS, are smoking, chemical exposure, drug-induced, arsenic, not drinking enough fluids, whites, males, family history, and structural defects. Those with bladder cancer at risk for COVID-19 are older age

(>60 years) and males.

Urothelial cancer begins in urothelial cells that line the urethra, bladder, ureters, renal pelvis, and other organs. Chakravarty *et al.* [27] compared the incidence and mortality rates of lung, breast, hematologic, prostate, colorectal, and urothelial cancer. Urothelial cancer had a low incidence rate of 5.48% and the highest mortality rate (38%), just behind lung cancer and was equal to colorectal cancer. ACE2 has shown medium expression in the bladder [66], which could indicate lower incidence rates of COVID-19 infection in bladder cancer compared to others. The higher mortality rate could be limited to the sample size but may also be the result of COVID-19 complications commonly seen in older adults with immunosuppression leading to multiorgan damage. As previously mentioned in section (d) regarding prostate cancer, Lundon *et al.* [61] conducted a retrospective study of 38,324 patients tested for SARS-CoV-2. Of this cohort, 113 had bladder cancer, and 25 (22.1%) tested positive. Another study evaluated the effects of intravesical BCG therapy and its role in high-risk nonmuscle-invasive bladder cancer [67]. Out of 71 patients, 26 had a COVID-19 polymerase chain reaction (PCR) test, and 4 were diagnosed with COVID-19 infection. A positive result was higher in individuals aged 50-64 years old and 65-80 years old than in similar age groups without the presence of bladder cancer. Therefore, intravesical BCG treatment may decrease the risk of COVID-19 infection in this particular patient population.

Pancreatic cancer and COVID-19

Pancreatic cancer is a rare disease but has a high mortality rate in the United States, which is the third leading cause of cancer death (University of Utah Health). Common risk factors listed on the ACS are tobacco use, lifestyle, overweight, diabetes, chronic pancreatitis, chemical exposure, age, gender (males), race (African Americans), family history, and genetics. Based on the results in Table 2, the patient parameters increasing the risk for pancreatic cancer patients with COVID-19 infection are older age (>60 years) and males.

Studies regarding COVID-19 and pancreatic cancer are limited at this time. Wang *et al.* [37] reported that 6.1% of 205 patients across 6 studies with COVID-19 had pancreatic cancer. This percentage was the second lowest incidence rate compared to lung, colorectal, breast, esophageal, bladder, and cervical cancer. This data is limited to sample size and the rarity of pancreatic cancer among other cancers.

ACE2 is highly expressed in the pancreas microvascular pericytes and moderately expressed in rare scattered ductal cells [68]. It is likely COVID-19 can enter the pancreas by binding to ACE2 for entry and fusion, similar to how COVID-19 infects other major organs. COVID-19 entry into the cancerous pancreas could lead to worse outcomes because of active cancer cells and reduced immune system function.

Cervical cancer and COVID-19

Cervical cancer occurs in the lower section of the uterus that connects to the vagina in females. Risk factors for cervical cancer, listed on the ACS, are females, human papillomavirus (HPV) infection, sexual history, smokers, immunosuppression, chlamydia infection, long-term use of oral contraceptives, having multiple full-term pregnancies, young age at first full-term pregnancy, economic status (low income), a diet low in fruits and vegetables, family history, and diethylstilbestrol (DES). The factors placing cervical cancer patients at risk for COVID-19 are older age (>60 years) and females, as listed in Table 2. Overall, males have an increased risk for COVID-19 hospitalization and death, but female cancer diseases could increase the risk for female hospitalization or death and should be considered for COVID-19 treatment and prevention. Studies are limited regarding the pathology of COVID-19 and how it causes complications or death in cervical cancer patients. Similar to other cancers, anticancer therapy and cancer likely play a role in decreasing immune function.

Head and neck cancer and COVID-19

Head and neck cancer begins in the squamous cells that line the mucosal surfaces of the head and neck, including the mouth, throat, and voice box. These cancers are known as squamous cell carcinomas of the head and neck. Risk factors from NCI are alcohol use, tobacco use, HPV, Epstein–Barr virus, and genetic disorders. Generally, patients diagnosed with head and neck cancer are over 50 years old, according to the CDC. Individual patient parameters putting head and neck cancer at risk for COVID-19 are those of advanced age. Male or female risk could not be defined based upon the available studies. Sharma and Crosby [38] reported 70% of deaths from head and neck cancer occurred in those >70 years, requiring better management of these patients during the COVID-19 pandemic. Increasing age, malignancy, and coexisting comorbidities are associated with increased COVID-19 disease severity. This places elderly individuals with head and neck cancer at risk for poor outcomes from both cancer disease and active COVID-19 infection. Additional studies are needed to adequately compare COVID-19 pathology for causing poor health outcomes in patients with head and neck cancer.

Potential Therapeutic Strategies

Cancer patients may require additional or alternate COVID-19 drug treatment to prevent and reduce the risk of COVID-19-induced complications and infectivity rates. Currently, the best preventative therapy for COVID-19 infection is receiving the recommended vaccinations. Pfizer-BioNTech and Moderna manufacturers designed the COVID-19 vaccine using mRNA technology, and each required a 2-dose series for potential full protection from COVID-19. These vaccines do not contain a live virus but contain mRNA that corresponds to a protein located on the SARS-CoV-2 virus, which triggers an immune response to produce antibodies. When the person comes in close contact with the SARS-CoV-2 virus post-vaccination, the antibodies will recognize the viral protein to inactivate the virus and prevent infection. The third COVID-19 vaccine is designed as an adenovirus vaccine and is marketed by Johnson and Johnson. The spike protein of the SARS-CoV-2 virus is placed in the adenovirus and induces an immune reaction after vaccination to form antibodies. Similar to the other two marketed mRNA COVID-19 vaccines, the antibodies will recognize and inactivate the SARS-CoV-2 virus when a person comes in close contact with it to prevent infection. It is important to note that no vaccines are 100% effective in preventing infection. Pfizer-BioNTech and Moderna vaccines are FDA approved for booster doses. Cancer patients may require more booster doses than the general population to remain protected against the new developing COVID-19 variants that are continually spreading across the world. The CDC recommends that cancer patients receive additional booster doses since this population is moderate to severely

immunocompromised and has an increased risk of severe COVID-19 disease or mortality. Cancer patients' immune response to vaccination may also be decreased due to their compromised immune system from the cancer disease and from anticancer therapy. Cancer patients are also at higher risk for COVID-19 transmissibility since they require more frequent follow-up and care from multiple healthcare professionals in different health institutions, which could put them at more risk of coming into contact with the SARS-CoV-2 virus.

Potential COVID-19 drug therapy for cancer patients to prevent infection risk may include Evusheld, a preexposure prophylactic agent for the prevention of COVID-19. Evusheld has an emergency use authorization (EUA) issued by the FDA that may be beneficial in patients who are moderate to severely immunocompromised or in those who do not induce a significant immune response post-vaccination. Cancer patients with COVID-19 who are hospitalized may require more aggressive therapy than noncancerous patients to reduce the risk of COVID-19-induced complications, mechanical ventilation, or death. A higher intensity of COVID-19 treatment may put the patient at elevated risk for side effects or require a longer hospital stay and recovery period. Early on during the COVID-19 pandemic, RAAS inhibitors, including angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), were suspected to increase the risk of COVID-19 infection, severe disease, and mortality [69]. This data was presented because SARS-CoV-2 was found to bind directly to the ACE2 receptor for entry into the host cells, and RAAS inhibition may upregulate these receptors based upon their mechanism of action for lowering blood pressure.

Chemotherapeutic drugs are commonly known to have cytotoxic properties causing increased side effects, such as hair loss, thinning skin, nausea, vomiting, anemia, and immunosuppression. Traditional chemotherapy targets both normal and tumor cells responsible for the extensive side effect profile. A dysregulated immune system, caused by immunosuppression, places the cancer patient at risk for contracting SARS-CoV-2 virus and severe disease. The immune system of a cancer patient does not have the strength and power to eradicate infection compared to a noncancerous patient. However, targeted chemotherapeutics are increasingly popular and are attracting much attention because the agents target specific enzymes or receptors on the tumor cell, creating a less severe side effect profile. Sengar *et al.* [70] recently published a study of 1253 patients with cancer who were diagnosed with COVID-19 in India. The patients presented with mild disease, but recent cancer therapy use did not impact COVID-19 outcomes. The risk factors associated with severe COVID-19 and mortality were advancing age, smoking history, concurrent comorbidities, and palliative intent of treatment.

Conclusion

Overall, it is clear that older age (> 60 years) and male sex are more at risk for severe COVID-19 in adult cancer patients. However, precaution is needed for female patients with female cancer types, as they are more likely to be at risk for COVID-19 infection and complications than the general population. Common pathologies linking COVID-19 infection to cancer are cytokine storm, hyperinflammatory processes, human host cell entry through ACE2/TMPRSS2, and various signaling pathways, including IFN-1, androgen receptors, and immune checkpoints. Further research discussing COVID-19 pathology in various cancer types and genetics is needed to confirm the increased risk of COVID-19 infection in the adult cancer patient population. Preventative care, cancer screenings, and COVID-19 vaccination are strategies that could decrease the incidences of COVID-19 severity, complications, and death in cancer patients.

Supplementary Data

Supplementary data is available at *Acta Biochimica et Biophysica Sinica* online.

Conflict of Interest

The authors declare that they have no conflict of interest.

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