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# Are All Patients with Cancer at Heightened Risk for Severe Coronavirus Disease 2019 (COVID-19)?

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Cancer patients are traditionally considered at high risk for complicated respiratory viral infections, due to their underlying immunosuppression. In line with this notion, early case series reported high mortality rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with malignancy. However, subsequent large, prospective, epidemiological surveys indicate that the risk for severe coronavirus disease 2019 (COVID-19) may be largely attributed to the multiple confounders operating in this highly heterogeneous population of patients, rather than the cancer or its treatment per se. We critically discuss the conundrums of SARS-CoV-2 infection in cancer patients and underscore mechanistic insights on the outcome of COVID-19 as it relates to cancer therapy and the type and status of the underlying malignancy. Not all cancer patients are similarly at risk for a complicated COVID-19 course. A roadmap is needed for translational and clinical research on COVID-19 in this challenging group of patients.

**Keywords.** COVID-19; SARS-CoV-2; cancer; malignancy; immunosuppression.

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, there has been an increasing concern of poor disease outcomes in cancer patients [1]. This reasonable postulation stems from the complicated course of respiratory viral infections in immunocompromised hosts [2, 3], and was reinforced by early case series describing worse outcomes of COVID-19 in cancer patients as compared to patients without malignancy [4–7], primarily reported from health-care settings that were overwhelmed by a burst of COVID-19 cases. Accordingly, oncology practices have been profoundly adjusted to mitigate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposures in cancer patients, at the potential risk of delaying timely diagnosis, staging, and optimal therapies of the underlying malignancy.

However, recent large epidemiological surveys in cancer patients with COVID-19 indicate that severe disease appears to be largely driven by poor performance status, frailty, advanced stage of malignancy, and/or other known contributing risk factors, such as older age, smoking history, and chronic cardiopulmonary or metabolic comorbid conditions [8–11]. Indeed, children with cancer have been reported to develop mild COVID-19 infections to date [12]. Although important, these

studies were retrospective, lacked an appropriate case-control design (ie, a comparison to patients without cancer and adjustment for comorbidities), and were subject to recall bias and missing data. Despite their limitations, these studies have not consistently shown an association between specific underlying cancers or specific types and/or recent receipt of chemotherapy, cancer-related surgery, or immunotherapy with poor outcomes in cancer patients with COVID-19 (Table 1). In this perspective, we reflect on the notion that not all patients with malignancy are at similarly high risk for severe COVID-19 complications derived from either uncontrolled viral proliferation or subsequent virus-driven hyper-inflammatory responses. In addition, we discuss a conceptual mechanistic framework related to the underlying malignancy and the potentially favorable or unfavorable impact of the various conventional and new targeted therapies employed in the cancer ecosystem on the outcome of SARS-CoV-2 infection, while we highlight currently unresolved questions.

## PATHOGENETIC ASPECTS OF COVID-19 RELATED TO MALIGNANCY

The greater expression of angiotensin-converting enzyme 2 (ACE2), the cell entry receptor for SARS-CoV-2 that is caused by older age, certain comorbidities (eg, chronic obstructive pulmonary disease), other accompanying risk factors (eg, smoking), or certain types of malignancy [13, 14], could enhance viral entry within respiratory epithelia and contribute to poor COVID-19 outcomes in certain cancer patients (Table 2). In contrast, inhibition of the androgen-dependent transmembrane serine protease 2 [15, 16], another key protein for

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**Table 1. Summary from Representative Published Studies on the Outcome of COVID-19 in Cancer Patients**

Type of study (Country)/n	Type of malignancy (%)	Active malignancy (refractory or relapsed)	Median age (% of males)	Recent (within 30 days) chemotherapy (% on CPIs)	Comorbidities	Mortality (mean follow up in days)	Clinical predictors of death (multivariate analysis)	Reference
Multicenter (China, Hubei)/205	Solid tumors (91%)	30% (27%)	63 (47%)	17% (2%)	HTN 33%, DM 11%, COPD 2%, CHF/CAD 8%, CKD 2%	20% (68)	Recent receipt of chemotherapy, male sex	Yang et al [4]
Multicenter (China, Wuhan)/232	Solid tumors (90%)	85% (15%)	64 (51%)	85% (14%)	Smoking 6%, HTN 41%, DM 24%, COPD 1%, CHF/CAD 9%, CKD 3%	20% (29)	Older age, poor performance status, lymphopenia, advanced cancer	Tian et al [5]
Single center (USA)/218	Solid tumors (75%)	38% (19%)	69 (58%)	19% (2%)	DM(38%, COPD 29%, CHF 15%, CKD 25%, CAD 19%	28% (21)	Older age, comorbidities	Mehta et al [6]
Multicenter (China, Hubei)/105	Solid tumors (91%)	64% (16%)	64 (57%)	16% (6%)	Smoking 34%, HTN 28%, DM 7%, COPD 6%, CHF 11%, CKD 6%	11% (27)	Older age, multiple comorbidities (DM)	Dai et al [7]
Multicenter (USA, Canada, UK, Spain)/928	Solid tumors (82%)	55% (11%)	66 (50%)	17% (4%)	Smoking 40%, obesity 19%, comorbidities (79%) <sup>a</sup>	13% (28)	Older age, male sex, smoking, comorbidities, active malignancy, poor performance status	Kuderer et al [8]
Multicenter (UK)/800	Solid tumors (78%)	67% (43%)	69 (56%)	35% (6%)	DM (16%), COPD (8%), CHF/CAD (14%), HTN (31%)	28% (28)	Older age, male sex, comorbidities	Lee et al [9]
Single center (USA)/423	Solid tumors (75%)	N/A (55%)	60 (50%)	45% (7%)	Obesity (40%), smoking (40%), DM (20%), COPD/asthma (17%), CHF (20%), CKD (9%)	9% (47)	Older age, hematological malignancy, CPI therapy, lymphopenia or steroids	Robilotti et al [10]
Multicenter (Global)/200	Thoracic malignancies (100%)	74% (21%)	68 (70%)	33% (37%)	Smoking (81%), DM (15%), COPD (26%), HTN (47%), CHF (15%), CKD (8%)	33% (24)	Smoking	Garassino et al [11]

We selected studies with a sizable number of patients (> 100) and a multivariate analysis design on clinical outcomes of cancer patients with COVID-19. Active malignancy was defined as need for treatment within a year from COVID-19 diagnosis. Abbreviations: CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CPI, checkpoint inhibitors; DM, diabetes mellitus; HTN, hypertension; N/A, not available.

<sup>a</sup>Details on comorbidities have not been provided.

**Table 2. Unique Pathogenetic Features of COVID-19 in Cancer Patients**

Mechanism of SARS-CoV-2 Infection	Predicted State in Cancer Patients	Comments
I) Viral uptake by epithelial and endothelial cells via the ACE2 receptor. High expression of ACE2 may facilitate viral entry and initiation of infection, and is triggered by Type I IFNs (Ziegler et al [17]).	Promoting	ACE2 is overexpressed in certain types of solid tumors, such as renal, breast, thyroid, liver, hepatocellular, stomach, and prostate adenocarcinomas (Dai et al [13]), or comorbid conditions associated with malignancy (eg, COPD/smoking; Leung et al [14]).
II) NRP-1 facilitates SARS-CoV-2 uptake by epithelial/endothelial cells following S protein cleavage by furin (Cantuni-Castelvetri et al [18]).	Promoting	NRPs are cell surface glycoproteins regulating fundamental processes in carcinogenesis, from tumor cell proliferation to angiogenesis to metastasis and immune escape (Napolitano and Tamagnone [19]). NRP-1 regulates the antitumor activity of immunotherapy with CPIs (Leclerc et al [20]).
III) Proteolytic cleavage of S protein by the TMPRSS2 allows viral fusion with host cellular membranes. Expression of TMPRSS2 is higher in prostate cancer and is androgen-dependent (Lucas et al [15]).	Promoting	TMPRSS2 is upregulated in prostate cancer; androgen-deprivation treatment in patients with prostate cancer has been associated with decreased risk of infection by SARS-CoV-2 in early clinical reports (Montopoli et al [16]).
IV) Delayed activation of Type I/III IFN signaling induced by SARS-CoV-2 (Channappanavar et al [21]; Zhou et al [43]; Prokunina-Olsson et al [23]).	Promoting	In immunocompromised patients, including those with cancer, viral-induced (eg, influenza, RSV) activation of Type I/III IFN signaling can be attenuated [2, 3]. This results in increased viral proliferation, prolonged viral shedding, greater potential for the development of resistance mutations to antiviral agents, and poor viral infection outcomes.
V) Depletion of alveolar macrophages; accumulation of inflammatory monocyte-derived macrophages and neutrophil influx; unabated release of proinflammatory cytokines, which promote tissue damage; and development of ARDS (Merad and Martin [24]; Liao et al [25]).	Protective	Chemotherapy-induced leukopenia attenuates immunopathology in animal models of MERS-CoV (Prescott et al [22]). Immunomodulation with inhibitors of immune signaling pathways (eg, BTK and JAK/STAT inhibitors) could have a protective effect against severe COVID-19 (Stebbing et al [26], Treon et al [27], Roschewski et al [28]). Epigenetic modulation of inflammatory responses in macrophages could be an investigational path in cancer patients with COVID-19 (Gilan et al [29]).
VI) Reduction and functional exhaustion of B-cells and T-cells induced by hyperinflammation and/or the virus itself, compromise antiviral immunity (Merad and Martin [24]; Liao et al [25]).	Promoting	Adaptive immune responses may be compromised in some malignancies by prolonged use of corticosteroids and/or other lymphocyte-depleting agents, leading to unrestricted viral proliferation of SARS-CoV-2 and impaired development of protective immunity [2]. Lymphopenia is a major predictor of poor outcomes of COVID-19 (Zhang et al [30]).
VII) High levels of expression of viral entry receptor ACE2 on endothelial cells might contribute to vascular tropism and thrombotic complications of COVID-19 (Varga et al [31]).	Promoting	Malignancy-induced prothrombotic states could aggravate SARS-CoV-2-induced thrombotic sequelae.
VIII) Endothelial inflammation exacerbated by NET formation might promote thrombotic and cardiovascular complications, which largely contribute to mortality (Ackermann et al [32]; Barnes et al [33]; Zuo et al [34]; Middleton et al [35]).	Protective	Inhibition of NET formation as a result of chemotherapy-induced neutropenia or targeted therapy with immunomodulators could prevent endothelial damage.
IX) Bacterial superinfection results in additional immunopathology following systemic and local immunoparalysis induced by the virus (Pillai et al [36]).	Promoting	Bacterial translocation due to chemotherapy-induced mucositis, changes in lung and/or gut microbiota due to cancer-induced dysbiosis, may result in increased rates of secondary infections. Immunoparalysis induced by viral sepsis and/or immunosuppressive therapies with c/steroids or cytokine inhibitors (eg, IL-6 inhibitors) might increase the risk for opportunistic infections (Rawson et al [37]; Somers et al [38]; Park et al [39]), including COVID-19-associated pulmonary aspergillosis; Arastehfar et al [40]).

Abbreviations: ACE2, angiotensin-converting enzyme 2; ARDS, Acute Respiratory Distress Syndrome; BTK, Bruton Tyrosine Kinase; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; IFN, interferon; JAK/STAT, Janus Kinase/Signal transducer and activator of transcription; IL, interleukin; MERS-CoV, Middle East Respiratory Syndrome-Coronavirus; NET, neutrophil extracellular traps; NRP, neuropilin; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane receptor serine protease 2.

SARS-CoV-2 entry in respiratory epithelia, in patients receiving androgen-deprivation therapy for prostate cancer could result in decreased SARS-CoV-2 infection efficiency and favorable COVID-19 outcomes (Table 2).

Furthermore, advanced metastatic malignancy and poor performance status are implicated as drivers of severe COVID-19 in cancer patients (Table 1). The etiology is likely multifactorial. The high levels of expression of the newly identified SARS-CoV-2

entry receptor neuropilin-1 in the epithelia and endothelia of patients with advanced cancer could facilitate viral proliferation [18, 19]. Malignancy- or drug-induced hypercoagulability states could also instigate thrombotic complications in patients with certain types of advanced malignancies, further aggravated by the prothrombotic state of severe COVID-19 [31–35]. Moreover, immunometabolic deregulation related to myeloid cell dysfunction, T-cell exhaustion, and cancer cachexia, all

prominent in advanced cancers, might have a negative impact on antiviral immunity [41, 42]. Hence, delays in the initiation of curative chemotherapy or surgery to control the underlying malignancy and limited access to supportive care could negatively affect the course of COVID-19 in these cancer patients.

Importantly, bacterial or fungal super-infections have been diagnosed in up to 50% of severely ill COVID-19 patients in intensive care units [37, 38]. Given the challenges in performing bronchoscopies to diagnose pneumonia in COVID-19 patients and the low autopsy rates, relative short-term follow-up, and limited patient-level information in most epidemiological studies thus far, the exact causes of death and the relative contributions of secondary infections on morbidity and mortality remain elusive and could be underestimated; this concern is especially relevant in cancer patients, who have excess risks for nosocomial and opportunistic infections [40].

### LYMPHOPENIA AND COVID-19

Lymphopenia compromises cytotoxic T-cell- and Natural Killer (NK)-cell-dependent antiviral responses and is consistently associated with an increased risk of poor outcomes in COVID-19 patients [30] (Table 2). Lymphopenia and lymphocyte dysfunction are prominent intrinsic features of lymphoid malignancies and conventional chemotherapeutic agents (eg, corticosteroids, purine analogs, cyclophosphamide/fludarabine prior to CAR T-cell therapy). In addition, targeted biologics (eg, alemtuzumab, rituximab, CD38-targeting monoclonal antibodies) given for lymphoid malignancies can induce profound and persistent lymphocytopenia and/or lymphocyte

dysfunction. Therefore, the quantitative and qualitative defects of T-cells and B-cells in certain hematological malignancy patients may contribute to poor COVID-19 outcomes due to unabated SARS-CoV-2 proliferation or impaired development of protective anti-SARS-CoV-2 antibodies [24, 25].

### COVID-19 IN THE NEUTROPENIC CANCER PATIENT

Emerging evidence implicates hyperinflammatory responses derived from monocytes/macrophages [24, 25, 43] and neutrophils [32–35] as a driver of immunopathology and poor outcomes in the late phase of severe COVID-19 infection. Accordingly, preclinical studies suggest that chemotherapy-induced leukocytopenia improves outcomes of SARS infection [21, 22]. In that light, it is plausible that cancer patients with chemotherapy-induced neutropenia and monocytopenia might have attenuated hyperinflammatory innate responses and abrogated tissue damage during COVID-19. This hypothesis is in line with the use of myeloablative regimens as front-line therapy for other, often virus-driven, conditions associated with cytokine storm and/or macrophage activation, such as hemophagocytic lymphohistiocytosis, and is supported by preliminary reports demonstrating no clear association between the recent receipt of cytotoxic chemotherapy and severe COVID-19 in cancer patients [2, 8–11] (Table 1). In addition, cancer patients with chemotherapy-induced neutropenia and accompanying thrombocytopenia might be less susceptible to developing thrombotic complications due to endothelial dysfunction, a hallmark histopathological feature of COVID-19 [32–35], which is thought to be driven by platelet activation and neutrophil extracellular

**Table 3. Unresolved Clinical Questions on SARS-CoV-2 Infection Course in Cancer Patients**

Do atypical (eg, extra-pulmonary disease, delayed macrophage activation, or thrombotic and cardiovascular complications following recovery from chemotherapy) or unique (eg, diffuse alveolar hemorrhage) clinical manifestations of COVID-19 occur?
What are the mimickers of COVID-19 in cancer patients? How can COVID-19-associated interstitial pneumonitis be discriminated from (1) drug- or radiation-induced pneumonitis; (2) other infections that present similarly (eg, PJP, influenza and other opportunistic viruses); (3) lung lymphangitic spread (solid tumors); or (4) extramedullary lung involvement (hematological cancers)?
What is the rate of viral shedding and what is the transmission potential of SARS-CoV-2 from and to cancer patients, given the frequently prolonged viral shedding in immunocompromised patients (2)? How can infection control measures be effectively implemented in asymptomatic cancer patients and prolonged shedding of SARS-CoV-2?
What is the effect of chemotherapy or radiotherapy-induced mucositis or chemotherapy of other drugs (eg, growth factors, TKIs, VEGF inhibitors) on the expression of SARS-CoV-2 uptake receptors (ACE2, neuropilin-1) in the respiratory epithelium and endothelia?
What is the impact of antiviral and/or ACE2 receptor modulating properties of some TKIs (eg, JAK/STAT, ABL kinase inhibitors) on clinical course of COVID-19?
What would the impact of immunotherapy with CPIs and CAR T-cells be on the outcome of SARS CoV-2 infection? What is the effect of SARS-CoV-2 infection in HSCT recipients pre- and postengraftment and the related risk for GvHD?
What is the effect of advanced malignancy on susceptibility to COVID-19? As chemotherapy-induced remission improves immunological responses, should we initiate timely chemotherapy (in full or attenuated doses) in asymptomatic COVID-19 patients with chemotherapy-sensitive cancers?
As high levels of IL-6 and other proinflammatory cytokines of severe COVID-19 are commonly elevated in certain malignancies (eg, leukemia, multiple myeloma) and/or advanced stages of disease, which would be the most reliable biomarkers of COVID-19 in cancer patients to guide personalized therapies and assess their efficacy? How safe are IL-6 blockage and/or corticosteroids as related to risks for superinfections and downstream opportunistic infections?
Would vaccination against COVID-19 be suboptimal or contraindicated in cancer patients?
Could trained immunity (innate immune memory) approaches (eg, BCG vaccines) induce beneficial or detrimental inflammatory responses in cancer patients with COVID-19?
How can attributable mortality of SARS-CoV-2 infection be evaluated in cancer patients? As outcome determinants are multifactorial, how should we develop and validate clinical prediction models to inform/triage level of care (eg, active chemotherapy, delayed or attenuated chemotherapy, ICU utilization, hospice care) and assess the impact of various antiviral and immunomodulatory therapies in cancer patients with COVID-19?

Abbreviations: ACE2, angiotensin-converting enzyme 2; BCG, Bacillus Calmette-Guérin; CAR, Chimeric Antigen Receptor; COVID-19, coronavirus disease 2019; CPI, checkpoint inhibitors; GvHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant; ICU, intensive care unit; IL, interleukin; JAK/STAT, Janus Kinase/Signal transducer and activator of transcription; PJP, Pneumocystis jirovecii pneumonia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TKI, tyrosine kinase inhibitors; VEGF, Vascular Endothelial Growth Factor.

trap formation (Table 2). In contrast, cancer patients might be at higher risk for COVID-19-associated hyperinflammatory and/or thrombotic complications during neutrophil recovery from chemotherapy-induced myelosuppression due to Immune Reconstitution Inflammatory Syndrome-like effects [39]. Therefore, future studies will be needed to define how the kinetics of chemotherapy-induced myelosuppression and recovery might affect the hyper-inflammatory and thrombotic complications of COVID-19 in cancer patients.

### CANCER PATIENTS RECEIVING PRECISION-MEDICINE BIOLOGICAL THERAPIES

Small molecule kinase inhibitors that are increasingly used in certain cancer types and target signaling pathways in immune cells (eg, Janus Kinase [JAKs], BTK) or the vascular endothelium (eg, VEGF) are under evaluation in randomized, placebo-controlled trials in patients with severe COVID-19, with the goal of ameliorating hyperinflammatory and/or thrombotic complications [26]. Thus, cancer patients already receiving such therapies might be protected from hyperinflammatory immunopathology; conversely, the discontinuation of such therapies in cancer patients infected with SARS-CoV-2 could instigate hyperinflammation, as recently suggested with BTK inhibition [27, 28], and also adversely affect the control and long-term outcomes of the underlying malignancy (Table 2). Because the epigenetic modulation of immune cells could impact the balance between host control of viral replication and hyperinflammatory responses in COVID-19, and because selective epigenetic inhibitors (eg, Bromodomain and Extra-terminal [BET] inhibitors) are promising therapies for inflammatory diseases [29] (Table 2), observational studies should examine the effects of hypo-methylating agents and other epigenetic therapies used for the treatment of acute leukemia in the clinical course of COVID-19 in such patients.

### CANCER PATIENTS ON IMMUNOTHERAPY

Given the widespread use of checkpoint inhibitors (CPI) in several malignancies, understanding the potential impact of CPI on COVID-19 severity and outcomes in patients with different types of cancer is of paramount importance. On one hand, CPI-induced autoimmune and inflammatory complications—including pneumonitis—may be triggered by viral infections, theoretically including SARS-CoV-2. On the other hand, CPI might block expression of the viral entry receptor neuropilin-1 [20], exert immune-enhancing effects in early control of SARS-CoV-2 proliferation, and impact the development of protective adaptive responses, as recently shown for other treatment-refractory viral infections, such as progressive multifocal leukoencephalopathy. Accordingly, the literature on the role of CPIs on SARS-CoV-2-induced immunopathology is conflicting to date, and more studies will be needed to define the clinical scenarios in which CPI might exert protective

or detrimental effects on the outcome of COVID-19 in cancer patients [44] (Table 1).

### HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Small case series suggest that COVID-19 is not associated with a complicated course either in adult [3] or pediatric hematopoietic stem cell transplant (HSCT) recipients [45]. Of interest, conventional therapies for graft-versus-host disease, including corticosteroids, calcineurin inhibitors, and JAK/STAT inhibitors, dampen inflammatory immunopathology and have a positive impact on COVID-19 outcomes [46–48]. There are no studies regarding the natural history of COVID-19 in the preengraftment period following conditioning chemotherapy for HSCT. Recent studies suggest that active SARS-CoV-2 infection might not be an absolute contraindication for the administration of life-saving cytotoxic chemotherapy in hematological malignancy patients [49]. Nonetheless, future studies are needed to determine whether SARS-CoV-2 infection during the preengraftment phase of HSCT could result in aggravated inflammatory lung responses or triggering of acute graft-versus-host disease upon engraftment (which could be attenuated by a preemptive short course of glucocorticosteroids).

In conclusion, COVID-19 is a novel viral disease with unique clinical, epidemiological, and pathogenetic features, many of which remain poorly understood (Table 2). Although cancer-intrinsic and treatment-induced immunosuppression traditionally confer increased risks for infectious complications, this might not be a universal feature of SARS-CoV-2 infection, in which hyperinflammatory responses appear to significantly contribute to morbidity and mortality. There is an unmet need for a better understanding of the epidemiology and pathogenesis of COVID-19, and for generating clinical prediction models of COVID-19 in cancer patients related to the various types of malignancies and their associated stages, comorbidities, and treatments, in order to optimize care in this complex and heterogeneous population (Table 3). Moving from a “one size fits all” concept to individualized approaches to manage COVID-19 in the various groups of cancer patients should help improve the outcomes of COVID-19 in cancer patients, while still delivering the best possible care for their underlying malignancy.

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