



Mechanisms in Which Smoking Increases the Risk of COVID-19 Infection: A Narrative Review

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Abstract

At present, COVID-19 continues to spread around the world. People are generally susceptible to SARS-CoV-2. The elderly, serious chronic underlying diseases, high-risk pregnancy, severe obesity and other factors are related to the progression of COVID-19 to severe, critical illness, and even death caused by deterioration of the disease. The relationship between smoking and COVID-19 seems to be controversial. The smoking rate of hospitalized COVID-19 patients is significantly lower than that of the general population. Therefore, smoking can reduce COVID-19 infection and protect the respiratory tract. Subsequently, many scholars have carried out research on this, thinking that this is a wrong and misleading conclusion. According to WHO, smoking is significantly related to the severity of COVID-19, which is one of the important risk factors for the deterioration and poor prognosis of COVID-19. This article reviews the mechanism of smoking increasing the risk of COVID-19 infection.

Keywords: COVID-19; Virus; Smoking

Introduction

COVID-19 is caused by a new type of pathogenic coronavirus—Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It is phylogenetically similar to SARS-CoV, with approximately 80% of the genome consistency (1). SARS-CoV-2 enters the human body mainly through the respiratory system. Clinical symptoms mainly include fever, dry cough, and fatigue. Some patients are accompanied by nasal congestion, runny nose, sore throat, myalgia and diarrhea. The vast majority of cases are mild, but some patients have severe disease outcomes by COVID-19 infection. The pneumonia in these cases progresses rapidly and may evolution into severe or critical forms of COVID-19. They began to show symptoms of respiratory failure requiring ventilator-assisted

ventilation. If the condition continues to deteriorate, the patient may experience shock or even death (2).

Currently, known risk factors related to the progression of COVID-19 to critical illness include: over 65 yr old; frequent hospitalizations; chronic obstructive pulmonary disease; moderate to severe asthma; severe or decompensated cardiac insufficiency; severe hypertension; using immunosuppressive drugs; uremia; high-risk pregnancy; severe obesity (BMI > 40); chronic liver disease, etc. (3). In addition, COVID-19 may also cause vascular endothelial dysfunction, leading to severe coagulation abnormalities and thrombosis (4).



However, until now, in the global guidelines for control of COVID-19, smoking has not been listed as one of the important risk factors. Since the outbreak of COVID-19, the relationship between smoking and COVID-19 seems to be very controversial. The cause of the controversy is that there are clinical data from multiple studies suggesting that the proportion of smokers among hospitalized COVID-19 patients is significantly lower than that of the general population. From the initial data from China (5,6), to later data from many countries including Italy, Spain, and the United States, all indicate that the smoking rate of COVID-19 hospitalized patients is significantly lower than that of the general population (7-9). Smoking can reduce the risk of contracting COVID-19 and has a protective effect on the respiratory tract. In a meta-analysis of 5 clinical data from China, the combined odds ratio (OR) of COVID-19 progression between smokers and non-smokers was 1.69 (95% confidence interval, CI, 0.41-6.92) (10). Based on this, "Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19)". In addition, the authors hold that smoking is a double-edged sword for COVID-19, while smokers are susceptible to COVID-19, smoking may also have a protective effect on the respiratory tract (11).

This study has been widely disseminated in scientific literature, the lay press and various online social networks, especially cited, posted or tweeted by researchers or subjects funded by the tobacco industry. This conclusion may make the public mistakenly believe that smoking can prevent COVID-19, and may mislead researchers and lead to research bias. Because in the two subsequent meta-analysis on the impact of smoking on COVID-19, researchers have cited these conclusions as the basis for the negative (12, 13). Nicotine may be used as a new therapy for COVID-19 and began to study its mechanism of protect the respiratory tract from infection (7).

Smoking is the main risk factor for respiratory infection and disease progression. Smokers are more susceptible to influenza than non-smokers

are, especially severe influenza are. The rate of influenza/bacterial pneumonia and tuberculosis in smokers has doubled compared with non-smokers (14). According to research reports on Middle East Respiratory Syndrome Coronavirus (MERS), smoking is an important risk factor for MERS-CoV infection and is associated with the high mortality rate of MERS (15). Therefore, long-term smoking destroys the defense mechanism of the respiratory system and easily leads to respiratory infections, which is the consensus of everyone. COVID-19 is now the only respiratory tract infectious disease that is not affected by smoking. This phenomenon is difficult to explain, because COVID-19 does show obvious invasiveness to the respiratory tract.

Firstly, how to explain that the rate of smoking among hospitalized COVID-19 patients is significantly lower than that of the general population. A meta-analysis of 28 published studies by researchers (16) found that 25 of them did not record the smoking history of patients. Therefore, it is questionable whether the non-smokers in the study have never smoked. Secondly, in some surveys, smoking status was divided into "smokers", "ex-smokers" and "non-smokers and those with missing information on smoking". It is misleading to classify "non-smokers" and "smokers with missing information" into the same category, which will lead the author to wrong conclusions. In addition, these 28 studies are all retrospective analysis. The clinical data used in these studies were obtained in an epidemiological context. Most of the data did not highlight smoking history. Therefore, the consistency and accuracy of the smoker status in most research records cannot be guaranteed. Due to the emergency of COVID-19, the smoking status of patients may not be accurately recorded. For example, some patients may already be in a critical state when they are hospitalized and cannot report their smoking status (17), this may lead to an underestimation of the number of smokers. Besides, smokers with severe COVID-19 symptoms may have quit smoking before being hospitalized and therefore are not recorded as smokers. However, the WHO defi-

inition of "ex-smoker" means quitting smoking for at least 6 months. Therefore, incomplete or incorrect information on the smoking history of hospitalized patients with COVID-19 may be the main reason for the low rate of smokers among hospitalized patients in some researches. Many researchers have questioned Lippi's research conclusions. Guo FR (17) pointed out that four of the five clinical data used by Lippi et al. had defects in data collection, and the number of cases was wrong, which directly led to incorrect meta-analysis results. The statistical method used by Lippi et al. is wrong, and it is inappropriate to use the null hypothesis significance test method to conclude that there is no correlation (18). Moreover, Lippi et al. made a common statistical error in their conclusions. That there is no statistically significant correlation between smoking and the severity of COVID-19 does not mean that smoking is clinically

unrelated to the severity of COVID-19 (19). Therefore, the incorrect meta-analysis made by Lippi and Henry (10) led to misleading conclusions (20). This is the only research report, which concluded that there is no relationship between smoking and the severity of COVID-19. Since then, at least 17 meta-analyses have been made for further research (12), providing clear evidence of the direct relationship between smoking and the severity and progression of COVID-19. Compared with non-smokers, smokers infected with COVID-19 are 3.25 times more likely to develop severe and critical illness (12). Smoking is clearly related to the severity of COVID-19, and is one of the important risk factors for the worsening of COVID-19 and poor prognosis. The mechanisms by which smokers are susceptible to COVID-19 and the disease tends to deteriorate include the following aspects (Fig.1).

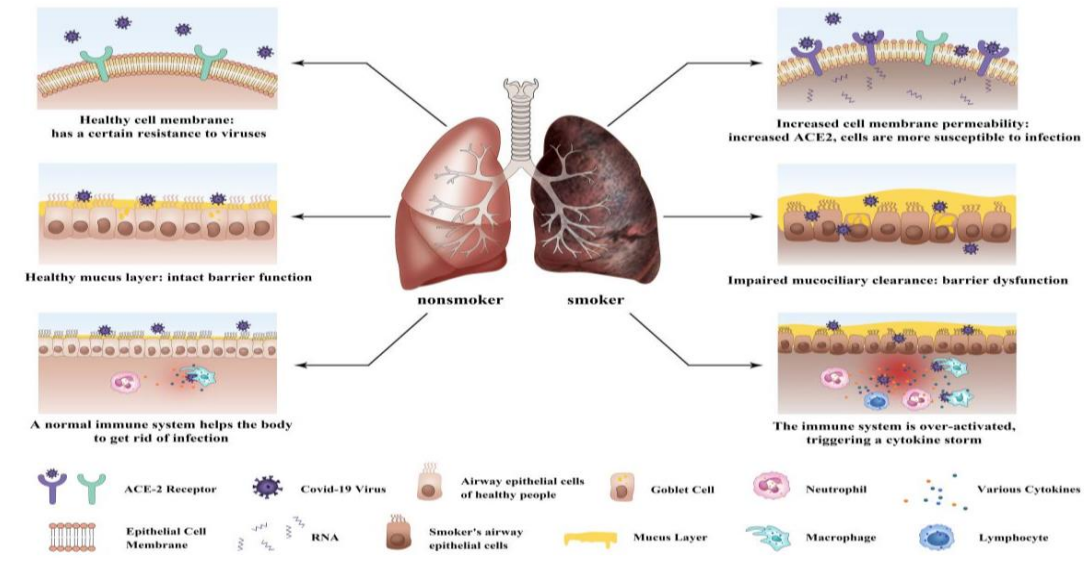


Fig. 1: Factors responsible for higher susceptibility of smokers against COVID-19 (Original)

In normal individuals, the first line of defense against exogenous pathogens is the mucociliary epithelium and mucous layers (in this review, COVID-19). When smoking, the clearance of this barrier is dysfunctional, which makes them more susceptible to infection. ACE2 receptors (binding sites for COVID-19) allow pathogens to enter host cells and protects the virus from host surveillance, highly expressed on the surface of smokers. In normal individuals, the virus infection could be detected in the following ways: (a) cytokines released from the type II pneumocytes, goblet cells, nasal epithelial / ciliated and oral mucosal cells, and (b) immune cells (macrophages, neutrophils and lymphocytes) infiltrating the infection site in order to curb further transmission. Smoking can make it easier to enter the host cells by weakening the immune system, and the virus multiplies rapidly followed by a hyperinflammatory response triggered by "cytokine storm" in the host body, resulting in damage to lung tissue eventually

1. Smoking increases the chance of viruses entering the body

When a smoker is smoking, his hands repeatedly touch his face, which increases the number of hand-to-mouth contacts and increases the chance of virus invading the human body. When smoking or exercising, the breathing rate and respiratory flow increases significantly. This leads to a change in the breathing state from the nose to the mouth, the mucosa of the respiratory tract gradually cools and dries, the movement of ciliated cells decreases, and the viscosity of the mucosa increases, resulting in a decrease in the filtering function of the upper respiratory tract for microorganisms. Viruses are more likely to bypass the natural defense barriers of the oral cavity and upper respiratory tract and penetrate into the lower respiratory tract and alveoli (21).

2. Smoking affects the mucosal epithelial barrier of the lung, leading to an increase in the permeability of epithelial cells

The changes in lung structure caused by smoking include increased mucosal permeability, widening of mucociliary spaces, peribronchial inflammation and fibrosis (airway remodeling). These pathological changes significantly reduce the resistance of smokers to virus invasion. Smoking can cause serious effects on the respiratory tract of smokers, such as causing oxidative stress and inflammation in the lungs, leading to dysfunction of the epithelial barrier and significantly increasing the permeability of epithelial cells. ROS produced by oxidative stress can directly affect the ACE2/angiotensin/adrenaline axis, increase the sensitivity of the respiratory tract to viral/bacterial infections, and make smokers more susceptible to bacterial/viral infections (22).

3. The role of epithelial cells and inflammation: ACE2 and TMPSSR2

SARS-CoV 2 belongs to the coronavirus family. It is named for its appearance similar to a crown. This appearance is due to two functional domains - S1 and S2 glycosylation of the spike protein on the cell surface. ACE 2 has been

proved the receptor for SARS-Cov-2 virus to enter the host cell (23). The S2 domain of the viral spike envelope has a high affinity for the ACE 2 receptor of the lung epithelium. It has been found that smokers and patients taking ACE antagonists (high blood pressure and diabetes) have higher expression of ACE 2 and are therefore more susceptible to COVID-19 (24). In addition, ACE 2 may be highly expressed in germ cells, that is, males express more than females. Males have more circulating ACE 2 than females, which may provide evidence for gender differences in the severity of COVID-19. ACE 2 receptors are widely distributed in lung epithelial cells, especially type II lung epithelial cells, goblet cells, nasal epithelial/ciliary cells, and oral mucosal cells (25). The SARS-CoV-2 response stimulated by interferon enters the cell through ACE2 and TMPSSR 2 proteases (26). ACE 2 expression is up-regulated in the small airway epithelium of smokers and patients with smoking-related diseases such as COPD and IPF (26, 27), so smokers are more likely to be infected with COVID-19. Although the virus enters the host cell mainly through ACE 2, the virus particles need the activation of cell protease to promote the phagocytosis of the virus. TMPRSS 2 protease, which is highly expressed in nasal ciliated cells and goblet cells, plays an important role in SARS-CoV-2 invading host cells. ACE2 uses cellular serine protease TMPRSS2 to act on S protein to invade host cells (26). In addition, through single-cell RNA sequencing analysis of multiple tissues, it was found that only a small part of ACE2+ cells expresses TMPRSS2, which indicates that there may be other proteases that play similar roles. Cathepsin B/L plays an equally important role when viruses invade cells (25). Smoking can increase the expression of cathepsin B, which may be one of the reasons why smokers are susceptible to COVID-19 (27). Another cell protease is Furin, which can cleave the S1/S2 site of the SARS-CoV-2 spike protein, which is essential for the spread of the virus between cells. There is evidence that the lack of Furin increases the possibility of mice being infected with the virus (influenza A) (28). Serpin

protease inhibitor (Serpin) can regulate and control the activity of Furin protease. The activity of Serpin in smokers is reduced, which affects the activity of Furin, so smokers are more susceptible to COVID-19 (29).

4. Smoking suppresses the body's immune system

The effects of smoking on the immune system include the following aspects: Firstly, smoking can reduce the number of CD4 + T cells (helper T cells), which can promote B cells to produce antibodies and activate killer T cells to attack pathogens. Secondly, nicotine, the main ingredient in tobacco products, can promote the secretion of catecholamines and corticosteroids, which will reduce the function of the immune system and inhibit the body's ability to resist bacterial/viral infections. Thirdly, studies have shown that nicotine can inhibit the production of interleukin-22, which helps to inhibit lung inflammation and repair damaged cells (30).

5. Smoking and "cytokine storm"

Acute respiratory distress syndrome (ARDS) is one of the most common serious complications of SARS-CoV-2 infection. It is the result of a "cytokine storm" caused by the release of pro-inflammatory cytokines/chemokines from immune cells. The pro-inflammatory mediators released by immune cells include IP-10, MCP-3, HGF, MIG, MIP-1 α , IL-6, TNF- α , IFN- γ , IL-2, IL-7 and GM-CSF, etc. (31). In long-term smokers, the expression of IL-6, TNF- α and other pro-inflammatory factors are increased, and the expression of two main effector proteins of natural killer (NK) cells and CD8 T lymphocytes: perforin and granzyme B are reduced. In addition, autopsy reports of COVID-19 patients showed that pulmonary capillaries were infiltrated with neutrophils, accompanied by fibrin deposition, and neutrophils had extravasated into the alveolar cavity (32). This indicates that the formation of neutrophil extracellular bactericidal networks (NETs) may be the cause of organ damage and lung structural remodeling in COVID-19 patients. Studies have

shown that smoking can affect the transport of neutrophils, the formation of NETs, inhibit body fluids and cell-mediated immune responses, and make the disease more likely to progress to ARDS, leading to worsening of the disease (32).

Conclusion

Smoking increases the possibility of COVID-19 infection and causes the disease to progress and worsen more easily. Nicotine seems to have the pharmacological effect of inhibiting the growth of SARS-CoV-2. However, common basic diseases that are susceptible to COVID-19, including hypertension, cardiovascular disease, diabetes, COPD, tumors, and chronic kidney disease, are all tobacco-related diseases. Therefore, smoking to prevent COVID-19 is tantamount to "drinking poison to quench thirst." At present, COVID-19 is still spreading all over the world. How to effectively prevent and control it is an urgent problem. Smoking is probably the most important and avoidable risk factor. Apart from preventing tobacco-related diseases, smoking cessation can also reduce the chance of SARS-CoV-2 infection.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that there is no conflict of interest.

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