# Reviewing immunopathology characteristics of SARS-CoV-2 for cancer entwisted with SARS-CoV-2

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## Abstract

In December 2019, the outbreak of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infection that started in Wuhan, Hubei Province, China, has spread to all world. Based on the accumulated data and knowledge on the coronavirus infection and immunology characteristics, this review would hope to give some hints on human immune response to SARS-CoV-2 infection in cancer patients. This insight may help in designing the appropriate immune intervention for treatment and the prophylactic/therapeutic methods against cancer under current coronavirus from immunopathology characteristics of SARS-CoV-2 and cancer entwisted with it. We should achieve accurate diagnosis and treatment for cancer patients through advantages of multidisciplinary diagnosis and treatment team. It is believed that we will eventually overcome the epidemic and win in the future.

## Introduction

In late 2019, the novel coronavirus outbreak in Wuhan, China, and had rapidly outbreaks outside China.[1,2] Coronavirus is not a new threat but an old lesson for us. Both highly pathogenic viruses, severe acute respiratory syndrome coronavirus (SARS-CoV) in Asia in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia in 2012 took the world by threat.

Individuals at highest risk of SARS-CoV-2 include immunocompromised people, pregnant women, and infants. People living with cancer which just belong to this kind of people form a vulnerable population for the onset of SARS-CoV-2 infection. Epidemiological data from China have shown that compared with the general population, cancer patients infected with SARS-CoV-2 have a lower resperitory conditions and a poorer prognosis.[3] Moreover, due to the large-scale explosion of the disease and the shortage of the medical resources, these people cannot get more efficient treatment.[4]

Based on existing data and knowledge, we hope to provide some hints for the cancer patients' response of human immune system to SARS-CoV-2 infection by this piece review. By analyzing immunopathological features in immunopathology characteristics of SARS-CoV-2 and cancer entwisted with SARS-CoV during the coronavirus epidemic, we may help against cancer through effective therapeutic and preventive immune intervention approaches.

## Immunopathology characteristics of SARS-CoV-2

SARS-CoV-2 has a probable asymptomatic incubation period between 2 and 14 days during which the virus can be transmitted.[5] The majority of SARS-CoV-2 cases (about 80%) presented with asymptomatic or with mild symptoms

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while the remainder are severe or critical.[6,7] It seems that the severity and fatality rate of SARS-CoV-2 are milder than that of SARS and MERS. The most common symptoms of SARS-CoV-2 are fever, fatigue, and respiratory symptoms, including cough, sore throat, and shortness of breath. Most patients also developed lymphopenia and pneumonia with characteristic pulmonary ground glass opacity changes. Studies have shown that the average age of severe cases of patients with SARS-CoV-2 infection is higher than that of mild cases (66 years and 51 years) and is more likely to be accompanied by other underlying diseases. The median time to diagnosis was also longer.

In addition, patients with high levels of proinflammatory cytokines including interleukin-2 (IL-2), interleukin-7 (IL-7), granulocyte colony-stimulating factor (G-CSF), interferon $\gamma$ inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), monocyte chemoattractant protein-1A (MIP-1A), and tumor necrosis factor (TNF$\alpha$) were observed in the SARS-CoV-2 severe cases.[4] Lymphopenia and "cytokine storm" may have a major role in the pathogenesis of SARS-CoV-2. From an immunological point of view, SAR-CoV-2 infection causes lymphopenia and the so-called cytokine storm syndrome. Cytokine storm can initiate viral sepsis and inflammatory-induced lung injury which lead to other complications including pneumonitis, acute respiratory distress syndrome (ARDS), respiratory failure, shock, organ failure, and potentially death.

Immune defense mechanisms include specific and non-specific immune responses. Specific immune response has a certain time limit for virus clearance. The endogenous protein synthesized by the virus in infected cells can activate virus-specific CD8$^+$ T cells through the major histocompatibility complex-I (MHC-I) pathway, thus promoting their proliferation, differentiation, and cytotoxicity on target cells.[6] CD4$^+$ T cells can also differentiate into different types of T helper (Th) after interacting with the MHC-II antigen-peptide complex of antigen-presenting cells, and participate in cell and humoral immune response processes.[8,9] Dendritic cell-specific ICAM-3 grabbing non-integrin (DC-SIGN) and L-SIGN (CD209L, DC-SIGNR, or liver/lymph specific SIGN) may have been involved in the pathogenesis, toxicity, and attenuation of the pathogens causing SAR-CoV-2.[10] In addition, antibodies produced by B lymphocytes can specifically neutralize the virus to block infection.[11] However, non-specific immune responses occur immediately after infection and participate in the whole viral clearance process which distinct from the specific immune responses. Macrophages, natural killer cells, and $\gamma\delta$T cells can directly recognize the virus through pattern recognition receptors and recruit neutrophils and monocytes.[12] On the one hand, it can cause "second-hit" injury to tissues by secreting a large number of active mediators and non-specific killing of virus-infected cells and normal cells which are near to it; on the other hand, it can limit the virus in the body by removing necrotic cells, activating the coagulation system and fibroblasts further diffusion.[13–15] However, after virus invasion, if the body cannot produce a strong specific immune response to effectively remove the virus, the non-specific inflammatory response will be constantly enhanced, and finally unable to remove the virus efficiently. The result will cause aggravate infection, tissue ischemia, hypoxia even necrosis, and eventually lead to uncontrolled inflammatory response and trigger cytokine storm.[16]

Researches in China analyzed immunological indicators in 33 intensive care unit (ICU) and non-ICU patients with SARS-CoV-2. It was observed that coronavirus can replicate in large numbers after recognizing angiotensin-converting enzyme 2 through spike protein, and then CD4$^+$ T cells were activated rapidly. They proliferate and differentiate into Th1 cells, meanwhile secreting proinflammatory cytokines such as IL-6, interferon gamma, and granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF can activate monocytes to further release IL-6 and other factors, leading to the formation of cytokine storm, which makes patients develop ARDS, multiple organ failure (MOF), and even die.[17–19] Therefore, IL-6 and GM-CSF released by T lymphocytes and monocytes may be the key point of SARS-CoV-2-induced cytokine storm.[20] As monocytes function as non-specific immune cells, it suggests that the mechanism of SARS-CoV-2 triggering cytokine storms may be closely related to the destruction of specific and non-specific immune balance. Therefore, these may indicate that the elderly and patients with underlying diseases such as cancers, due to the degradation or low immune function of the body, cannot be completed or require long-term induction to develop an effective specific immune response. In a word, if a longer period of time after infection can only rely on a continuously increasing non-specific inflammatory response to resist the invasion and spread of the virus, it will result in a greater risk of triggering cytokine storm, an earlier onset of severe illness, and a higher mortality rate.

## Cancer entwisted with SARS-CoV-2

A nationwide analysis in China for cancer patients in SARS-CoV-2 infection demonstrated that Patients with cancer are more susceptible to infection than individuals without cancer because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments, such as chemotherapy orsurgery.[21–23] Therefore, these patients might have a higher risk of SARS-CoV-2 and a poorer prognosis. The pathological manifestations of lung cancer with SARS-CoV-2 infections can be characterized by edema and prominent proteinaceous exudates, vascular congestion, and inflammatory clusters with fibrinoid material and multinucleated giant cells. Reactive alveolar epithelial hyperplasia and fibroblastic proliferation are indicative of early remodeling. Most importantly, compared with non-cancer patients, cancer patients have a higher risk of severe events.[3]

Combining antiviral and anti-inflammatory treatments is currently recommended for the therapies of patients with SARS-CoV-2 pneumonia and has been clinically proven effective, such as Lopinavir / Ritonavir (LR). Through the database, anti-tumor drugs interacting with antiviral drugs

such as LR were screened.[24] Small-molecule targeted drugs are mostly metabolized by CYP450. Therefore, they mostly interacted with LR, mainly because LR inhibits metabolic enzymes such as CYP3A4 and improves target drug levels. Targeted drugs can also inhibit or induce LR metabolism-related enzymes to change the pharmacokinetics of LR in vivo. Although Sorafenib have no significant pharmacokinetic interaction with LR, they increase the risk of adverse reactions.[25] Most monoclonal antibodies clinically have no significant pharmacokinetic interactions with LR, such as programmed death receptor 1 (PD-1) inhibitors, cetuximab, and so on. The pharmacokinetics of chemotherapeutic drugs metabolized by CYP450 or glucuronidation may be changed by LR, and endocrine therapy drugs also interact with antitumor drugs. There are drug interactions with most tumor-targeted therapeutic drugs, some chemotherapy drugs, some monoclonal antibodies, some endocrine therapeutic drugs, and adjuvant therapeutic drugs. Combination with a few antitumor drugs can even cause serious adverse reactions or lethal risks. Therefore, the application of LR in cancer patients should be closely monitored for drug interactions to improve the effectiveness and safety of patients' medication.

## Prospective

The site of initial infection with SARS-CoV-2 is unknown and the pathogenesis of SARS-CoV-2 is still under investigation. For most patients, SARS-CoV-2 might affect only the lungs because it is mainly a respiratory disease. Elderly patients and/or with basic diseases such as cancer need long-term induction to develop an effective specific immune response due to the degradation of their immune function.[26] Therefore, a longer period of time after infection can only rely on a continuously increasing non-specific inflammatory response to resist the invasion and spread of the virus; it will lead to a greater risk of triggering cytokine storm, an earlier occurrence of severe illness, and a higher mortality rate.

At present, the mortality rate of SARS-CoV-2 worldwide is approximately 2.4% which are caused by multi-organ failure especially in elderly people and people with underlying health conditions such as cancer, hypertension, cardiovascular disease, and diabetes.[27,28] DC/L SIGNs the hope in the SARS-CoV-2 pandemic.[10] Nevertheless, we believe it is imperative to report the findings of immunopathology characteristics of SARS-CoV-2 and cancer entwisted with SARS-CoV-2 for better understanding of the mechanism by which the SARS-CoV-2 causes lung injury in Wuhan and worldwide.

Therefore, we propose three suggestions for cancer patients with SARS-CoV-2. First, an intentional postponing of adjuvant chemotherapy or elective surgery for stable cancer should be considered in this situation. Second, personal protections should be strengthened for patients with cancer. Third, more intensive surveillance or treatment, especially the interaction among drugs, should be considered when patients with cancer are infected with SARS-CoV-2, especially in older patients or those with other comorbidities. For example, LR has drug interactions with most tumor-targeted therapies, some chemotherapeutics, some monoclonal antibodies, some endocrine therapies, and adjuvant therapies, and the combination with a few antitumor drugs can even cause serious adverse reactions or lethal risks. Therefore, the application of LR in cancer patients should be closely monitored for drug interactions to improve the effectiveness and safety of patient medication.

## Conclusion

During the fight against the epidemic, the routine diagnosis and treatment process of cancer patients has been affected. We should achieve accurate diagnosis and treatment for cancer patients through advantages of multidisciplinary diagnosis and treatment team. Although the medical resources were limited for these patients, we provide support to help them through the outbreak and adjust the treatment strategy in a timely and appropriate manner to minimize the adverse effects of the epidemic. It is believed that we will eventually overcome the epidemic and win in the near future.

## Limitations

The review introduced some hints on human immune response to SARS-CoV-2 infection that patients also experienced with cancer. This insight may help in designing the appropriate immune intervention for treatment and the prophylactic/therapeutic methods against cancer under current coronavirus from immunopathology characteristics of COVID-19 and cancer entwisted with COVID-19. However, in this case the data about the covid infection in cancer patients are limited. It needs to provide further strong supports.

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