SARS-CoV-2 Infection: A Possible Risk Factor for Incidence and Recurrence of Cancers

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ABSTRACT
COVID-19 and malignancy can affect the susceptibility of one another. Clinically recovered COVID-19 individuals display immune abnormalities that persist several months after discharge. The lymphopenia-related immunosuppression, functional exhaustion of cytotoxic lymphocytes (such as CD8+ cytotoxic T-cells and natural killer cells), hyperinflammatory responses, oxidative stress, downregulation of interferon response, development of the myeloid-derived suppressor cells, downregulation of tumor suppressor proteins and perhaps reactivation of the latent oncogenic viruses may directly and/or indirectly play a role in the cancer development and recurrence in severe COVID-19 patients. SARS-CoV-2-infected malignant patients may be at higher risk of death of their cancer than SARS-CoV-2-uninfected patients with the same cancers. On the other side, the patients with some types of cancers may be more vulnerable to SARS-CoV-2 infection compared with the non-cancerous individuals, due to their immunocompromised state resulted from malignancy, chemotherapy, and other concomitant abnormalities as well as perhaps greater expression of angiotensin-converting enzyme 2. SARS-CoV-2-infected cancerous patients are unable to produce an effective anti-virus immune response and may exhibit more severe forms of COVID-19. This review described the possible impacts of SARS-CoV-2 infection on cancer development and recurrence, and the potential cancer impacts on COVID-19 development, while the possible interventions are highlighted.

Keywords: COVID-19; Cancer; SARS-CoV-2; Immunosuppression; Inflammation; Oncology; Malignancy

INTRODUCTION
The SARS-CoV-2-mediated coronavirus disease 2019 (COVID-19) pandemic has affected a great number of populations in about 200 countries and territories1. SARS-CoV-2 is transmitted predominantly by symptomatic, pre-symptomatic, and asymptomatic carriers, mainly via respiratory droplets during face-to-face exposure such as coughing, talking, and sneezing. Aerosols and to a smaller extent, infected surfaces may also spread the virus 2.
Patients with underlying disorders, including diabetes, hypertension, cancer, chronic respiratory disease, and cardiovascular diseases are more vulnerable to COVID-19. The elderly individuals and those with impaired immune system are at a greater risk of developing serious and even deadly respiratory disorders. The COVID-19-related symptoms appear after an incubation time with a median of approximately 5 days. The period from the initiation of COVID-19 signs to possible dying differs from 6 to 41 days with an average of 14 days. It was estimated that approximately 10.0% of patients with COVID-19 experience prolonged manifestations (for over 3 weeks) and in 1.5%-2.0% of patients, signs persist for over 90 days. Some cases have been considered as chronic COVID-19 when symptoms extending beyond 12 weeks. Long COVID-19 can be the result of low grades of the virus being sequestered in certain tissues, making it impossible to be identified by conventional diagnostic tests. In the patients with long COVID-19, the virus can exert profound modulatory effects on the immune system and induce low-grade chronic inflammatory responses. Thus, SARS-CoV-2 infection, especially in its long term, can act as a risk factor in cancer development.

Data reported from Wuhan, China showed that about 1.0-2.0% of COVID-19 patients were diagnosed with malignancy. However, about 6.0% of hospitalized subjects with COVID-19 from New York City had cancer, and about 8.0% of COVID-19 patients who needed the ICU facilities had an active or early history of malignancy. In another study from Italy, about 20.0% of the COVID-19-related deaths occurred in patients with active malignancy.

The immune system performs an essential role in defending against tumor cells. As a result, the occurrence of malignancy is significantly higher in immune-compromised hosts. Based on immune surveillance concepts, an essential duty of the immune system is to carefully examine the development of malignancy in the body and eliminate tumor cells as they emerge. In the immune system, the Th1 cells show potent antitumorigenic effects via recruitment of the natural killer (NK) cells, M1 type macrophages, and CD8+ cytotoxic T lymphocytes (CTLs). Conversely, type 2 macrophages (M2), myeloid-derived suppressor cells (MDSCs), Th2 cells, and regulatory T (Treg) cells inhibit the anti-tumor immune responses. Tumor cells also escape immune-mediated recognition/elimination by a number of mechanisms, particularly down-regulating of antitumoral immune responses. Clinically recovered COVID-19 individuals display profound immunologic alterations in both innate and adaptive immunity compartments that persist several months after discharge. Anti-tumor immune responses can be weakened because of these immunologic changes.

The malignant patients exhibit a greater risk of SARS-CoV-2 infection. The results from a study conducted in Spain indicated that 31.4% of the cancer patients were seropositive for specific IgG or IgM against SARS-CoV-2, while seropositivity in the general population was 10.0%. In the general population, the fatality rate of COVID-19 is estimated to range from 2 to 3%. However, cancer patients are more susceptible to COVID-19 and have a 25.0%-39.0% mortality risk if infected with SARS-CoV-2. Thus, COVID-19 and malignancy can influence each other susceptibility. SARS-CoV-2 infection may profoundly attenuate the anti-tumoral immune responses. Therefore, the COVID-19 patients may be immunocompromised to an extent where the anti-tumor response is depleted causing cancer development and cancer recurrence. This review explains the possible SARS-CoV-2-mediated impacts on the development of cancer and cancer recurrence, and the potential cancer impacts on the COVID-19, while the possible interventions are highlighted.

Pathophysiology of COVID-19

Four main structural proteins of coronaviruses include spike (S), nucleocapsid (N), envelope (E), and membrane (M), among which S protein plays a fundamental role in the virus binding to its cell receptor, angiotensin-converting enzyme-2 (ACE2). Upon respiratory infection with SARS-CoV-2, an initial proper IFN response (primarily type III IFNs) effectively eliminate the virus without the expression of the clinical symptoms or with the expression of mild signs. If the patient is...
immunocompromised or if the initial IFN response fails, the virus expands, then enters the bloodstream from the lungs and infects ACE2 expressing organs. The tissues and cells that express ACE2 are considered as the possible target of SARS-CoV-2. The greatest expression of ACE2 has been recorded in the gastrointestinal tract, testis, and kidneys. In the lungs, ACE2 is highly expressed by type II alveolar cells, and in the liver, ACE2 expression was observed in cholangiocytes. The entocytes of the small intestine express more ACE2 compared with those from colon regions. ACE2 is also expressed by stratified epithelial cells of the esophagus, proximal tubule cells of kidney, and urothelial cells of the bladder. ACE2 expression has also been documented in CNS blood vessels that provide a direct route for SARS-CoV-2 entry into the brain. Coronaviruses can also attack the peripheral nerves, and then reach the CNS via the synaptic pathway. Collectively, the massive virus replication, viral-mediated ACE2 downregulation, immune dysfunction, over-inflammatory reactions, cytokine storm, lymphopenia, enormous cell death (in particular endothelial and epithelial cells) through apoptosis, necrosis and pyroptosis, coagulopathy, vascular leaks, and lung fibrosis can play prominent roles in the COVID-19 pathogenesis. The anti-virus IFN response is impaired in severe COVID-19 patients, however, these patients experience a destructive cytokine storm which is characterized by a dangerous increase in the circulatory quantities of cytokines such as IL-6, TNF-α, IL-1β, IL-2, IL-7, IL-8, MIP-1α, CCL2 and CXCL10 (IP-10). Cytokine storm can promote viral sepsis and contributes to coagulopathy, vascular leak, multiple organ failure, in particular, acute respiratory distress syndrome (ARDS). In the lung-related innate immunity, viral-derived RNAs are sensed by toll-like receptors (such as TLR7 and TLR8) and cytoplasmic sensors [such as retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA-5)] leading to the IFN production. However, SARS-CoV-2 can effectively downregulate anti-virus IFN response. Moreover, a number of SARS-CoV2-derived molecules activate NLRP3 inflammasome resulting in the pyroptosis and releasing of IL-1β and IL-18 which promote HMGB1 release, Th17 cell activation, neutrophil recruitment, macrophage activation and cytokine storm. Direct interaction between SARS-CoV-2 with platelets, virus-induced complement activation and microvascular damage over-activate platelets which can lead to thrombosis. Among inflammatory markers, IL-6 and CRP support thrombosis state. Diverse cytokines have been implicated in the process of lung fibrosis such as TGF-β and IL-6. During COVID-19, TGF-β is produced by various types of cells such as platelets, macrophages and infected type 2 alveolar cells. TGF-β exerts fibrogenic activity via inducing the proliferation and migration of fibroblasts and stimulating the formation of the extracellular matrix. Local IL-6 overexpression also exacerbated fibrosis through the promotion of the pro-fibrotic activity of M2 macrophages. IL-6-dependent signaling in the vascular epithelial cells lead to up-regulation of the VEGF and downregulation of the E-cadherin promoting vascular permeability and leakage. COVID-19 patients, in particular, those with severe forms of illness have lower blood numbers of CD3+ T lymphocytes, B lymphocytes, CD4+ T cells, CD8+ T cells, and NK cells. The results from different studies indicate that approximately 33.0%–96.0% of patients with the severe form of COVID-19 display lymphopenia which has a close relationship with illness progression and fatality rate. Lymphopenia can lead to immune depression and promote cytokine storm, both of which play important roles in virus dissemination and multi-organ failure. Moreover, total lymphocyte counts are significantly decreased in COVID-19 patients > 50 years old than those < 50. Additionally, a small subset of monocytes, macrophages and T cells may also be infected by SARS-CoV-2 via ACE2-dependent and ACE2-independent process using L-SIGN, DC-SIGN, CD147, antibody-dependent enhancement (ADE), and perhaps phagocytosis of apoptotic bodies containing the virus. The infection of some types of leukocytes by SARS-CoV-2 can compromise the innate and adaptive immune responses. SARS-CoV-2 can effectively suppress the anti-viral interferon (IFN) response in antigen presenting cells (APCs).
such as monocytes and macrophages and dendritic cells (DCs)\textsuperscript{4,45}.

In convalescent patients, the functional abnormalities of the T and B cells also persist up to 6 months after discharging from hospital\textsuperscript{22}. Yang et al. also indicated that the clinically recovered COVID-19 individuals display immune abnormalities such as lower circulatory numbers of Th1-, Th2-, Th17-, Th1-, memory B-, and central memory T cells within 4-11 weeks after discharge\textsuperscript{21}. Kostopoulos et al. also indicated that some immunologic alterations such as reduction of circulatory B cells persist up to eight months after SARS-CoV-2 infection\textsuperscript{23}. Therefore, SARS-CoV-2 infection-related immune abnormalities, especially in its long term can disrupt the anti-tumoral immune responses.

Risk of tumor development can be enhanced after SARS-CoV-2 infection

1) Anti-tumoral immune responses are compromised after SARS-CoV-2 infection

In the immune system, NK cells are the first line of protection against tumor- and virus-infected cells\textsuperscript{46}. Positivity for the CD16 and CD56 expression is among the most important of NK cell features\textsuperscript{47}. The NK cell activity is controlled by a number of activating and inhibitory receptors. The NK cell-mediated elimination of the target cells depends on the balance between activating and inhibitory receptors, causing the NK cell to discriminate normal cells from unwanted cells\textsuperscript{48}. In the adaptive immunity, the CD8\textsuperscript{+} T cells kill cancerous- and viral-infected cells following the identification of the tumor- and viral-related antigenic peptides bound to MHC class I molecules expressed by target cells. CD4\textsuperscript{+} T cells provide the necessary signals for activating of the CD8\textsuperscript{+} T cells, which are then differentiated to effector CTLs that kill target cells via release of granules or by FasL-mediated apoptosis\textsuperscript{49}.
The number of CD16\textsuperscript{+}CD56\textsuperscript{+} NK cells are markedly diminished in severe COVID-19 than in mild cases and healthy people\textsuperscript{50-52}. In the severe COVID-19 patients, the total counts of CD4\textsuperscript{+} T and CD8\textsuperscript{+} T cells are also reduced compared with other patients, which indicate that COVID-19 can exert profound impacts on lymphocyte\textsuperscript{40,50-52}. The reduced numbers of CD56\textsuperscript{dim} NK cells (a subset of NK cells with cytotoxicity activity), and the reduced levels of NK cell-activating cytokines (including IL-12, IL-15, and IL-21) were indicated in the severe COVID-19 patients\textsuperscript{53}. The overexpression of an inhibitory receptor, called NK group 2 member A (NKG2A), occurs by CD8\textsuperscript{+} T- and NK cells from COVID-19 patients in comparison to healthy people\textsuperscript{51,54,55}. Lower counts of NK and CD8\textsuperscript{+} T cells expressing CD107a (an activation marker), IFN-γ, and IL-2, were detected in COVID-19 patients in comparison with healthy controls\textsuperscript{51}. The intensity of granzyme B expression was also diminished in the NK and CD8\textsuperscript{+} T cells from COVID-19 patients compared with healthy individuals\textsuperscript{51}. The percentages of the TNF-α\textsuperscript{+} NK-cells were also diminished in COVID-19 patients\textsuperscript{51}. The overexpression of NKG2A on CTLs and NK cells from COVID-19 patients is associated with the small expression of IFN-γ, IL-2, TNF-α, CD107a, and granzyme B\textsuperscript{51}. Thereby, the overexpression of NKG2A leads to the functional exhaustion of CD8\textsuperscript{+} T and NK cells in COVID-19 patients compromising immune responses against the cancers and viral pathogens\textsuperscript{51,54,55}. In convalescent COVID-19 patients, the functional abnormalities of the CD8\textsuperscript{+} T cells persist up to 6 months after discharge from the hospital\textsuperscript{22}.
The NKG2A overexpression and next exhaustion of T lymphocytes and NK cells occur in some types of cancer displaying tumor growth\textsuperscript{54,56}. The binding of NKG2A to its relevant ligands prevents CD8\textsuperscript{+} T and NK cell-mediated activities, whereas NKG2A blocking on CTLs and NK cells diminishes tumor growth through improving the CD8\textsuperscript{+} T- and NK cell-mediated activities\textsuperscript{54,57}. Therefore, it is important to improve the NK cells and CTL-related activity and avoid their exhaustion to prevent the damping of anti-tumor immunity during SARS-CoV-2 infection. The targeting of NKG2A may repress the NK cell and CTL exhaustion and thus cause virus clearance in the initial step of SARS-CoV-2 infection\textsuperscript{51}. Monalizumab, an anti-NKG2A monoclonal antibody, improves the CD8\textsuperscript{+} CTL and NK cell-mediated responses in cancers and successfully prevents the progression of tumors with no major harmful impacts in phase 2 clinical trials\textsuperscript{57,58}. COVID-19 patients also have greater plasma quantities of IL-6 and TNF-α which may
impair the NK cell activity, thus the targeting of TNF-α and IL-6 can improve the NK cell activity in COVID-19 patients. It should also be noted that CD4+ T lymphocytes play a central role in the induction of anti-tumoral and anti-viral immunity. CD4+ T lymphocytes recognize antigenic peptides associated with the MHC class II molecules on the membrane of APCs and provide aid for NK cells and CD8+ CTLs to exert anti-tumoral and anti-viral effects. The marked reduction of the MHC II molecules expression on CD14+ monocytes was also reported in severe cases of COVID-19, which has been associated with profound depletion of CD4+ T- and NK cells. The low expression of MHC II molecules on CD14+ monocytes has been attributed to the IL-6 and in vitro experiments using tocilizumab prevent the reduction of the expression of MHC II molecules by monocytes incubated with plasma samples collected from immunocompromised COVID-19 patients. Collectively, the results from aforesaid studies clearly demonstrate that the SARS-CoV-2 infection attenuates the immunosurveillance against tumors that may increase the tumor incidence or tumor recurrence in COVID-19 patients.

2) SARS-CoV-2 infection promotes pro-tumoral inflammatory responses

Tumor-promoting inflammation is one of the main characteristics of cancers. Both chronic and acute inflammation potently affect cancer development. The inflammatory-related mediators can aid tumor development through inducing cell proliferation, angiogenesis, DNA damage, cytoskeleton remodeling, and degradation of the extra-cellular matrix. Inflammation may promote metastasis by producing mediators that enhance vascular permeability. Some cytokines present in the tumor microenvironment, such as IL-6 and TNF-α, and epieregulin can enhance the survival of the metastatic cancer cells. Hyperinflammatory responses and elevated quantities of inflammatory cytokines are hallmarks of the severe form of COVID-19. Cytokine storm is a harmful systemic inflammatory reaction emerging from the releasing of the vast amounts of pro-inflammatory cytokines and chemokines, which operate a crucial role in the occurrence of some main SARS-CoV-2-related complications, such as ARDS. TNF-α and IL-6 are the main players of cytokine storm that were correlated with COVID-19 severity. The IL-6 and TNF-α concentrations are inversely associated with lymphocyte count, which means that the cytokine syndrome may dampen the specific immune response against SARS-CoV-2 infection. TNF-α and IL-6 promote carcinogenesis and contribute to metastasis, tumor invasion, and angiogenesis. Hospitalized subjects with cancer who have elevated IL-6 and TNF-α levels are at greater risk of death. Both cytokines may play key roles in the tumor progression in malignant patients infected with SARS-CoV-2. Reducing the development of tumors in COVID-19 patients by targeting IL-6 and TNF-α needs to be clarified in future studies.

Elevated levels of the chemokines including CCL2, CCL4, CXCL8, CXCL9, and CXCL10 have been also demonstrated in patients with COVID-19 patients. The mentioned chemokines could contribute in cancer development via several mechanisms such as tumor cell expansion, cancer stem cell proliferation, metastasis, angiogenesis, tumor invasion, epithelial-mesenchymal transition (EMT) induction, MDSC attraction, and fibroblast recruitment. The appearance of various subsets of MDSCs was indicated in COVID-19 patients correlating with viral load and disease severity. Hence, the elevated expression of the chemokines can support tumor progression in malignant patients with COVID-19. Thus, targeting tumor-promoting chemokines or blocking their receptors could reduce tumor progression.

ACE2 exerts anti-inflammatory and anti-oxidative effects during infection. The SARS-CoV-2-dependent depletion of ACE2 potentiates the pro-inflammatory and oxidative impacts of angiotensin II. Oxidative stress acts as a starter and enhancer of carcinogenesis as this phenomenon promotes cell proliferation, tumor invasion, angiogenesis, tumor cell survival, chemo-resistance, and radio-resistance.
3) SARS-CoV-2 can exert direct oncogenic impacts
A direct relation has been postulated between coronavirus infection and dysregulation of the cell cycle leading to the cellular transformation. The Nsp3 and Nsp15 of SARS-CoV have been implicated in the degradation of the tumor suppressor proteins P53 and retinoblastoma (pRb), respectively. Similarly, Nsp3 and Nsp15 of SARS-CoV-2 can affect tumor suppressor proteins. The results from an in silico analysis indicated that the S2 subunit of SARS-CoV-2 potently interacts with tumor suppressors P53 and BRCA1/2.

SARS-CoV-2-induced alteration in the activity of E2F transcription factors and RB1 can also promote malignancies. Rb controls the movement from the G1 phase to the S phase in the cell cycle by modulating the E2F activity. The RB1 activity was remarkably reduced, whereas the activity of E2F was enhanced in COVID-19 patients indicating that SARS-CoV-2 may inactivate tumor suppressor Rb resulting in the elevated E2F activity that promotes cell proliferation same as some other oncogenic viruses.

The MAPK, JAK-STAT and NF-κB-mediated signaling pathways may also contribute to the tumorigenesis in SARS-CoV-2-infected individuals. The SARS-CoV-2-derived molecules, such as S protein can be identified by some TLRs such as TLR2, which activates the transcription factors NF-κB and MAPKs through recruitment of MyD88. Furthermore, JAK-STAT signaling pathway is activated following the binding some cytokines to their relevant receptors. The involvements of the MAPK and JAK-STAT-mediated signaling pathways in the development of numerous cancers have been indicated. The targeting of MAPK and JAK-STAT-mediated signaling pathways may interfere with tumorigenesis.

4) Possible reactivation of oncogenic viruses may lead to cancer development after SARS-CoV-2 infection
Infections play a key role in the development of human malignancies, as about 15.0% of cancers are attributed to oncogenic infectious agents. Some infectious agents such as HTLV-1, HPV, EBV, and KSHV cause latent infection, where most infected persons are asymptomatic. The viral oncoproteins exclusively produced in HTLV-1-, HPV-, EBV-, and KSHV-infected cells support cell proliferation. However, HIV itself may have not a direct oncogenic impact, but it increases the risk of cancers by enabling oncogenic agents to expand in co-infected individuals. Similarly, SARS-CoV-2-mediated immune impairment may allow oncogenic pathogens to transform normal cells into malignant cells. It has been reported that some SARS-CoV-2-related proteins and some therapeutic agents can reactivate KSHV which may enhance the risk of cancer development, even in fully recovered COVID-19 patients. Furthermore, the possible presence of SARS-CoV-2-derived oncoproteins that can transform the normal cells into malignant cells needs to be clarified in future studies.

Malignancy promotes the COVID-19 severity
As mentioned above, in innate immunity, IFNs including type I and type III IFNs, serve as the first line of protection against viruses such as coronaviruses. An early proper IFN response can effectively control SARS-CoV-2 infection. Following the initial innate response, induction of an appropriate adaptive immune response is also necessary to clear SARS-CoV-2 and prevent disease progression to severe phases. Both innate and adaptive immune responses are impaired in malignant patients. Lymphopenia (an independent poor predictor in COVID-19 patients) is common in cancer patients who are under active or even watchful treatment. Thus, the immunocompromised state in cancer patients makes these patients more susceptible to COVID-19, and SARS-CoV-2-infected cancerous patients exhibit more severe complications of COVID-19.

The infection rate of SARS-COV-2 in cancer patients is greater than the general population, and cancer patients with COVID-19 showed worsening symptoms and bad outcomes. Malignant patients with COVID-19 display a greater risk of developing serious and even deadly respiratory disorders. It has also been observed that patients with hematological cancers exhibit more serious COVID-19-related complications and more deaths compared with non-malignant care professionals with COVID-19. The patients with lung cancer also
develop severe COVID-19-related lung complications and therefore are at higher risk of dying from SARS-CoV-2 infection. The ACE2 upregulation was commonly found in patients suffering from lung cancer. As a result, the increased ACE2 expression in lung cancer could likely promote the susceptibility of lung cancer patients to SARS-CoV-2 infection.

CONCLUSION
SARS-CoV-2-mediated immunosuppression, hyper-inflammation, and oxidative stress may direct and/or indirectly promote the development of some cancers in predisposed individuals who are infected with SARS-CoV-2 (Figure 1). Furthermore, downregulation of the tumor suppressor proteins and possible reactivation of latent oncogenic viruses in COVID-19 patients can enhance the risk of certain cancers after SARS-CoV-2 infection. The possible presence of the oncogenes in the SARS-CoV-2 needs to be evaluated in future studies. Some COVID-19 patients experience prolonged manifestations which may persist for several months after infection. Moreover, clinically recovered COVID-19 individuals display profound immunologic alterations that extend several months after discharge. Thus, SARS-CoV-2-infected individuals, especially chronic cases, may need post-infection monitoring for cancer development. On the other hand, patients with malignancy are more vulnerable to SARS-CoV-2 and are at higher risk of developing severe symptoms of COVID-19 (Figure 1). Therefore, SARS-CoV-2-infected cancerous patients may be at greater risk of death from COVID-19-related complications. It should also be noted that COVID-19 and malignancy may have some similarities regarding their pathogenicity. Therefore, the identification and the targeting of common pathways between COVID-19 and cancers need more attention in an attempt to treat both diseases using similar therapeutic agents. Ultimately, even during a pandemic, cancer patients need a timely diagnosis, treatment, and monitoring. Moreover, the major risk for cancerous patients in the COVID-19 outbreak may be due to the inability to earn sufficient healthcare facilities.

Figure 1: Impacts of COVID-19 and cancer on each other. The SARS-CoV-2 infection may enhance the risk of cancer development and recurrence through induction of exhaustion of cytotoxic lymphocytes, stimulation of hyper-inflammatory responses, induction of oxidative stress, reduction of the number of lymphocytes and NK cells, down-regulation of IFN response, induction of the pro-tumoral cells such as MDSCs and M2 macrophages, downregulation of tumor suppressor proteins, and perhaps through re-activation of the oncogenic viruses. On the other side, the malignancy can enhance the susceptibility to SARS-CoV-2 infection and increases the severity of COVID-19-related complications through impairing both innate- and adaptive immune responses to virus as well as upregulation of angiotensin-converting enzyme 2 (ACE2) in certain cancers such as lung cancer.
CONFLICTS OF INTEREST
The authors declare no conflict of interests.

Abbreviations
ARDS: Acute respiratory distress syndrome
COVID-19: Novel coronavirus disease 2019
EBV: Epstein-Barr virus
HIV: Human immunodeficiency virus
HPV: Human papillomavirus
HTLV-1: Human T-cell lymphotrophic virus type 1
ICU: Intensive care unit
IFN: Interferon
JAK–STAT: Janus kinase–signal transducer and activator of transcription
KSHV: Kaposi sarcoma–associated herpesvirus
MAPK: Mitogen-activated protein kinase
MHC: Major histocompatibility complex
MyD88: Myeloid differentiation factor 88
NF-kB: Nuclear factor kappa B
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2
TNF: Tumor necrosis factor

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