

COVID-19 in cancer patients

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has currently affected >220 million individuals worldwide. The complex interplay of immune dysfunction, active malignancy, the effect of cancer treatment on the immune system and additional comorbidities associated with cancer and COVID-19 all affect the outcomes of COVID-19 in patients with cancer. We have discussed the published findings (through the end of September 2021) on the effects of cancer on the morbidity and mortality of COVID-19, common factors between cancer and COVID-19, the interaction of cancer and COVID-19 treatments, the impact of COVID-19 on cancer clinical services, immune test findings in cancer patients with COVID-19 and the long-term effects of COVID-19 on cancer survivors.

Keywords: cancer, COVID-19, haematologic malignancies, immunology, outcomes, solid malignancies

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has currently affected >220 million individuals worldwide.¹ COVID-19 has been shown to cause more severe disease and increased mortality in patients with active cancer.^{2–5} The complex interplay of immune dysfunction, active malignancy, the effects of cancer treatment on the immune system and additional comorbidities associated with cancer and COVID-19 all affect the outcomes of COVID-19 in patients with cancer. The emergence of the Delta variant, which has been shown to have higher transmissibility, cause more severe disease among the unvaccinated and have somewhat less responsiveness to current COVID-19 vaccines⁶ may further alter the current landscape with regard to COVID-19 infections in patients with cancer. The effect of cancer on COVID-19 has also been shown to vary according to the type of cancer.⁷ The emergence of variants of SARS-CoV-2 has also led to changes in clinical presentations in cancer patients. In this article we discuss what is known about the effect of cancer on the morbidity and mortality of COVID-19, common factors that are shared between cancer and COVID-19, the interaction of cancer and COVID-19 treatments, the impact of COVID-19 on cancer clinical services, immune test findings in cancer patients with COVID-19 and the long-term effects of COVID-19 on cancer survivors.

Literature search

The PubMed and Google Scholar databases were searched from 1 January 2020 to 30 September 2021 using the search terms ‘COVID AND cancer screening OR cancer diagnosis OR cancer management’, ‘COVID AND cancer AND seroconversion OR immunity OR antibodies’ and ‘COVID AND cancer AND mortality OR outcomes OR clinical characteristics’. Retrospective and prospective observational and cohort studies describing clinical outcomes and changes in the immunity of cancer patients with COVID-19 and the impact on cancer services due to COVID-19 were included in the review after eliminating duplicates and irrelevant articles (Figure 1).

The immune system in cancer

When the immune system does not function properly one may get autoimmunity, allergy or cancer. Cancer occurs when the immune system fails to get rid of cancerous cells. When the immune system detects cancerous cells, it secretes several chemicals, including cytotoxic granules, cytokines and chemokines, and activates various immune cells that together act to eliminate the cancerous cells.⁸ At times, the cancerous cells escape such immune processes and start multiplying, leading to growth and spread of the cancer. The immune system applies a selective pressure to tumour development and

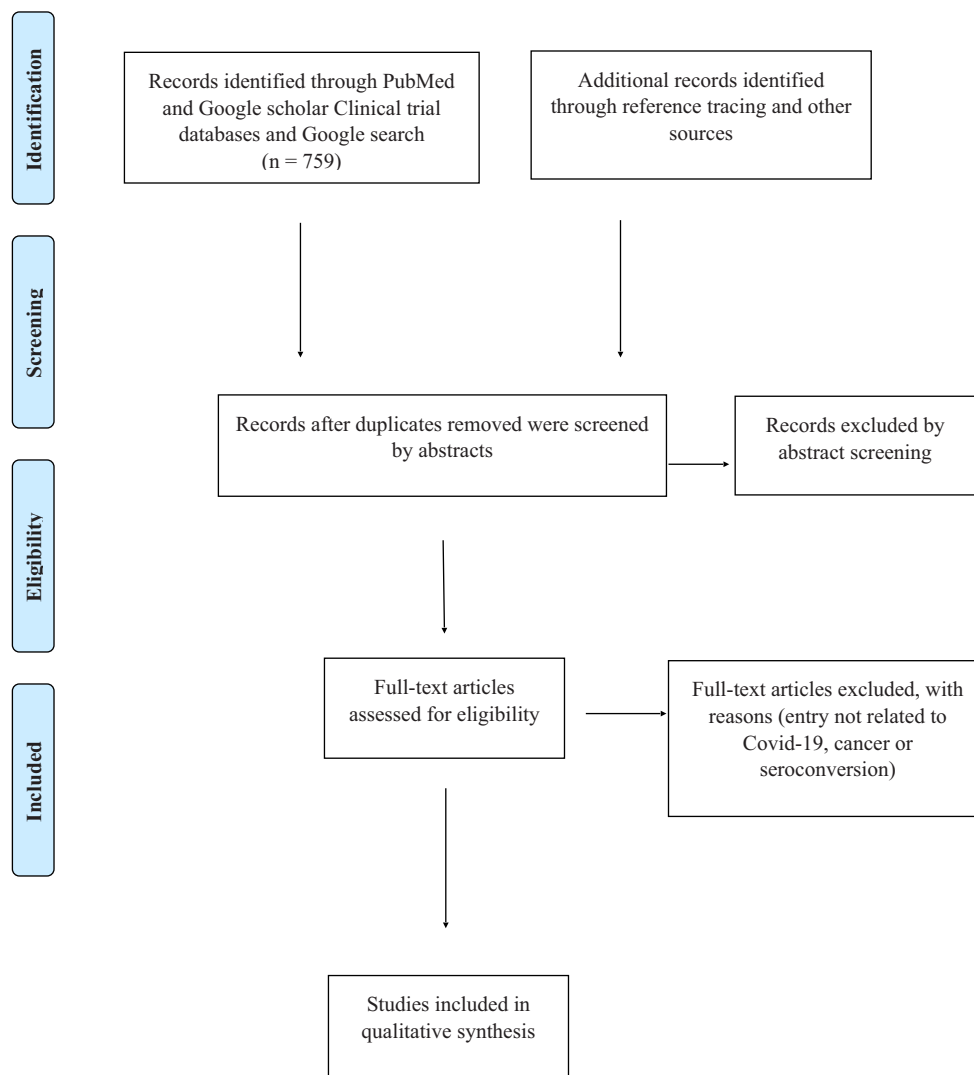


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

growth and tumours are forced to edit the immune components that surround it, which is known as cancer immunoeediting. There are three phases of cancer immunoeediting: tumour dormancy/equilibrium, where the immune system fights against the cancerous cells and both are at an equilibrium; tumour immunity/elimination, where the immune system eliminates the cancerous cells; and tumour progression/escape, where the tumour overtakes the immune system and evades the immune surveillance.⁹ Tumour cells evade immune attack by avoiding immune recognition and instigating an immunosuppressive tumour microenvironment.⁸ Tumour-induced immune defects may weaken the host immune response, and this is a common feature in patients with haematologic malignancies such as leukaemia.¹⁰

In certain haematologic malignancies, such as multiple myeloma and chronic lymphocytic leukaemia (CLL), the tumour cells need to share the same developmental space with normal immune cells and this may lead to immunoparesis. Some haema-

tologic malignancies are characterised by systemic involvement of secondary lymphoid organs. The bone marrow represents a distinct immune tissue and haematopoietic stem cell involvement in leukaemia leads to cytopenia.¹¹ These distinct biological characteristics of haematologic malignancies reflect the immunosuppression associated with these malignancies. Cancer treatments such as chemotherapy, immunotherapy, targeted therapy and haematopoietic stem cell transplantation (HSCT) may also lead to myelosuppression and immunosuppression in cancer patients.

The viral envelope of SARS-CoV-2 is typically made up of three proteins that include the membrane, envelope and spike proteins. The latter helps the virus to bind to and enter host cells.^{12,13} Here it multiplies and then spreads from cell to cell and person to person. The immune system is activated in different ways, including increased or decreased proliferation of various cells and secretion of cytokines and downstream effects due to this. The immune system produces different CD4 and CD8 T cells against different

parts of the virus and the process of vaccination tries to mimic this before the infection occurs.^{12,13} Thus a person with cancer, in whom the immune system is weak due to the cancer and the various treatments received, may be more prone to getting COVID-19 and getting severe disease with adverse clinical outcomes including death.

Coronavirus infections in cancer patients

Studies have assessed the effects of SARS-CoV-1 and Middle East respiratory syndrome-related coronavirus (MERS-CoV) infections in cancer patients. Information on the mortality and morbidity of cancer patients following SARS-CoV-1 infection are sparse. A patient with acute myeloid leukaemia (AML) and SARS-CoV-1 infection developed bilateral infiltrates on chest radiography but did not require intubation and was discharged uneventfully from the hospital.¹⁴ On the other hand, there is high morbidity and mortality among cancer patients infected with MERS-CoV, especially in those with haematologic malignancies. Atypical presentations of MERS-CoV infections were seen in those with a current or recent history of blood cancers. These included delayed symptom development, 20-d incubation period and persistent viral shedding without clinical deterioration.¹⁵ Multiple studies have found higher mortality rates among blood cancer patients who developed MERS-CoV infection. One study found MERS-CoV infection in blood cancer patients to have a very poor prognosis regardless of the status of the underlying disease.¹⁶ Other studies found the disease to be more severe among patients with cancers,¹⁷ with a 100% case fatality rate among patients with haematologic malignancies and advanced solid cancers. The major causes of death were multi-organ failure and septic shock.¹⁸

Common factors in cancer and COVID-19

Cancer is a genetic disease that is influenced by the tissue microenvironment and COVID-19 is an infectious disease.¹⁹ There are several similarities between cancer and COVID-19 with regards to risk factors for severe disease and immune changes, such as overproduction of some cytokines (e.g. interleukin-6 [IL-6] and type I interferon [IFN-I]), the involvement of androgen receptors and immune checkpoint signalling.²⁰ Studies have clearly shown gender, age, ethnicity, comorbidities (including cardiovascular and respiratory), obesity, smoking and various medical conditions significantly impact the morbidity and mortality rates in COVID-19.^{3,21,22} The same factors are known to have a significant adverse impact on cancer patients as well. Socio-economic factors, including the gross domestic product, may also affect the association between cancer and COVID-19.^{20,23} Further similarities between cancer and COVID-19 have been elucidated at a molecular level by Zong et al.²⁰ Four major signalling pathways— androgen receptor (AR), cytokine, IFN-I and immune checkpoint signalling—have been shown to govern the incidence and severity of both diseases.¹⁹

Angiotensin-converting enzyme 2 (ACE2) expression in lung tissue has been found to increase with age.^{24,25} Since most cancers occur in older individuals, high ACE expression has been suggested as a mechanism mediating adverse clinical outcomes in older cancer patients.²⁶ Furthermore, smoking increases ACE2 expression in the lung tissue. There is a dose-response relation-

ship between the number of pack-years of smoking and ACE2 expression.^{27,28} Smoking also correlates with adverse outcomes in patients with COVID-19.²⁹

The S protein of coronavirus consists of two components, S1 and S2. S1 is involved in recognizing and binding the virus to the host cell surface, while S2 is involved in fusing the viral and cell membranes, allowing viral entry into the cell. TMPRSS2 is the protease that mediates S protein cleavage, setting S1 and S2 apart. This event is called S protein priming and is believed to be essential for the interaction of SARS-CoV-2 with ACE2 and cell entry.³⁰ Co-expression of ACE2 and TMPRSS2 in such cells as type II pneumocytes, absorptive enterocytes of the small intestine and nasal goblet secretory cells reflects the high susceptibility of these cells to SARS-CoV-2.³¹ ACE2 is also highly expressed in males, especially in urogenital organs such as the prostate. It was demonstrated in a recent study that patients with chronic urinary diseases are highly prone to SARS-CoV-2 infection.³²

Further, expression of TMPRSS2, one of the target genes of ARs, has an impact on both cancer and COVID-19. TMPRSS2 expression is modulated by the ARs in normal prostate secretory epithelium and prostate cancer. TMPRSS2 has also been found to be expressed in lung tissue.³³ Recent studies suggest that patients with prostate cancer treated by androgen deprivation therapy (ADT) were less likely to be infected by SARS-CoV-2 compared with those not on ADT or those with other tumour types.³⁴ They are also less likely to develop adverse clinical outcomes (hospitalization and oxygen supplementation).³⁵ Patients with pre-existing primary or secondary immune dysregulation are at an increased risk of adverse or severe outcomes following COVID-19.³⁶

Severe COVID-19 is associated with increased levels of cytokines such as IL-6, leading to a cytokine storm.^{26,37-40} IL-6 is also overexpressed in almost all types of tumours and is one of the major cytokines in the tumour microenvironment and a driver of tumour progression.⁴¹ On the other hand, one study showed that IFN-I levels are reduced in COVID-19 infection.⁴² IFN-I is implicated in inhibiting tumour growth and promoting tumour cell senescence and death.⁴³ Decreased levels of IFN-I and IFN-stimulated genes along with increased levels of IL-6 has been demonstrated in peripheral blood samples from critical COVID-19 patients.⁴⁴ In contrast, a few studies have demonstrated elevated IFN-I levels along with high IFN-stimulated genes in bronchoalveolar lavage or peripheral blood mononuclear cells of COVID-19 patients.^{45,46} Immune checkpoint molecules are expressed on a considerable proportion of tumour cells in many different cancers, including some haematologic malignancies such as Hodgkin lymphoma and primary mediastinal B cell lymphoma.⁴⁷ Several studies have shown an upregulation of checkpoint receptors in association with T cell exhaustion and lymphopenia in severe COVID-19 cases.⁴⁸⁻⁵¹

Both cancer and COVID-19 have an increased risk of venous thromboembolic events (or, more rarely, arterial thromboses).⁵² The mechanisms involved in COVID-19 coagulopathy include inflammation and activation of the innate immune system that in turn activates the systemic coagulation pathways.⁵²⁻⁵⁴ Viral endotheliopathy and microcirculatory dysfunction may further contribute to the thrombotic complications seen in COVID-19.⁵³⁻⁵⁵ In cancer patients, local or systemic therapy, multiple comorbidities and cancer cells expressing coagulation factors have been implicated in the pro-coagulant state.⁵⁶

Morbidity and mortality patterns of COVID-19 in cancer patients

Both cancer and COVID-19 may have some common predisposing factors, including increased age, obesity and immunosuppression, and these may also increase the chance of a person getting severe COVID-19. In cancer, there may be a greater chance of the immune system becoming further dysregulated by COVID-19 as compared with a healthy person. The outcomes in patients with cancer who develop COVID-19 can be divided into three facets: clinical, laboratory and general management outcomes. Table 1 outlines the significant findings with regard to changes in outcomes of patients with solid and/or haematologic malignancies following COVID-19 infection.^{3,5,7,21,22,29,57-108}

Solid malignancies

In studies that included solid cancer patients, those who got COVID-19 had a higher probability of death compared with patients without cancer.^{7,57,60} Several risk factors for increased mortality have been identified, including advanced age, male sex, smoking history, metastatic cancer, the presence of lung or bone metastases, higher C-reactive protein levels, the number of comorbidities and poor performance status.^{7,21} Some studies found the age cut-off for worse prognosis to be 65 y,⁹⁶ while others found it to be 75 y.²¹ Severe lung involvement due to cancer is an important determinant,²² and those from ethnic minorities have a worse prognosis.³

Those with lung, digestive (excluding colorectal), nasopharyngeal, brain and skin cancers had high mortality, with lung cancer as the highest.^{7,57,101} Moderately higher mortality was noted with genitourinary, female genital tract, breast and thyroid cancers.⁵⁷ One study found genitourinary malignancies to not have a higher risk for mortality compared with the general population⁹¹ and another found those with gynaecologic cancer to have a similar age-specific mortality risk.⁷¹ Non-metastatic cancer patients experience similar frequencies of severe conditions as patients without cancer.⁶³ Another study reported gastrointestinal tract cancer (together with lymphoma or other haematologic neoplasms) had the highest excess of hospitalization, while cancers of the urinary tract, female genital organs and melanoma had the highest excess mortality.⁹⁷ Those with solid cancers had a higher risk of thromboembolism and sepsis,⁵⁹ acute respiratory and kidney failure, venous thrombosis, atrial fibrillation,⁷ acute respiratory distress syndrome (ARDS),⁶⁰ liver injury, myocardial injury, renal insufficiency and multi-organ dysfunction syndrome (MODS).⁸¹

Haematologic malignancies

Owing to high immunosuppression as a result of underlying disease, patients with haematologic malignancies are at significantly higher risk of a variety of severe infections, including COVID-19. They often receive myelosuppressive and immunosuppressive treatment, which further reduces their immune responses and further increases their risk of infections.

Increased mortality from COVID-19 infection has been reported in patients with immunosuppression (including those taking methotrexate). In particular, those with haematologic

malignancies had a 2.5-fold increased risk.¹⁰⁹ A retrospective study found that patients with both COVID-19 infection and progressive cancer had a fivefold increase in the risk of 30-d mortality compared with COVID-19-positive cancer patients who were in remission or had no evidence of cancer.²⁹ A retrospective Italian study early in the pandemic also showed higher mortality in haemato-oncology patients with COVID-19 infection on the order of 39.2%, which was significantly higher when compared with rates for non-haematologic patients with COVID-19 (23.5%) and uninfected haematologic controls (3%).⁶¹ A large retrospective study by Passamonti et al.¹¹⁰ from Italy revealed increased mortality of patients with haematologic malignancies infected with COVID-19 when compared with a non-COVID-19 cohort with haematologic malignancies. Older age, progressive disease status, diagnosis of AML, indolent non-Hodgkin lymphoma, aggressive non-Hodgkin lymphoma or plasma cell neoplasms and severe or critical COVID-19 were associated with worse overall survival in this study. A meta-analysis of 34 adult and 5 paediatric studies from Asia, Europe and North America that included 3377 predominantly hospitalised haemato-oncology patients reported a comparable risk of death on the order of 34%.¹¹¹ Patients >60 y of age had a significantly higher relative risk of death compared with those <60 y of age. Several more studies have demonstrated higher mortality in patients with haematologic malignancies following COVID-19 infection compared with solid cancer patients.^{73,79,82,90} Children with blood cancers seem to have a low risk of death and the risk is higher in those with blood compared with solid organ cancers.¹¹¹

A multicentre audit in six National Health Service (NHS) centres revealed that patients with haematologic malignancies treated with chemotherapy in the preceding 28 d to COVID-19 diagnosis and nosocomial COVID-19 infection had a significantly higher mortality rate than those with solid malignancies.¹¹² In contrast, the aforementioned Italian study by Passamonti et al.¹¹⁰ found that recent therapy had no association with mortality. This finding is consistent with the studies of patients with cancer in general and provides reassurance of the general safety of cancer treatment during the pandemic, although it is not a guarantee for every specific treatment in every clinical scenario.²⁷ Several studies have shown haematologic malignancies adversely affect COVID-19 severity. A study conducted at two centres in Wuhan, China among haematologic malignancy patients found no differences in baseline characteristics between those who did or did not develop COVID-19. However, the haematologic malignancy patients with COVID-19 had a higher mortality rate than those without COVID-19.¹¹³ Patients with haematologic malignancies have significantly more admissions to the intensive care unit (ICU) than those without cancer.⁷ Factors that adversely affected prognosis were advanced age, male sex, presence of lung or bone metastases, higher C-reactive protein levels, lymphopenia, non-Hispanic black race and Hispanic ethnicity, the number of comorbidities and poor performance status.^{3,7,21}

Immune test findings in cancer patients with COVID-19

Table 2 outlines the significant immune test findings in cancer patients with COVID-19.^{86,114-124} Laboratory studies have found weaker SARS-CoV-2 antibody responses in patients with cancer compared with those without.¹¹⁹ A study found seroconversion

Table 1. Studies on COVID-19 in cancer patients

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Alpert, 2020 November ⁵⁹ (USA)	S, H	Compared clinical characteristics of COVID-19 patients with and without cancer	421 (S 325, H 96)	Retrospective. In-patient or emergency care at Mount Sinai Health System (March–May 2020)	Cancer patients – higher risk for adverse outcomes (thromboembolism, sepsis). No difference in AKI, ICU admissions and mortality
Bange, 2020 May ⁸⁶ (USA)	H	Compared mortality in haematologic and solid cancer patients with COVID-19	100	Prospective, multicentre, observational (April–September 2020)	Haematologic cancer – higher mortality than solid cancer. Those with high CD8 T cell responses had better outcomes
Bernard, 2021 March ⁷ (France)	S, H	Compare clinical findings in hospitalised patients	6201	Retrospective study. Assessed French national database of hospitalized COVID-19 patients (March–April 2020)	COVID-19 and cancer – twofold higher risk of death vs COVID-19 without cancer. Blood cancer – admission to ICU significantly more frequent (24.8% vs 16.4%). Lung, digestive (excluding colorectal cancer) and metastatic solid cancers – higher risk of death
Cai, 2021 January ⁸⁷ (China)	S, H	COVID-19 with cancer vs those without cancer	93	Multicentre, retrospective, cohort study. Compared the immunological characteristics of both cancer and non-cancer patients (February–March 2020)	COVID-19 patients with cancer – poorer prognosis vs non-cancer patients due to dysregulated immune responses. Higher mortality in patients with cancer compared with healthy controls
Calles, 2020 September ⁶⁰ (Spain)	S (lung)	Assess outcomes of lung cancer patients affected by COVID-19	23	Prospective study. Evaluated patients with lung cancer treated at a medical centre in Spain and diagnosed with COVID-19 (March–May 2020)	Lung cancer patients – high rate of hospitalization, onset of ARDS and high mortality rate
Cattaneo, 2020 September ⁶¹ (Italy)	H	Determine clinical characteristics and risk factors for mortality in haematologic patients affected by COVID-19	102	Retrospective cohort study. (March 2020)	Chronic myeloproliferative neoplasms – lower risk of acquiring COVID-19. Immune-mediated anaemia and on immunosuppressive-related treatments – higher risk of acquiring COVID-19. Haematologic patients – higher mortality than non-haematologic patients with COVID-19 and uninfected haematologic patients. Worst prognosis among patients on active haematologic treatment

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Chai, 2021 July ⁵⁷ (China)	S, H	Assess mortality and consequences of COVID-19 in cancer patients	166	Multicentre comparative cohort study. Compared COVID-19 patients with cancer and non-cancer COVID-19 patients and non-COVID cancer patients (January–March 2020)	If cancer patients with COVID-19 survive acute COVID-19 infection, long-term mortality appears similar to the cancer patients without COVID-19 and their long-term clinical sequelae are similar to COVID-19 patients without cancer. High risk – haematologic, nasopharyngeal, brain, digestive system and lung tumours. Moderate risk – genitourinary, female genital, breast and thyroid tumours
Costa, 2021 August ⁵⁸ (Brazil)	S, H	Evaluate risk factors of in-hospital mortality among COVID-19 patients with and without cancer	Cancer: 7406; no Cancer: 315 410	Retrospective study (March–December 2020)	COVID-19 patients with cancer – higher disease severity, higher risk of mortality, longer hospital stay, higher ICU admissions, receive more invasive mechanical ventilation than patients without cancer. Haematologic neoplasia – higher risk of mortality than solid tumours
Crolley, 2020 October ⁶² (UK)	S, H	Assess whether cancer patients (on systemic anticancer therapies) are at greater risk of contracting COVID-19 or having more severe outcomes	68	Retrospective study (March–May 2020)	Patients on SACT – higher mortality if they contract COVID-19. Receiving chemotherapy – increased risk of developing COVID-19 (high-dose chemotherapy – significantly high risk). Respiratory or intrathoracic neoplasm – increased risk of developing COVID-19. Receiving targeted treatment – protective effect. Solid vs haematologic cancer – no significant effect on risk
Dai, 2020 January ⁶³ (China)	S, H	Determine clinical characteristics and outcomes of COVID-19 patients with cancer	105	Multicentre retrospective study (January–February 2020)	COVID-19 patients with cancer – higher risks of severe outcomes. Haematologic cancer, lung cancer or with metastatic cancer (stage 4) – highest frequency of severe events. Non-metastatic cancer – frequency of severe conditions similar to patients without cancer. Patients who underwent surgery – had higher risks of severe events. Only radiotherapy – no significant differences in severe events compared to patients without cancer

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
De Azambuja, 2020 August ⁶⁴ (Belgium)	S	Determine the in-hospital mortality within 30 d of COVID-19 diagnosis among patients with solid cancer compared with patients without cancer	Cancer: 1187; no cancer: 12 407	Retrospective study. Data from adult patients registered until 24 May 2020 in the Belgian nationwide database of Sciensano were used (April–May 2020)	Solid cancer – adverse prognostic factor for in-hospital mortality. Younger patients and without other comorbidities – adverse effect more pronounced
De Melo, 2020 October ²¹ (Brazil)	S, H	Describe the outcomes, demographics and clinical characteristics of cancer in patients with COVID-19	181	Retrospective cohort study. Cancer patients admitted to the Brazilian National Cancer Institute were assessed (April–May 2020)	Cancer – important prognostic factor for patients with COVID-19. Higher rates of complications (respiratory failure, septic shock, AKI) and COVID-19-specific death. COVID-19-specific mortality associated with age > 75 y, metastatic cancer, ≥ 2 sites of metastases, presence of lung/bone metastases, non-curative treatment or best supportive care intent, higher CRP levels, admission due to COVID-19 and antibiotics use
Elkrief, 2020 November ⁶⁵ (Canada)	S, H	Determine the incidence and impact of hospital-acquired COVID-19 in cancer patients	252	Prospective observational cohort study. Used provincial registries and hospital databases (March–May 2020)	Hospital-acquired COVID-19-increased mortality in the cancer population. Age and advanced stage of cancer were negative predictive factors for COVID-19 severity
Erdal, 2021 January ²² (Turkey)	S, H	Investigate clinical course and the factors affecting mortality in cancer patients affected by COVID-19	77	Single-centre retrospective study. Compared cancer patients with non-cancer patients who were admitted to a hospital in Istanbul with COVID-19 infection (March–May 2020)	Cancer patients – severe disease and mortality higher vs non-cancer patients. Associations with severe disease and mortality – stage of the disease, receiving chemotherapy in the last 30 d, lymphopenia, elevated troponin I, D-dimer and CRP. Most important factors influencing survival – severe lung involvement and lymphopenia
Fernandes, 2021 February ⁸⁸ (Brazil)	S, H	To analyse COVID-19 mortality in cancer patients and associated factors	51	Cross-sectional retrospective study (April–August 2020)	Higher fatality – lung and haematologic cancers, age > 60 y, currently undergoing cancer treatment

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Ferrari, 2021 January ⁸⁹ (Brazil)	S, H	Investigate the predictors of death after COVID-19 diagnosis in patients with cancer	S: 167; H: 31	Longitudinal multicentre cohort study (March–July 2020)	Factors associated with death – age ≥ 60 y, current/former smoking, coexisting comorbidities, respiratory tract cancer. COVID-19 rates similar to general population if otherwise healthy and have curable malignancies
Fillmore, 2020 October ⁶⁶ (USA)	S, H	Evaluate prevalence and outcome of COVID-19 infection in cancer patients and identify risk factors associated with infection and outcomes	1794	Retrospective study. Data from the Veterans Affairs Corporate Data Warehouse (January–May 2020)	Cancer – high susceptibility to COVID-19 infection and severe eventual outcome. Determinants of mortality – age, comorbidity and specific cancer types. COVID-19-attributable mortality similar in patients recently treated for cancer vs treated > 6 months ago or never treated with systemic therapy. Mortality in patients using ICI within the last 6 months significantly lower (7%) vs patients receiving chemotherapy (14.0%), hormone therapy (16.2%) or targeted therapy (14.1%)
Ganatra, 2020 November ⁶⁷ (USA)	S, H	Evaluate outcomes in patients with COVID-19 with both cancer and comorbid CVD	Total: 2476; cancer: 195	Retrospective study (March–May 2020)	Cancer was an independent predictor of severe disease. Patients with both cancer and CVD had a higher risk of severe disease and death vs only cancer or only CVD. Arrhythmias and encephalopathy more frequent with both cancer and CVD vs cancer alone
Grivas, 2021 June ³ (USA)	S, H	Identify prognostic clinical factors, including laboratory measurements and anticancer therapies	4966	Retrospective, observational cohort study (March–November 2020)	Associations with higher COVID-19 severity – older age, male sex, obesity, cardiovascular and pulmonary comorbidities, renal disease, diabetes mellitus, non-Hispanic black race, Hispanic ethnicity, performance status, recent cytotoxic chemotherapy and haematologic malignancy. Among hospitalized patients, associations with higher COVID-19 severity – low/high absolute lymphocyte count, high absolute neutrophil count, low platelet count, abnormal creatinine, troponin, lactate dehydrogenase, and CRP. Higher mortality with anticancer therapies like R-CHOP, platinum combined with etoposide and DNA methyltransferase inhibitors

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Höllerin, 2021 January ⁹⁰ (Germany)	S, H	Determine the immune competence of individual patients by assessing absolute numbers of CD4 ⁺ T-cells, CD8 ⁺ T-cells, CD19 ⁺ B cells and CD16 ⁺ /CD56 ⁺ NK cells in peripheral blood	S: 5; H: 12	Retrospective study. Patients with cancer and COVID-19 treated in haematology and oncology centres from the greater Munich area (March–May 2020)	Haematologic cancers – higher risk for a severe course of COVID-19 compared with solid tumours. Cancer patients – higher risk of dying from COVID-19 than patients without cancer
Jee, 2020 August ⁶⁸ (USA)	S, H	Analyse the outcomes of cancer patients with COVID-19 and determine the impact of recent cytotoxic chemotherapy	309	Retrospective study. Patients with cancer and concurrent COVID-19 at Memorial Sloan Kettering Cancer Centre (March–April 2020)	Recent cytotoxic chemotherapy treatment not associated with adverse COVID-19 outcomes. Associations with worse outcomes – active haematologic or lung malignancies, peri-COVID-19 lymphopenia or baseline neutropenia. Rate of adverse events lower in cancer patients without COVID-19
Kabarriti, 2020 August ⁶⁹ (USA)	S (lung)	Assess impact of prior lung irradiation on death as a result of COVID-19 infection	107	Retrospective study (March–April 2020)	History of radiation therapy (between 1 month and 1 y before COVID-19 testing) for cancer – poor prognosis. Mortality risk associated with the extent of lung irradiation
Khusid, 2021 February ⁹¹ (USA)	S, H	Evaluate COVID-19 patients with a history of malignancy with regard to adverse clinical outcomes	374	Multicentre retrospective cohort study (March 2020–August 2020)	History of cancer – no greater risk for AKI or ICU admissions but higher risk for mortality vs without a history of cancer. Pulmonary neoplasm – higher mortality. History of genitourinary malignancies – not at higher risk for AKI or for mortality compared with the general population

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Kuderer, 2020 June ²⁹ (USA, Canada and Spain)	S, H	Characterise the outcomes of patients with cancer and COVID-19 and identify potential prognostic factors for mortality and severe illness	928	Retrospective cohort study. Data on cancer patients ≥ 18 y of age with COVID-19 infection from the USA, Canada and Spain from the COVID-19 and Cancer Consortium database (March–April 2020)	30-d all-cause mortality high in cancer patients. Associated with general risk factors and risk factors unique to patients with cancer (cancer status –remission vs active disease, responding to treatment vs progressing, active anticancer therapy). No associations with mortality – race and ethnicity, obesity status, cancer type, type of anticancer therapy and recent surgery
Lara Álvarez, 2020 September ⁷⁰ (Spain)	S	Determine the mortality due to COVID-19 in cancer patients during the first 3 weeks of the epidemic	36 cancer (15 deaths), 1033 non-cancer (117 deaths)	Retrospective study. Cancer patients who died of COVID-19 were reviewed (March 2020)	COVID-19 mortality in cancer patients four times higher than that of the general population
Lara, 2020 July ⁷¹ (USA)	S (gynaecologic cancer)	Determine the clinical characteristics and outcomes of patients with gynaecologic cancer with COVID-19 infection	121	Retrospective, observational study (March–April 2020)	Mortality 14% (risk of death similar to the age-specific mortality risk). Associations with increased risk of mortality – recent immunotherapy use. Associations with hospitalization – age ≥ 64 y, African American race and ≥ 3 comorbidities. Chemotherapy and recent major surgery not predictive of COVID-19 severity or mortality. Patients with cancer had a higher risk of intensive care need and death
Larfors, 2020 December ⁹² (Sweden)	S, H	Evaluate COVID-19 intensive care admissions and mortality among patients with cancer	2278 cancer and non-cancer COVID patients admitted to the ICU (104 cancer patients); 5027 total deaths (461 cancer patients)	Retrospective, observational study. Data extracted from the Swedish Intensive Care Registry (March–June 2020)	Associations with risk of death – advanced age, male gender, presence of other comorbidities such as hypertension and cardiovascular disease. Chemotherapy in the past 4 weeks had no significant effect on mortality vs patients with cancer who had not received recent chemotherapy. Immunotherapy, hormone therapy, targeted therapy or radiotherapy use within the past 4 weeks had no significant effect on mortality
Lee, 2020 June ¹⁰⁸ (UK)	S, H	Describe the clinical and demographic characteristics and COVID-19 outcomes in patients with cancer	800	Prospective cohort study (March–April 2020)	Associations with risk of death – advanced age, male gender, presence of other comorbidities such as hypertension and cardiovascular disease. Chemotherapy in the past 4 weeks had no significant effect on mortality vs patients with cancer who had not received recent chemotherapy. Immunotherapy, hormone therapy, targeted therapy or radiotherapy use within the past 4 weeks had no significant effect on mortality

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Lee, 2020 October ¹⁰⁷ (UK)	S, H	Determine COVID-19 risk according to tumour subtype and patient demographics in patients with cancer	1044	Prospective cohort study (March–May 2020)	Associations with risk of death – increasing age. Haematologic malignancies had a more severe COVID-19 clinical course compared with solid organ tumours. Patients with leukaemia – significantly increased case fatality rate. Haematologic malignancies with recent chemotherapy – increased risk of death during COVID-19-associated hospital admission
Liang, 2021 March ⁹³ (China)	S, H	Assess the clinical characteristics and risk factors for mortality in cancer patients with COVID-19	109	Retrospective study (January–March 2020)	Cancer patients – higher risk of COVID-19 infection and poorer prognosis vs patients without cancer. Higher risk of mortality in advanced tumour stage or recent adjuvant therapy (<1 month)
Lunski, 2020 October ⁹⁴ (USA)	No specific type of cancer men-mentioned	Evaluate the difference in mortality from COVID-19 between patients with cancer and patients without cancer	Cancer: 312; without cancer: 4833	Retrospective study (March–April 2020)	Patients with cancer – higher mortality vs controls. Greatest risk – patients with cancer age ≥65 y and those with certain comorbidities, male sex, history of CKD, obesity or recent therapy. Laboratory measures – decreased absolute lymphocyte counts, thrombocytopenia, elevated creatinine, lactic acidosis and elevated procalcitonin increased the risk of death
Mangone, 2021 April ⁹⁵ (Italy)	S, H	Evaluate the impact of having had cancer on COVID-19 risk and prognosis during the first wave of the pandemic	407	Population-based cohort study. Used registry data from the Reggio Emilia province (January–May 2020)	Cancer patients – greater risk of hospitalization and death, especially if <70 y of age or recent diagnosis. Greatest risk of hospitalization – cancers of the GI tract, lymphoma or other haematologic neoplasms. Strongest excess mortality – cancer of the urinary tract, other haematologic neoplasms, melanoma and female genital organs
Mehta, 2020 July ⁷² (USA)	S, H	Evaluate case fatality rate of different cancer types who acquired with COVID-19	218	Retrospective study (March–April 2020)	Cancer patients – significant increase in mortality. Highest susceptibility in haematologic or lung malignancies

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Meng, 2020 June ⁷³ (China)	S, H	Evaluate the risk of cancer history and mortality in COVID-19 patients	109	Retrospective study (January–March 2020)	Cancer patients with COVID-19 – higher risk of mortality. Cancer history only independent risk factor for COVID-19. Haematologic malignancies – worse clinical outcomes (mortality rate twice that of patients with solid tumours [50% vs 26.1%]). Elevations in ferritin, high-sensitivity CRP, ESR, procalcitonin, prothrombin time, IL-2 receptor and IL-6 seen in cancer patients
Mohamed, 2021 January ⁹⁶ (UK)	S (renal transplant patients)	Compare waitlisted and transplant patients who got COVID-19 and assess clinical outcomes	60 (32 active waitlisted patients and 28 functioning renal transplants)	Single-centre prospective study. COVID-19-positive waitlisted and transplant patients were compared and assess clinical outcomes were assessed (beginning of the pandemic–end of April 2020)	Both groups – CRP at 48 h and peak CRP associated with mortality. Incidence of COVID-19 higher in the waitlisted population. Transplant patients have more severe disease and higher mortality. CRP at 48 h can be used as a predictive tool
Mushtaq, 2021 September ⁹⁷ (USA)	H (HSCT)	Evaluate the impact of SARS-CoV-2 in HSCT and CAR T cell therapy recipients	58 HCT/CAR T cell therapy patients (32 allogeneic HSCT, 23 autologous HSCT)	Single-centre prospective study (March–May 2021)	COVID-19 caused significant mortality in patients undergoing HCT and CAR T cell therapy, especially among allogeneic HCT recipients
Nakamura, 2020 November ⁹⁸ (Japan)	S, H	Evaluate the association between clinical outcomes and potential prognostic factors	32	Retrospective study (January–May 2020)	Associations with mortality – lymphocyte count, albumin, LDH, serum ferritin and CRP on admission. Patients who received cytotoxic chemotherapy recently or were treated with chemotherapy had a poor prognosis and prolonged periods of viral shedding
Nie, 2020 November ⁹⁹ (China)	S (lung)	Determine the clinical characteristics and risk factors for in-hospital mortality of lung cancer patients with COVID-19	45	Multicentre retrospective study (January–May 2020)	Lung cancer patients – atypical presentation of COVID-19. Associations with increased risk of in-hospital mortality – prolonged PT and elevated high-sensitivity cardiac troponin I

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Pinato, 2020 July ⁷⁴ (UK)	S, H	Describe the outcomes in cancer patients during the initial outbreak of COVID-19 in Europe	204	Retrospective, multicentre observational study (February–April 2020)	Associations with mortality – age ≥ 65 y, multiple comorbidities. No associations – tumour stage, disease activity, provision of active anticancer therapy at COVID-19 diagnosis
Ramachandran, 2020 October ⁷⁵ (USA)	S, H	Compare clinical characteristics and outcomes of patients with and without a cancer history who were infected with COVID-19	Cancer: 53; non-cancer: 135	Retrospective observational study (March–April 2020)	Cancer patients – higher levels of lactic acidosis, CRP, LDH and ALP vs non-cancer patients. Age ≥ 60 y – rapid clinical deterioration. Higher mortality – age ≥ 60 y, especially when they had concomitant hypertension and elevated levels of CRP and LDH
Rogado, 2020 August ⁷⁷ (Spain)	S (lung)	Determine whether there is a difference in incidence and severity of COVID-19 infection in lung cancer patients	17	Retrospective study (March–April 2020)	Lung cancer patients had a higher mortality rate than the general population
Rogado, 2020 May ⁷⁶ (Spain)	S	Describe COVID-19 cumulative incidence, treatment outcome, mortality and associated risk factors	45	Retrospective study. Reviewed medical records of cancer patients admitted at an oncology department between 1 February and 7 April 2020 (February–April 2020)	Cancer patients – vulnerable to COVID-19, increased complications. Indicators of mortality – severity of the infection at admission, elderly patients
Rogiers Aljosja, 2021 January ¹⁰⁰ (multiple countries)	S (mainly melanoma, non-small cell lung cancer, renal cell carcinoma)	Determine clinical impact of COVID-19 on patients with cancer treated with ICIs	110	Multicentre, retrospective, cohort study. 19 centres across 9 countries (Australia, Canada, France, Germany, Italy, Switzerland, The Netherlands, UK and USA) (March–May 2020)	Cancer patients – higher risk of severe COVID-19 infection vs individuals without comorbidities. Treatment with ICI not associated with severe COVID-19 infection in patients with cancer. Increased risk for hospital admission – treatment with combination ICI and the presence of COVID-19 symptoms

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Russell, 2020 July ⁷⁸ (UK)	S, H	Determine factors affecting COVID-19 outcomes in cancer patients	156	Retrospective study (February–May 2020)	Associations with severe COVID-19 – initial cancer diagnosis >24 months before COVID-19, presenting with fever, dyspnoea, GI symptoms and higher levels of CRP. Associations with COVID-19 death – Asian ethnicity, receiving palliative treatment, having an initial cancer diagnosis >24 months before, dyspnoea and increased CRP levels. Inverse association observed with increased levels of albumin Associations of higher mortality – male sex, advanced age and active malignancy. Outcome of COVID-19 comparable after adjusting for age, sex and comorbidities for cancer vs non-cancer patients
Rüthrich, 2020 November ¹⁰¹ (Europe)	S, H	Determine the clinical characteristics and outcomes	Cancer: 435; non-cancer 2636	Retrospective study (March–August 2020)	Factors influencing death – nausea, mechanical ventilation, admission to the ICU and length of hospital stay in the ward
Safari, 2021 August ¹⁰² (Iran)	S, H	Investigate the epidemiology of cancer patients and identify risk factors affecting their mortality	66	Retrospective cohort study of hospitalized patients with cancer and COVID-19 in Hamadan (2020)	Recipients of autologous and allogeneic HSCT – poor survival. Associations with higher risk of mortality – age ≥ 50 y, male sex, development of COVID-19 ≤ 12 months after transplantation. Disease indication of lymphoma associated with a higher risk of mortality vs plasma cell disorder/myeloma
Sharma, 2021 March ¹⁰³ (USA)	H (allogeneic HSCT recipients)	Describe the characteristics and outcomes of HSCT recipients after developing COVID-19	318	Observational cohort study (March–August 2020)	Associations with mortality – dyspnoea, history of cancer, impaired consciousness level, tachypnoea, tachycardia, leucocytosis and thrombocytopenia. Haematologic cancer had a higher mortality than solid tumours (63% vs 37%)
Sorouri, 2020 December ⁷⁹ (Iran)	S, H	Determine the clinical characteristics, outcomes and risk factors for mortality in hospitalized patients with COVID-19 and cancer	Cancer 53; non-cancer 106	Case–control study (February–April 2020)	Associations with higher hospitalization and mortality – smoking status, comorbidities and a diagnosis of cancer
Sun, 2021 January ¹⁰⁴ (USA)	S, H	Outcomes in cancer compared with non-cancer patients who got COVID-19	Cancer 67; non-cancer 256	Retrospective study. Cancer patients and non-cancer patients were compared (June 2020)	

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Tian, 2020 July ⁵ (China)	S, H (malignant solid tumours and haematologic malignancy)	Determine clinical features and determine risk factors of COVID-19 disease severity for patients with cancer and COVID-19	232	Multicentre, retrospective, cohort study (January–March 2020)	Patients with cancer – severe COVID. Risk factors – elevated TNF- α and NT-proBNP and decreased CD4 ⁺ T cells or albumin:globulin ratio, advanced tumour stage (previously reported risk factors of older age; elevated IL-6, procalcitonin and D-dimer; and decreased lymphocytes)
Trapani, 2020 December ¹⁰⁵ (Italy)	S (solid organ transplantation recipients)	Compare risk of infection, hospitalization and admission in the ICU and mortality among solid organ transplant recipients and non-solid organ transplant recipients who got COVID-19	450	Nationwide population-based study. Assessed the cumulative incidence and outcome of COVID-19 in solid organ transplant recipients and compared the results with those of COVID-19 non-transplanted patients (January–June 2020)	Higher mortality (30.6%) in transplant patients than in non-solid organ transplant recipients (15.4%). Solid organ transplant recipients – higher risk of infection, hospitalization and admission in the ICU and mortality vs non-solid organ transplant recipients
Wang, 2020 May ⁸⁰ (China)	S, H	Assess the clinical characteristics and outcomes of COVID-19-infected cancer patients	283	Retrospective study. Data of cancer patients admitted to 33 designated hospitals for COVID-19 in Hubei province, China (December 2019–March 2020)	Associations with worse outcome – current cancer patients (vs former cancer patients), lymphohaematopoietic malignancies. Mortality higher among patients receiving recent chemotherapy (33%), surgery (26%), other anti-tumour treatments (19%) and no anti-tumour treatment (15%)
Wang, 2020 December ¹⁰⁶ (USA)	S, H	Investigate how patients with specific types of cancer are at risk for COVID-19 infection and its adverse outcomes and to study cancer-specific race disparities for COVID-19 infection	1200	Retrospective case-control study (August 2020)	Patients with cancer had a high risk for COVID-19 infection and worse outcomes. This was further exacerbated among African Americans

Table 1. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Yang, 2020 May ⁸¹ (China)	S	Determine clinical characteristics and outcomes of cancer patients with COVID-19	52	Retrospective study (January–April 2020)	Cancer patients had a higher risk of COVID-19 vs the general population. Complications – liver injury, ARDS, sepsis, myocardial injury, renal insufficiency and MODS are common in cancer patients
Yang, 2020 July ⁸² (China)	S, H	Describe clinical characteristics and outcomes of patients with cancer and COVID-19 and examine risk factors for mortality	205	Retrospective, multicentre, cohort study (January–March 2020)	Poor prognosis (death during admission to hospital) – haematologic malignancies (vs solid tumours), receiving chemotherapy within 4 weeks before symptom onset and male sex were risk factors
Zhang, 2020 October ⁸³ (China)	S (breast)	Evaluate characteristics and outcomes of breast cancer patients infected with COVID-19	35	Retrospective study. Five designated tertiary hospitals for the treatment of COVID-19 in Wuhan, China (January–May 2020)	Breast cancer patients had less severe disease compared with other cancer patients when infected with COVID-19
Zhang, 2020 July ⁸⁴ (China)	S	Determine clinical characteristics of COVID-19-infected cancer patients and assess the risk factors associated with severe events	28	Retrospective cohort study (January–February 2020)	Cancer patients – poor outcomes. Risk factors for severe disease – last anti-tumour treatment within 14 d, patchy consolidation on CT on admission
Zhou, 2020 July ⁸⁵ (China)	H	Determine the clinical characteristics of haematologic patients who were infected with COVID-19	9	Retrospective study (February 2020)	Patients had atypical clinical features, defective viral clearance and a lower level of SARS-CoV-2-specific antibodies

AKI: acute kidney injury; ALP: alkaline phosphatase; ARDS: acute respiratory distress syndrome; CAR: chimeric antigen receptor; CKD: chronic kidney disease; CRP: C-reactive protein; CT: computed tomography; CVD: cardiovascular disease; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; H: haematologic cancer; HCT: haematocrit; HSCT: haematopoietic stem cell transplant; ICI: immune checkpoint inhibitor; IL: interleukin; LDH: lactate dehydrogenase; MODS: multiorgan dysfunction syndrome; NK: natural killer; NT-proBNP: N-terminal brain natriuretic peptide; PT: prothrombin time; R-CHOP: rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine sulphate and prednisone; S: solid cancer; SACT: systemic anticancer therapy; TNF: tumour necrosis factor.

Table 2. Studies on SARS-CoV-2-related immune responses in cancer patients

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Abdul-Jawad, 2021 January ¹¹⁷ (UK)	S, H	Determine how the immune system is affected by SARS-CoV-2 infection of cancer patients	41 (23 S, 18 H)	Prospective study (March–May 2020)	Haematologic malignancies – heterogeneous humoral responses, exhausted T cell phenotype and high prevalence of prolonged virus shedding. Recovered haematologic cancer patients – lingering immunological legacies. Recovered solid cancer patients’ immunophenotypes almost similar to those of non-virus-exposed cancer patients
Annika, 2021 September ¹¹⁸ (UK)	S, H	Compare humoral and cellular immunity against SARS-CoV-2 in solid and haematologic cancer patients	357	Prospective, longitudinal cohort study (May 2020–March 2021)	Solid malignancies – capable of developing humoral and cellular immunity against SARS-CoV-2. Haematologic malignancies – impaired humoral response associated with malignancy type and anti-CD20 treatments
Bange, 2021 May ⁸⁶ (USA)	H	Determine immune parameters that lead to clinical outcomes	100	Prospective observational cohort study of patients with cancer who were hospitalized with COVID-19 (April–September 2020)	Patients with cancer – significantly reduced SARS-CoV-2-specific IgG and IgM antibodies than patients without cancer; most prominent in haematologic cancer patients; solid cancer patients had IgG and IgM antibody responses that were more similar to patients without cancer
Esperança, 2021 May ¹¹⁹ (Portugal)	S, H	Determine the humoral immune response of patients with cancer against SARS-CoV-2	72 (19 cancer, 53 controls)	Single-centre, retrospective study (March–June 2020)	Patients with cancer – weaker SARS-CoV-2 antibody response compared with those without cancer. Associations with persistently weak serological responses – treatment with chemotherapy within 14 d before positivity

Table 2. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Hempel, 2020 January ¹²⁰ (Germany)	S, H	Analyse development of antibodies in patients with cancer following SARS-CoV-2	77	Multicentre, prospective study (April–2020)	Patients with cancer had poorly developed antibodies following infection
Huang, 2021 February ¹²¹ (USA)	H	Study underlying immune mechanisms leading to increased mortality in cancer patients with COVID-19	Cancer 106, non-cancer controls 113	Prospective study (April–September 2020)	Haematologic cancer – significant impairment of B cells and SARS-CoV-2-specific antibody responses. Solid cancer – immune phenotype similar to non-cancer patients. Even in haematologic cancers if preserved CD8 T cells they had a lower viral load and mortality. Even if depletion of B cells with anti-CD20 therapy resulted in complete impairment of SARS-CoV-2-specific IgG and IgM antibodies, mortality was not increased if adequate CD8 T cells were present
Huang, 2020 September ¹¹⁴ (China)	S, H	Describe the characteristics, screening methods and outcomes of cancer patients with asymptomatic COVID-19 infection	16	Retrospective study (February–April 2020)	Lymphocyte counts were normal in all asymptomatic carriers (host immunity of asymptomatic carriers is not significantly disrupted by COVID-19)
Liu, 2020 June ¹¹⁵ (China)	S, H	Compare the antibody response to SARS-CoV-2 in cancer patients and non-cancer patients	Cancer 40, non-cancer 1430	Prospective study (February–April 2020)	Prevalence of IgG antibodies to SARS-CoV-2 in cancer patients with COVID-19 was much lower than in patients without cancer
Marra, 2020 January ¹²² (France)	S, H	Determine seroconversion rates of cancer patients and COVID-19	Cancer 61, non-cancer 105 (86 PCR positive)	Multicentre, observational, prospective study (March–May 2020)	No difference in SARS-CoV-2-specific IgG antibody detection in cancer patients and healthy subjects

Table 2. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Paschold, 2020 October ¹²³ (Germany)	S, H	Determine SARS-CoV-2-specific antibody rearrangements of immune systems of cancer patients in order to explain the outcome	Cancer 500, healthy controls 200	Prospective study (July 2020)	B cell response restriction in aging and cancer
Solodky, 2020 May ¹¹⁶ (France)	S, H	Compare the SARS-CoV-2 antibodies in cancer patients versus healthcare workers after symptomatic COVID-19	85	Retrospective study (March–April 2020)	Seroconversion rate significantly lower in cancer patients. Antibodies almost undetectable in patients receiving cancer treatments in the month before antibody testing
Thakkar, 2021 March ¹²⁴ (USA)	S, H	Evaluate the rate of seroconversion for SARS-CoV-2 IgG for patients with cancer and its association with the type of malignancy and type of anticancer therapy	261	Observational, retrospective exploratory cohort study (March–September 2020)	Significantly reduced (absent) seroconversion observed in haematologic malignancies, patients receiving anti-CD20 therapy, CAR T cell therapy and stem cell transplant

CAR: chimeric antigen receptor; H: haematologic cancer; PCR: polymerase chain reaction; S: solid cancer.

following COVID-19 to be lower in patients with haematologic malignancies and those who had received rituximab or a stem cell transplant.¹²⁴ Thus a differential rate of seroconversion was seen in different cancer patient groups. Another study found survival to be lower in patients with blood cancers compared with those with solid organ cancers. In this study there was greater impairment of B cell and SARS-CoV-2-specific antibody responses in those with blood cancers compared with solid cancers.⁸⁶ Significantly reduced immunoglobulin G (IgG) and IgM antibodies to SARS-CoV-2 are seen among blood cancer patients compared with solid cancer patients following COVID-19.⁸⁶ However, a subset of patients developed good CD4⁺ and CD8⁺ T cell responses and those with good CD8⁺ T cell responses were able to compensate for the weak antibody responses.⁸⁶

Impairment of B cells has been found in other studies as well.^{121,123} In one study there were heterogeneous humoral responses and an exhausted T cell phenotype in blood cancer patients. There is compelling evidence from case reports and series that immunosuppressed patients, including those with cancers, are also at increased risk of prolonged, persistent SARS-CoV-2 infection and viral shedding, accelerated viral evolution during infection and treatment, emergence of viral variants that show evidence of reduced susceptibility to neutralizing antibodies and low antibody titres to SARS-CoV-2 variants.¹²⁵⁻¹³⁵ The immunophenotypes of recovered solid cancer patients were similar to non-virus-exposed cancer individuals, while recovered blood cancer patients showed a weak immune response.¹¹⁷ Anti-cancer therapy has been reported to be associated with impaired seroconversion. Patients receiving anti-CD20 therapy and chimeric antigen receptor (CAR) T cell therapy have absent seroconversion.¹²⁴

However, some studies reported SARS-CoV-2-specific IgG antibody detection did not differ between cancer patients and healthy individuals.^{122,136} Furthermore, immune disruption is higher in symptomatic COVID-19 patients, while asymptomatic carriers have normal immunity and lymphocyte counts.¹¹⁴ Finally, the resolution of any immune dysfunction that follows COVID-19 occurs faster and better in those with a solid cancer. There is delayed or absent antibody responses in patients with haematologic malignancies and these patients will take longer time to clear the virus.¹³⁷

Interaction of cancer and COVID-19 treatments

The treatment of cancer patients with COVID-19 may be complicated by changes in immunity when using certain medications and drug interactions. In Hodgkin lymphoma, bleomycin needs to be used with caution, owing to its lung toxicity.¹³⁸ Immune checkpoint inhibitor (ICI)-induced pneumonitis has made clinicians cautious about using this class of medicines. Concomitant ICI-induced pneumonitis and COVID-19 pneumonia may potentially increase the risk of lung damage.¹³⁹ Among those with cancer that develop COVID-19, those receiving ICI therapy had worse outcomes in some studies⁴⁰ but not in others.¹⁰² Several cancer treatment protocols or regimens do not affect the outcomes of COVID-19 and have thus been recommended for use in cancer patients during the pandemic.¹⁴⁰ Immunotherapy, hormone therapy or radiotherapy in the month prior to SARS-CoV-2 infection is not associated with an increased risk of mortality among

cancer patients with COVID-19.³⁴ Androgen therapy reduces the risk of contracting COVID-19 among patients with prostate cancer.

The Bruton tyrosine kinase inhibitors (BTKis) are used to treat CLL, Waldenström macroglobulinaemia and chronic graft-vs-host disease and have been shown to have potent anti-inflammatory effects resulting in decreased levels of pro-inflammatory cytokines that are commonly elevated in severe COVID-19.¹⁴¹ Thus some authors have suggested a protective role of BTKis from severe COVID-19 morbidity due to an attenuated inflammatory response.^{142,143}

It is recommended that granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) be stopped in patients with cancer and COVID-19 who do not have bacterial or fungal infections, to avoid the potential risk of increasing inflammatory cytokine levels and pulmonary inflammation.^{144,145} On the other hand, it is recommended that G-CSF be given with chemotherapy regimens to reduce the risk of febrile neutropenia in patients with COVID-19.¹⁴⁶ Thus, further trials on this aspect are urgently needed.

With CAR T cell and bispecific T cell engineer therapy, cytokine release syndrome is a known complication and shares many similarities with the COVID-19-associated cytokine storm.¹⁴⁷ The optimal time interval between resolution of infection and initiating or restarting cancer-directed therapy is still to be determined. Currently it has been recommended that treatment be withheld until COVID-19 symptoms have resolved.¹⁴⁰ With radiation therapy, hypofractionation has been suggested to minimize the number of hospital visits during the pandemic.¹⁴⁸

The overall recommendations for treating COVID-19 in cancer patients are similar to those for the general population.¹⁴⁰ Dexamethasone has been found to reduce mortality rates in patients with COVID-19 who require supplemental oxygen or invasive mechanical ventilation.¹⁴⁹ In cancer patients, dexamethasone is used for several reasons, including preventing chemotherapy-induced nausea and to treat inflammation associated with brain metastasis or spinal cord compression and as part of treatment protocols in acute lymphoblastic leukaemia and multiple myeloma. The side effects of dexamethasone are expected to be similar in patients with cancer to those without.¹⁴⁰ However, as dexamethasone is a weak to moderate cytochrome P450 (CYP3A4) inducer, possible interactions do need to be considered.¹⁴⁰

Interactions are seen between medications that are used to treat cancer and COVID-19.¹⁵⁰ Tocilizumab is known to interact with vincristine and doxorubicin. Some COVID-19 treatments may cause QT interval prolongation and thus need to be used with caution in patients receiving a bcl-2 inhibitor (venetoclax) or tyrosine kinase inhibitors (such as gilteritinib or nilotinib). Lopinavir/ritonavir are CYP3A4 inhibitors and may increase methotrexate, vincristine or ruxolitinib concentrations.^{151,152}

Impact of COVID-19 on cancer clinical services

Taking into account the impact of COVID-19 on cancer clinical services, clinicians have had to rethink and remodel the provision of curative care for such patients. Table 3 outlines important findings with regard to the impact on clinical services and psychological aspects of cancer patients due to the COVID-19

Table 3. Studies on the effect of COVID-19 on cancer services

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Blay, 2021 April ¹⁶² (France)	S	Determine impact of COVID-19 on cancer patient management	N/A	Retrospective study. The number of patients diagnosed and treated within 17 of the 18 Uni cancer centres was collected in 2020 and compared with the same periods between 2016 and 2019 (January–July 2020)	Delays in cancer patient management – only for newly diagnosed patients, more frequently in women, for breast cancer, prostate cancer, and non-metastatic cancers
Dimmohamed, 2020 April ¹⁵³ (The Netherlands)	N/A	Evaluate the impact of the COVID-19 pandemic on cancer diagnosis	N/A	Retrospective observational study (February–April 2020)	Significant decrease in cancer diagnoses mainly in skin cancers. Probable causes for barriers in cancer diagnosis – barriers to consulting a GP, GP consultations for non-acute issues transitioned to telehealth, hospitals postponed diagnostic evaluation and temporary discontinuation of national screening programmes for breast, colorectal, and cervical cancer
Gathani, 2020 November ¹⁶³ (UK)	S (breast)	Analyse the impact on diagnosis due to COVID-19 by comparing activity for breast cancer in the first 6 months of 2020 compared with the same time period in 2019	N/A	Retrospective observational study (January–June 2020)	Number of breast cancers diagnosed during the first half of 2020 is not significantly low compared with the first half of 2019
Güven, 2020 July ¹⁵⁴ (Turkey)	S, H	Evaluate the early changes in the inpatient and outpatient oncology clinics	N/A	Retrospective study. Patients admitted to four medical centres in Massachusetts were recruited (March–May 2020)	Significant decrease in newly diagnosed patients, patients having elective interventional procedures and patients in palliative care services. The frequency of hospitalisations for chemotherapy was higher than in previous years

Table 3. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Jazieh, 2020 September ¹⁵⁵ (Global)	N/A	Evaluate the impact of the COVID-19 pandemic on cancer care worldwide	N/A	Cross-sectional study (April–May 2020)	Cancer care affected worldwide. Main reasons for restricted cancer care – overwhelmed system, lack of personal protective equipment, staff shortage and restricted access to medications
Juanjuan, 2020 October ¹⁵⁶ (China)	S (breast)	Analyse the psychological status of patients with breast cancer during the pandemic	658	Retrospective study. Evaluated patients with breast cancer recruited from multiple breast cancer centres in Hubei Province and assessed the psychological impact by assessing anxiety, depression, distress and insomnia (February 2020)	High rates of anxiety, depression, distress and insomnia were observed. Independent factors associated with anxiety – poor general condition, shorter duration after breast cancer diagnosis, aggressive breast cancer molecular subtypes and close contact with patients with COVID-19. Factors independently associated with depression – poor general condition and central venous catheter flushing delay. Independent factors associated with insomnia – poor general condition. Independent factors associated with distress – poor physical condition and treatment discontinuation
Lai, 2020 June ¹³⁷ (UK)	N/A	Evaluate the impact of the COVID-19 pandemic on cancer services	3 862 012	Multicentre retrospective observational study (through April 2020)	Decreases in admissions for chemotherapy and urgent referrals for early cancer diagnosis
Maringe, 2020 August ¹⁵⁷ (UK)	S (breast, colorectal and oesophageal cancer and lung cancer)	Estimate the impact of delays in diagnosis on cancer survival outcomes in four major tumour types	32 583 patients with breast cancer, 24 975 with colorectal cancer, 6744 with oesophageal cancer and 29 305 with lung cancer	National population-based modelling study (retrospective observational and modelling) (March 2020–March 2021)	An increase in the number of avoidable cancer deaths is expected as a result of diagnostic delays due to the pandemic in the UK

Table 3. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Morris, 2021 March ¹⁶⁴ (UK)	S (col-orectal)	Investigate the impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England	N/A	Retrospective observational study. Used data from four population-based datasets spanning NHS England (National Cancer Waiting Time Monitoring, Monthly Diagnostic, Secondary Uses Service Admitted Patient Care and the National Radiotherapy datasets) (January 2020–October 2020)	Reduction in the number of people referred, diagnosed and treated for colorectal cancer. Reduced number of colonoscopies performed. Reduction in patients receiving surgery. Lower proportion of laparoscopic and greater proportion of stoma-forming procedures. For rectal cancer, increase in the use of neoadjuvant radiotherapy due to a greater use of short-course regimens
Patt, 2020 November ¹⁵⁸ (USA)	N/A	Evaluate the impact of COVID-19 on the US cancer population, including identification of new patients, access to care, and disruption of treatment	N/A	Retrospective observational study (March–July 2020)	Decreases and delays in identifying new cancers, delivery of treatment, cancer screenings, visits, therapy and surgeries. Mastectomies, colectomies and prostatectomies mainly affected
Rutter, 2020 July ¹⁶⁵ (UK)	S (GI cancer)	Analyse the impact of the COVID-19 pandemic on endoscopy services and endoscopic cancer diagnosis	N/A	Retrospective study. The average weekly number of cancers, proportion of missing cancers and cancer detection rates were calculated (January–May 2020)	Reduction in endoscopic services and a resultant reduction in cancer detection
Sozutek, 2021 February ¹⁶⁶ (Turkey)	S (GI cancer surgery)	Evaluate the feasibility of performing elective GI cancer surgery during the COVID-19 pandemic	176 patients	Observational unicentric cohort study. Conducted to evaluate whether surgery could be safely performed during the COVID-19 pandemic (March–November 2020)	GI cancer surgery can be safely performed even within a pandemic hospital if proper isolation measures can be achieved for both patients and health workers

Table 3. Continued

First author, year and month (country)	Type of cancer	Objective	Cancer cohort size	Methodology and duration of study	Significant findings
Van Haren, 2021 April ¹⁶⁷ (USA)	S (lung)	Examine the impact of COVID-19 on lung cancer screening and subsequent cancer diagnosis	N/A	Prospective study. Analysis of the prospective institutional low-dose CT screening database (March–July 2020)	Significant disruption in lung cancer screening with a resultant decrease in the number of new patients screened and an increase in the proportion of nodules suspicious for malignancy once screening was resumed
Vanni, 2020 June ¹⁵⁹ (Italy)	S (breast)	Estimate the impact of anxiety among breast cancer patients due to COVID-19	160	Retrospective study (January–March 2020)	Higher rates of procedure refusal and surgical refusal. Infection risk was the primary reason for refusal
Wang, 2020 July ¹⁶⁰ (China)	S, H	Explore mental health problems in patients diagnosed with cancer during the COVID-19 pandemic	6213	Cross-sectional study (April 2020)	High prevalence of depression, anxiety, PTSD and hostility. Risk factors for mental health problems – history of mental disorder, excessive alcohol consumption, higher frequency of worrying about cancer management due to COVID-19, higher frequency of a feeling of overwhelming psychological pressure from COVID-19 and a higher level of fatigue and pain. Only 1.6% sought psychological counselling during COVID-19. Protective factors associated with a lower risk of mental health problems among cancer patients – better quality of life, good relationships with family members
Zadnik, 2020 July ¹⁶¹ (Slovenia)	N/A	Analyse whether cancer diagnosis and management were affected during the COVID-19 epidemic in Slovenia	N/A	Retrospective observational study. Used data from the Slovenian Cancer Registry (November 2019–May 2020)	Significant decrease in first referrals for oncological services, first visits, imaging studies and cancer notifications

CT: computed tomography; GI: gastrointestinal; GP: general practitioner; H: haematologic cancer; N/A: not applicable; PTSD: post-traumatic stress disorder; S: solid cancer.

pandemic.^{137,153-167} One study suggested that while appropriate therapy is continuing, physicians should take steps to reduce the risk from COVID-19, such as the selection of oral over intravenous treatment regimens wherever there is equipoise, the more judicious use of growth factor support and reducing surveillance laboratory and radiologic evaluations when possible.^{144,145,148} Another study discussed the use of tele-oncology services to reduce the risk of cancer patients being exposed to SARS-CoV-2.¹⁶⁸ There is a need for clear communication and education about hand hygiene, infection control measures, high-risk exposure and awareness of the signs and symptoms of COVID-19. Some have suggested the need to individually evaluate the necessity of active intervention, postponing elective surgery or adjuvant chemotherapy for patients with a low risk of progression and minimizing outpatient visits to mitigate exposure and transmission.¹⁶⁹

Optimal protection of healthcare staff is important during the pandemic. Rapid response by institutions, adjustments to organizational structure, strategic planning, developing and implementing effective guidelines and providing effective and alternative ways to protect and support clinical staff, employees and patients are key to achieving good care during the pandemic.

Many patients with haematologic malignancies rely on clinical trials to receive their care, but during the pandemic the conduct of several clinical trials has been affected. The risk of adverse events from cancer therapies is unlikely to be increased.¹⁷⁰ Haematologic malignancy treatment units should be SARS-CoV-2 free zones, dedicated solely to haematologic treatment. Patients should strictly comply with social distancing and hospital outpatient visits should be reduced.

During the pandemic, cancer patients may experience adverse impacts from a screening, treatment or psychological perspective. Two-thirds of new cancer patients have presented at a more advanced stage. Nearly 75% missed their cancer screening appointment and two-thirds of patients who are already on cancer treatment have had their treatment interrupted.¹⁷¹ A significant proportion of screening and diagnostic investigations have had to be postponed due to the pandemic. There has been a large effect on endoscopic services, leading to reductions in cancer detection.¹⁶⁵ Significant disruption has been seen in lung cancer screening¹⁶⁷ and imaging studies.¹⁶¹ Urgent referrals for early cancer diagnosis were significantly reduced.¹³⁷ National screening programmes for breast, colorectal and cervical cancer were temporarily stopped or reduced due to the pandemic.¹⁵³

An Israeli national survey among haemato-oncology patients reported a delay in treatment among 9.1% of patients.¹⁷² Interruptions to treatment at any stage have been reported by 77.5% of breast cancer patients during the pandemic.¹⁵⁶ A systematic review of 62 descriptive studies showed that interruptions and disruptions largely affected facilities up to 77.5%, the supply chain up to 79% and personnel availability up to 60%.¹⁷³ Despite repeated reassurances from officials that the UK's NHS remained open for urgent care, it was estimated that 45% of those with potential cancer symptoms did not contact their doctor during the UK's first wave of the pandemic from March to August 2020. The main reasons cited were fear of contracting COVID-19 and avoiding placing extra strain on the NHS. Consequently, suspected cancer referrals fell by 350 000 compared with the same period in 2019.¹⁷⁴ By April 2021, the UK NHS had >4.6 million

cases on the waiting list for surgery and >300 000 have a waiting time of >12 months, a considerable proportion of which are for cancer.¹⁷⁴

There have been disruptions to interventional procedures, palliative care services¹⁵⁴ and therapeutic surgeries,^{158,164,175} with decreases in admissions for chemotherapy.¹³⁷ One study found the delay occurred among newly diagnosed patients with breast, prostate and non-metastatic cancers.¹⁶² Some of the reasons for delayed and disrupted care included an overwhelmed health system, lack of personal protective equipment, staff shortages, restricted access to medications¹⁵⁵ and barriers to consulting a general practitioner.¹⁵³ A 20% increase of cancer deaths has been predicted in England due to COVID-19 because of delays in patients seeking care, getting referred or receiving their chemotherapy.¹³⁷

During the COVID-19 pandemic, adverse psychological effects have been noted among cancer patients. A high prevalence of mental health problems among cancer patients has been observed.¹⁶⁰ Patients with breast cancer were reported to have high rates of anxiety, depression, distress and insomnia.¹⁵⁶ COVID-19-related anxiety among breast cancer patients may affect their decision-making process, such as attending diagnostic and therapeutic procedures.¹⁵⁹ The aforementioned Israeli national survey including >400 haemato-oncology patients recorded high rates of depression, and it was more evident among patients with chronic myeloid leukaemia.¹⁷² A prospective study that included 77 lymphoma patients from Italy reported anxiety in 36% of patients, depression in 31% when the Hospital and Anxiety Depression Scale was administered and post-traumatic stress disorder (PTSD) among 36%.¹⁷⁶ Some may develop issues with a range of addictions.¹⁷⁷

Long-term effects of COVID-19 on cancer

Cancer patients are at an increased risk of developing post-COVID complications,¹⁷⁸ mainly affecting their heart, lung, kidney, skin and brain.¹⁷⁹ At least 15% of patients with cancer who have recovered from COVID-19 experience at least one post-infection sequelae,¹⁸⁰ such as respiratory symptoms, fatigue, neurocognitive dysfunction and weight loss.¹⁸¹ Those at higher risk of long-term sequelae include men, those ≥ 65 y of age, having two or more comorbidities and a history of smoking.¹⁷⁸ One study found that if cancer patients with COVID-19 survive the immediate sequelae, their long-term sequelae and mortality are similar to those of cancer patients without COVID-19.⁵⁷

Interestingly, due to mounting evidence that SARS-CoV-2 is able to modulate certain oncogenic pathways, promote chronic low-grade inflammation and cause tissue damage, it has been hypothesised that long COVID-19 may predispose recovered patients to cancer development and accelerate cancer progression.¹⁸² Comprehensive studies are urgently required to elucidate the effects of long COVID-19 on cancer susceptibility.

Conclusions

COVID-19 has significant adverse clinical, laboratory, socio-economic and psychological effects among patients with malignancies. This is more prominent in those with haematologic

malignancies compared with solid malignancies and the magnitude of the risk has implications for clinical decision making. Those with lung cancer have the highest mortality among solid cancers from COVID-19. COVID-19 and cancer intersect at a molecular level, which may have therapeutic implications in cancer patients with COVID-19. Certain oncogenic molecular pathways commonly involved by cancer are also affected by COVID-19. Autoantibodies against IFN-I have been found in patients with life-threatening COVID-19.¹⁸³ Comprehensive studies are required to elucidate long-term sequelae of COVID-19 on cancer survivors. The COVID-19 pandemic has caused major disruptions to clinical services for cancer patients worldwide. Delayed presentations and diagnosis due to strained health systems and patients' reluctance to seek medical care during the pandemic have caused a considerable impact on cancer survival. In order to mitigate the catastrophic effects of the pandemic on cancer care, a thorough and collaborative effort is required at the national and international level. Findings from various studies have important policy implications, including, but not limited to, the need for increased surveillance and testing for SARS-CoV-2, minimising healthcare system exposure and reconsideration of procedures and treatments in patients with cancer in order to minimise the morbidity and mortality caused by COVID-19. Vaccination is an important preventive measure for patients with solid and haematologic malignancies against getting severe COVID-19.

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