Relationship Between Smoking and Viral Pneumonia: A Narrative Review

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Abstract
Viral pneumonia affects about 200 million people each year. Viral pneumonias have a seasonal pattern and are more common among children and the elderly. The most common virus in children is respiratory syncytial virus (RSV) and it is the influenza virus in adults. The world has been fighting the COVID-19 pandemic since December 2019. Among all the epidemiological risk factors, the role of smoking as a risk factor for pneumonia is controversial. Cigarette smoke contains about 5000 chemicals that weaken the defense mechanisms of the respiratory system and increase the risk of various respiratory infections. The present review study was carried out on 105 articles that were obtained from searches in Scopus, PubMed, and Google Scholar search engines using the keywords viral pneumonia, COVID-19, influenza, cigarette, smoking, respiratory syncytial virus, and SARS-CoV-2. A total of 55 articles that focused on the effect of smoking on the incidence and mortality of pneumonia due to RSV, influenza, and coronavirus were selected. Exposure to secondhand smoke makes children more susceptible to RSV infection. Smokers are also more likely to become infected and die from the flu. The effect of smoking on the risk of COVID-19 is controversial. In this regard, the results of a number of studies show that smokers are at a greater risk of developing COVID-19 infection and death. However, there are other studies suggesting that smoking has no effect on COVID-19 infection and that smoking reduces the risk of developing COVID-19.

Keywords: Viral pneumonia, COVID-19, Influenza, Cigarette, Smoking, Respiratory syncytial virus, SARS-CoV-2

Introduction
The World Health Organization (WHO) estimates that there are 450 million cases of pneumonia each year, about 200 million of which are caused by viruses, and approximately 4 million people die from the disease. A total of 1.6 million children under the age of 5 died of pneumonia in 2008. In developing countries, the incidence rate can be five times higher compared to developed countries. A total of 156 million pneumonia cases among children are registered annually, of which 151 million are registered in developing countries (1–4). Additionally, 5 million cases of community-acquired pneumonia are reported in children living in developed countries, but mortality has dropped dramatically and is now very rare (5). The highest prevalence of viral pneumonia is found in children under 5 years of age and in adults over 75 years of age (6).

Molecular diagnostic tests have greatly enhanced our understanding of the role of viruses in pneumonia, and the findings suggest that the incidence of viral pneumonia is underestimated. In developed and developing countries, the most common viral agents detected in children include respiratory syncytial virus (RSV), rhinovirus, human metapneumovirus, human bocavirus, and parainfluenza viruses. Moreover, dual infections are common, and one-third of children have symptoms of a viral-bacterial co-infection. In adults, viruses, especially influenza viruses, rhinoviruses, and coronaviruses, make up about one-third of all cases of pneumonia. Bacteria continue to play a major role in adults with pneumonia. The presence of viral epidemics in the community, patient's age, disease onset, symptoms, biomarkers, radiographic changes, and response to treatment can help differentiate viral pneumonia from bacterial pneumonia (3).

Among all the epidemiological risk factors, the role of smoking as a risk factor for pneumonia is controversial (7). Cigarette smoke contains chemicals and high concentrations of free radicals and other oxidants such as retinoic acid, which can increase the risk and severity of viral and bacterial infections (8-12).

Cigarette smoke can directly damage the airway epithelial barrier, including ciliated cells, basal cells,
and submucosal secretory glands. Duffney et al found that exposure to secondhand smoke disrupted antiviral responses in lung epithelial cells by reducing phosphorylation of antiviral transcription factor. Besides, cigarette smoke can inhibit the expression and secretion of effector cytokines in peripheral blood mononuclear cells, thereby reducing the immune response (12,13).

The number of smokers in the world is reported to be 1.1 billion in 2019, and according to statistics from the WHO, more than 8 million people die each year due to smoking (12,14). Evidence shows that smokers are 7 times more exposed to the virus than non-smokers, and the death rate from pneumonia in smokers is significantly higher (8,15).

In the United States alone, the economic burden of community-acquired pneumonia (CAP) is estimated at > $17 billion annually (16).

Based on the relevant literature, although numerous articles have been written, such as many of the articles cited in the references, there has been no comprehensive article on the effects of smoking on viral pneumonia. The aim of the present study was to investigate the association between smoking and pneumonia caused by influenza virus, coronavirus, and RSV.

Methods
In this review article, using keywords including viral pneumonia, COVID-19, influenza, cigarette, smoking, respiratory syncytial virus, and SARS-CoV-2 in the title and abstract, articles were collected from Scopus, PubMed, and Google Scholar search engines. Articles were searched without time limit. Inclusion criteria included being written in English and having full text availability. Conference articles were excluded. After reviewing the titles and abstracts of 105 articles, 55 relevant articles were selected.

The Effect of Smoking on the Respiratory System
Cigarette smoke contains 5000 different chemicals that can impair the body's ability to produce and transport oxygen by affecting peripheral arteries, causing them to contract, and producing carbon monoxide. Cigarette nicotine also has adrenergic effects that can affect this mechanism (11,17).

Cigarette smoke can cause irritation, inflammation, and changes in the function of the respiratory system and lungs, such as increased mucus excretion, airway closure, tissue hypoxia, and fatigue (17,18), as well as upregulation of inflammatory cytokines, burning of the eyes, nose, and throat, increased breathing rate, and increased heart rate (18).

Results of a study on the effect of passive inhalation of cigarette smoke on piglets showed that inhalation of cigarette smoke increased mast cell degranulation. It also causes oxidative stress by significantly increasing the level of reduced glutathione (18).

Viral Pneumonia

Prevalence and Epidemiology
Annually, 200 million people become infected with viral pneumonia, half of whom are children (3). Viral pneumonia has a seasonal pattern. Influenza peaks occur in late fall and early winter, while RSV causes epidemics in the fall each year or every other year (19). However, bacterial pneumonia has the same incidence rate throughout the year (20). Viral pneumonia is more common in children under 5 years of age and older adults. Among viruses, the most common cause of childhood pneumonia is RSV (3,21). The incidence of childhood viral pneumonia decreases with age so that the highest incidence rate is found among children aged under 2 years of age. The small share of viral pneumonia cases and deaths in developed countries is because of the high level of health and medical care as compared to developing countries (21). The most common cause of viral pneumonia in adults is influenza virus, and RSVs, parainfluenza virus, and adenoviruses are the most commonly detected respiratory viruses. Viral pneumonia is now doubly important following the reduction in the incidence of pneumococcal pneumonia because of pneumococcal vaccination among older adults, the high ability of polymerase chain reaction (PCR) to detect viral pathogens that were undetectable by previous methods, the population aging, and greater susceptibility of this age group to viral pneumonia (22).

Pathophysiology of Viral Pneumonia
Viral agents cause edema of the alveoli by provoking inflammation in the lung parenchyma, which in turn disrupts gas exchange on the alveolar surface. If the inflammation is not controlled, the patient dies. Underlying heart disease, chronic obstructive pulmonary disease (COPD), and pregnancy predispose the person to viral pneumonia. Viral pneumonia predisposes the patient to a secondary bacterial infection by invading the mucosa. Influenza virus and RSV enter the respiratory tract through the inhalation of aerosolized droplets from the cough or sneeze of infected individuals and penetrate to the bronchioles and alveoli (23).

The most common clinical symptoms of viral pneumonia include rhinitis and wheezing (3). In viral pneumonia, the number of coughs and the incidence of pleuritic chest pain were relatively lower than in bacterial pneumonia (24). However, bacterial pneumonia is characterized by fever above 38.5°C, respiratory rate above 50 beats per minute, and chest recession (25). Leukocytosis is not observed in viral pneumonia and C-reactive protein (CRP) level is not high upon admission, while we see leukocytosis as well as an acute increase in CRP level in bacterial pneumonia (20). However, serum procalcitonin is a highly sensitive
biomarker for differentiating between viral and bacterial pneumonia, which increases in bacterial pneumonia and largely prevents the overuse of antibiotics (26). The secretion of Tumor necrosis factor alpha (TNF-α) is suppressed in viral pneumonia, due to the secretion of interferon gamma (IFN-γ) from macrophages, and therefore, unlike bacterial pneumonia, there is no increase in procalcitonin level in viral pneumonia (27). In radiographic images, bilateral interstitial infiltration is associated with viral pneumonia and focal alveolar infiltration is associated with bacterial pneumonia (28).

**Respiratory Syncytial Virus and Cigarettes**

According to the PERCH study, viruses, especially RSV, are among the main causes of pneumonia in hospitalized children with positive chest radiology (29). Global data show that approximately 36 000 deaths from RSV pneumonia occur in children under 5 years of age (30).

Risk factors for severe pneumonia include very young age, immunodeficiency, malnutrition, chronic underlying diseases, HIV infection, HIV exposure in infants, young maternal age, low maternal education, poor economic and social status, the home environment, and the smoking status of each family member. Exposure to environmental tobacco smoke increases the risk of developing RSV infection among children. Since smoking is very common in society today, the association between infectious diseases of children such as pneumonia and smoking is very important (31,32).

Smoking is a well-known and important risk factor for CAP through changes in mechanisms of the host defense system. The increased risk of CAP was found to be associated with smoking status, the number of cigarettes smoked per day, and lifetime smoking. There is strong evidence that smokers are more likely to have respiratory infections than non-smokers and that there is a link between pneumonia and smoking habits (30).

Among people with early-life lower respiratory illness caused by respiratory syncytial virus (RSV-LRI), active smokers were 1.7 times more likely to have pneumonia; therefore, there is a significant relationship between the risk of LRI caused by RSV and active smoking (33).

**Oswald** et al reported for the first time that adults with a history of childhood respiratory infections were more likely to develop chronic respiratory illnesses. Subsequently, Burrows et al found that adults with a history of childhood respiratory problems were more likely to be affected by smoking-related side effects (34,35).

Subsequent studies conducted in Derbyshire, England, showed that 70-year-old people with a history of pneumonia had an increase in respiratory symptoms and evidence of respiratory distress (36). These results hypothesize that infection during rapid physical growth can impair the normal growth of the airways and that childhood respiratory diseases may be among the factors that determine vulnerability to smoking. The most common cause of severe lower respiratory tract infection during early life is RSV (33-37).

Early-life RSV infection may play a direct role in predisposing the host to pneumonia, lung dysfunction, and airway hyperreactivity by altering immune responses or causing airway damage. Findings have shown that RSV prevention can be effective in reducing subsequent RSV-related complications in high-risk infants (33).

Pre-existing airway hyperreactivity may be a common predisposition to both viral LRIs and asthma. The interaction between airway hyperresponsiveness and smoking has been shown to improve airway obstruction in people with COPD. Therefore, it can be hypothesized that airway response may be responsible for the association between RSV, smoking, and pneumonia (33).

**Influenza Virus and Smoking**

Influenza virus is a single-stranded negative-sense RNA virus of the orthomyxovirus family (38,39). This virus causes infection of the upper and lower respiratory tract (8,39). The severe form of the disease affects 3 to 5 million people annually and causes the death of about 290 000 to 650 000 people (40).

Influenza virus can cause many complications such as pneumonia, acute respiratory distress syndrome, myocarditis, and encephalitis. Influenza pneumonia is a rare complication that can be caused by primary viral pneumonia, a secondary bacterial infection, or a mixed viral/bacterial infection, which is one of the most common causes of death in these patients (39,41).

The severity of the disease in each individual depends on the interplay between the innate immune response of the host and the viral virulence (39). Evidence shows that smokers are seven times more likely to be exposed to the flu virus and that smokers are significantly more likely to die from the flu virus (8,15).

Smoking has a negative effect on the flu virus. The results of a study on mice exposed to cigarette smoke showed that the flu infection could increase the development of a fibroblastic response in the lungs (41). Results of a study on infants showed that the rates of parental smoking were significantly higher among infants with influenza and other viral infections than among healthy group, and cigarette smoke can be a significant risk factor for viral infections such as the flu (42).

The results of a study showed that mice with the flu infection that were exposed to secondhand smoke were more likely to develop inflammation of the airways and alveoli than mice that did not inhale secondhand smoke (43).

RIG-I (retinoic acid-inducible gene 1) plays an important role in the diagnosis of and response to RNA viruses such as influenza virus. The innate immune and...
antiviral responses are suppressed in people exposed to secondhand smoke by oxidative inhibition of RIG-I (8,39). Results of a study showed that overexpression of RIG-I restored the anti-inflammatory and anti-viral response in mice with the flu that were exposed to secondhand smoke (39).

Exposure to secondhand smoke (directly and indirectly) inhibits the production of proinflammatory cytokines (such as interleukin-6, interleukin-8, interleukin-18) as well as viral cytokines (such as interferon-gamma and IP-10) (12,39).

Cigarette smoke also interferes with the production and activation of the TGF-β, an anti-inflammatory cytokine, in influenza patients (41). Influenza virus leads to the production of cytokines and overexpression of proteases in the lung (43). Elevated protease activity is observed in smokers and those with influenza infection (38).

Mucosal immunoglobulins A (IgA) responses are critical for protecting the lungs against infectious agents. Results of a study on mice showed that cigarette smoke inhibited lung mucosal IgA responses against influenza virus (9).

Nicotine is one of the main components of cigarettes that binds to nicotinic acetylcholine to activate cholinergic anti-inflammatory drugs and suppress the immune system (11).

SARS-CoV-2 and Smoking
SARS-CoV-2 is an mRNA virus that binds to angiotensin-converting enzyme 2 (ACE2) via spike proteins and enters its host cell (44). The SARS-CoV-2 epidemic emerged in China in December 2019 and soon became a pandemic (45). The viruses of this family caused severe respiratory diseases in China under the name of SARS-CoV in 2002-2003 and under the name of MERS-CoV in Saudi Arabia in 2012 (46,47). SARS-CoV-2 spreads through human-to-human contact (48) and the disease begins with flu-like symptoms and, if progressing, leads to fluid accumulation in the alveoli and acute respiratory distress syndrome symptoms such as shortness of breath and hypoxemia (49). Underlying diseases were reported to play a role in increasing COVID-19-related admission rates and mortality. The most common comorbidities associated with poorer prognosis included COPD, diabetes, hypertension, and malignancy (50). Among all the epidemiological risk factors for COVID-19, the role of smoking is controversial (7). The results of the largest systematic review on the effect of smoking on the severity and mortality of COVID-19 show that there were higher percentages of smokers and former smokers among patients who were admitted to an ICU, needed a ventilator to breathe, or died. The risk of developing severe COVID-19 form in these people is 1.4 times higher and the risk of ICU admission is 2.4 times higher compared to non-smokers (51). In a study, Guo reported that the odds ratio of the disease was 4.30 and 1.98 in COPD patients and smokers, respectively, which confirms the effect of smoking as an important risk factor for COVID-19 (52). Results of another meta-analysis show that ACE2 expression is higher in smokers and COPD patients, which indicates that smokers have a higher risk of developing COVID-19 (53). In a review of seven cohort studies from settings outside of China, Rodgers et al also show that smoking increases the risk of developing COVID-19 and the disease severity (54), but there are studies that deny any association between smoking and the risk of COVID-19. Results of a meta-analysis show no significant relationship between smoking and the progression of COVID-19 (55,56). However, there is a hypothesis that justifies the lack of association between smoking and the risk of developing COVID-19 in some studies. Older adults account for the majority of people who are hospitalized or die from COVID-19 (> 65 years). In this age range, the prevalence of smoking is extremely low compared to the general population, hence, the number of smokers is not high among ICU patients (7). However, there may be another reason beyond the results of studies that do not suggest an association between smoking and COVID-19 infection. Surprisingly, Tomchaney et al showed that ACE2 expression was lower in the alveolar and bronchiolar epithelium of people with COPD as compared to healthy smokers and non-smokers. In addition, smoking has been shown to reduce virus replication in the epithelium in vitro (57). According to the results of another study conducted using the data from the UK Biobank, smokers are less likely to develop COVID-19, but if they do, they develop a more severe form and are at greater risk of hospital admission (58). In the meantime, there is a need for a large-scale study to investigate the effect of smoking on COVID-19 patients in order to address confounders such as hypertension, obesity, race, gender, and COPD that may adversely affect the COVID-19 prognosis (59).

Conclusion
According to the different results obtained from the previous studies, exposure to secondhand smoke, which contains a variety of chemicals, affects the respiratory system, increasing the risk of severe viral pneumonia, especially in children, and is known as a risk factor for influenza and RSV infections. However, some studies do not consider smoking as a risk factor for COVID-19 and there are various debates in this area that require a large-scale study and a detailed investigation of the mechanisms. Additionally, there are very few studies on the effects of smoking on the flu among humans and further relevant studies are needed to confirm the present results.

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