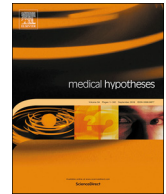




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## Is the presence of lung injury in COVID-19 an independent risk factor for secondary lung cancer?



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### ABSTRACT

The morbidity and mortality of lung cancer are increasing. The Corona Virus Disease 2019 (COVID-19) is caused by novel coronavirus 2019-nCoV-2, leading to subsequent pulmonary interstitial fibrosis with chronic inflammatory changes, e.g., inflammatory factors repeatedly continuously stimulating and attacking the alveolar epithelial cells. Meanwhile, 2019-nCoV-2 can activate PI3K/Akt and ERK signaling pathways, which can play the double roles as both anti-inflammatory and carcinogenic factors. Moreover, hypoxemia may be developed, resulting in the up-regulation of HIF-1  $\alpha$  expression, which can be involved in the occurrence, angiogenesis, invasion and metastasis of lung cancer. Additionally, the immune system in 2019-nCoV-2 infected cases can be suppressed to cause tumor immune evasion. Therefore, we speculate that COVID-19 may be a risk factor of secondary lung cancer.

Lung cancer is one of the most common malignancy with rising morbidity and mortality, as a great threat to public health. Currently, it annually induces nearly 20% of all cancer-related deaths, and become the leading killer among the cancers [1,2]. Smoking, air pollution, and histories of other bronchial-pulmonary diseases, e.g., chronic bronchitis, asthma, pneumonia and tuberculosis were proved to be the possible risk factors of lung cancer [3]. However, the etiology and epidemiology of lung cancer is still complex and warrants further study.

Currently, an acute respiratory infectious disease(COVID-19) caused by a novel coronavirus (2019-nCoV-2) is spreading and prevailing worldwide[4]. With the accumulation of pathological knowledge and treatment experience, the cure rate has been improved greatly, and the mortality has decreased gradually [5]. However, the issues arise regarding management and follow-up of these cured case population. Will COVID-19 induce secondary lung diseases, e.g., LUNG CANCER?

### COVID-19 can cause varying degrees of chronic airway inflammation and pulmonary fibrosis which may induce lung cancer

The pathophysiological mechanisms of COVID-19 seemed to be very similar to those of SARS-CoV and MERS-CoV, which can cause acute

respiratory distress syndrome and Middle East respiratory syndrome, respectively [6]. Transmitted by droplets, the coronavirus may enter human respiratory tract and infect epithelial cells of trachea, bronchi and alveoli [7]. Furthermore, 2019-nCoV-2 can cause the systemic inflammation and multi-organ injuries, mainly targeting lung. Its main pulmonary pathological features include hyaline membrane consisting of monocytes, multinucleated giant cells and macrophages in the alveolar cavity, hyperplasia and abscission of type II alveolar epithelial cells, congestion and edema of alveolar septum, focal hemorrhage and necrosis of lung tissue, exudation from alveoli, and formation of pulmonary interstitial fibrosis [8].

Following COVID-19 goes through the acute stage, it can be classified as chronic inflammatory changes of trachea, bronchus and alveoli. The essences of chronic inflammation include a variety of inflammatory factors repeatedly and continuously stimulating the alveolar epithelium, leading to damage, shedding, proliferation and repair, and finally the atypical hyperplasia, metaplasia and even canceration of squamous cell epithelium [9]. Furthermore, 2019-nCoV-2 can trigger some inflamed cells, e.g., neutrophils and macrophages, to reach and gather in the infected alveoli, leading to the release of inflammatory mediators, e.g., protease and reactive oxygen free radicals, which can enhance fibroblast migration, proliferation, differentiation,

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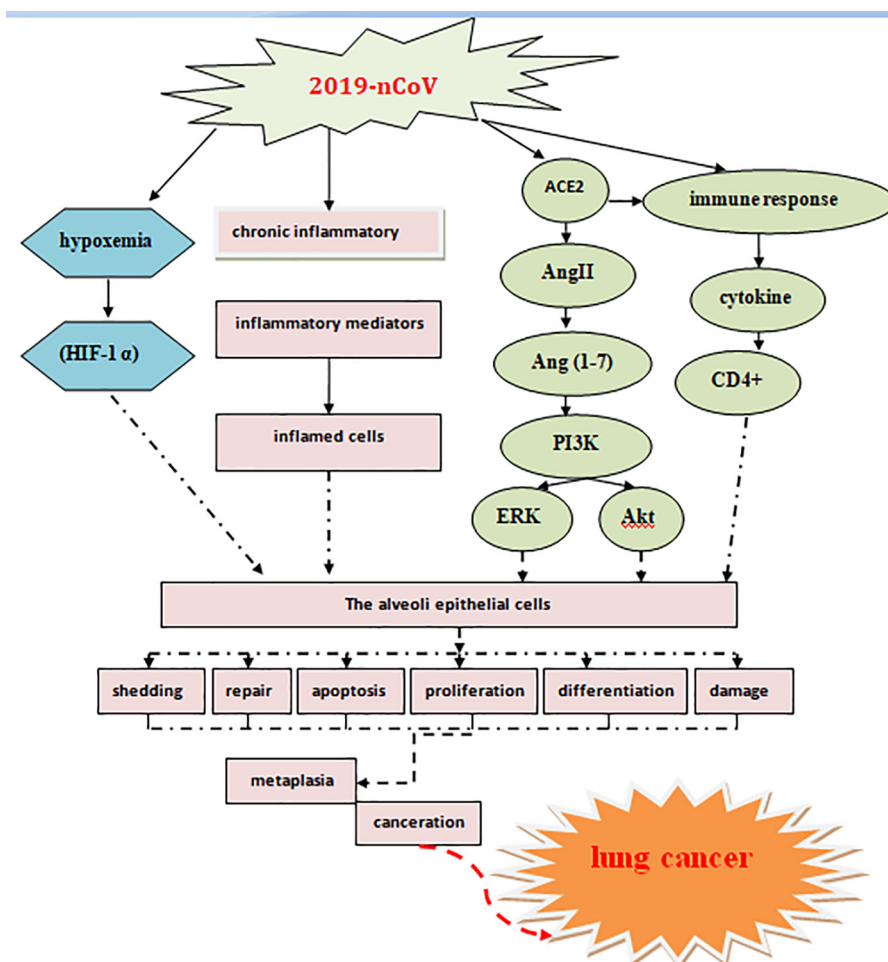


Fig. 1. The possible mechanism that COVID-19 may increase the risk of secondary lung cancer.

resistance to apoptosis, metaplasia and even canceration of alveoli epithelial cells [10].

Additionally, COVID-19 associated chronic inflammation can stimulate and damage alveolar epithelial tissues leading to pulmonary fibrosis which may eventually induce lung cancer [11]. Actually, pulmonary fibrosis may be the pathological changes associating with end-stage of pulmonary inflammations, e.g., pneumonia, chronic obstructive pulmonary disease and tuberculosis, with a variety of genetic mutations and angiogenesis leading to high risks of lung cancer [12]. Over the past 10 years, the understanding of the inflammatory micro-environment of malignant tissues has supported Virchow's hypothesis on the connections between inflammation and cancer initially recognized by Rudolf Virchow in the nineteenth century [13]. The studies focusing on these abovementioned connections have clinical implications for cancer prevention and treatment [14].

#### Potential molecular mechanisms caused by COVID-19 may trigger the incidence of lung cancer

The spike protein on capsule surface of 2019-nCoV-2 can bind to angiotensin-converting enzyme 2 (ACE2) on cytomembrane of alveolar epithelial cell II, and thereafter enter the alveolar epithelial cell and replicate substantially, causing excessive inflammatory response and cytokine storm. Normally, ACE2 can degrade AngII in alveolar epithelial cell II into Ang (1-7). AngII can directly bind to NF- $\kappa$ B to promote the expression of inflammatory cytokines, while Ang (1-7) can bind to its specific receptor to up regulate PI3K/Akt and ERK signaling pathway to play an anti-inflammatory effect [15,16]. The pathological

combination of coronavirus and ACE2 results in reduction of free ACE2 and the subsequent accumulation of AngII, which aggravates the inflammatory response and pulmonary fibrosis. Meanwhile, PI3K/Akt and ERK signaling pathways can also be activated and participate in the occurrence and development of tumors, despite of relatively weak anti-inflammatory roles of these carcinogenic pathways [17,18].

COVID-19 can induce hypoxemia and up regulate the expressions of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), vascular cell adhesion molecule-1 (VACM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin and other adhesion molecules. All these adhesion molecules can increase the adhesion between leukocytes and pulmonary vascular endothelial cells, causing the infiltration of inflammatory cells, secretion of numerous inflammatory factors by alveolar macrophages in lung tissues, up regulation of Toll-like receptor 4 (TLR4) by lipopolysaccharide (LPS) signal pathway, and amplification of inflammatory response [19]. Indeed, the expression of HIF-1 $\alpha$  is up-regulated, which may be involved in the genesis, angiogenesis, invasion and metastasis of lung cancer [20].

#### COVID-19 leads to immune deficiency potentially leading to lung cancer

Based on previous studies regarding SARS, lymphocytes was found to be sensitized after SARS-CoV infection, and likely to enter the infected tissues, rather than lymphocyte circulation pool, leading to increasing of lymphocyte apoptosis and decreasing of peripheral blood lymphocytes. As per autopsy of COVID-19, numerous apoptotic cells was found to be increased significantly in the spleen, lung, lymph nodes

and other tissues, e.g., lung cells, lymphocytes and monocytes, resulting in low or suppressed immune system function [21,22]. Theoretically, immune system has the balance of immune monitoring to recognize and eliminate these “non self” cells in case of appearance of tumor cells. Compromised immune system can allow tumor cells escape immune surveillance [23]. For instance, the incidence of cancer in organ transplant patients will raise 2–4 times as compared with general population. In COVID-19 patients, especially those aged and severe cases, the abundance of CD8+ or CD4+ T cells in circulation is lower than healthy controls, however, these T cells are very critical to antigen presentation and anti-tumor immunology. Studies show that a decrease in immune cell count increases the risk of lung cancer and is associated with a later stage of lung cancer at diagnosis [24,25].

Collectively, the morbidity and mortality of lung cancer are increasing. The causes and risk factors of lung cancer are relatively complex. The COVID-19 is an acute respiratory infectious disease caused by novel coronavirus 2019-nCoV-2. Epithelial cells of trachea, bronchi and alveoli can be infected, leading to the formation of hyaline membrane in alveolar cavity, exudation from alveoli, and subsequent pulmonary interstitial fibrosis. The essence of pulmonary fibrosis is the chronic inflammatory changes with a variety of inflammatory factors repeatedly continuously stimulating and attacking the alveolar epithelial cells and causing proliferation, squamous cell epithelial atypical hyperplasia, metaplasia and possible canceration. Meanwhile, 2019-nCoV-2 can activate PI3K/Akt and ERK signaling pathways by combining with ACE2 on cell membrane. PI3K/Akt and ERK signaling pathways can play the double roles as both anti-inflammatory and carcinogenic factors. Moreover, patients with COVID-19 may develop hypoxemia, resulting in the up-regulation of HIF-1  $\alpha$  expression, which may be involved in the occurrence, angiogenesis, invasion and metastasis of lung cancer. In addition, following 2019-nCoV-2 infection, the immune system of the body can be suppressed, and the incidence of tumor is significantly increased. Therefore, as shown in Fig. 1, we speculate that COVID-19 may be a risk factor of secondary lung cancer.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2020.110074>.

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