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The Paradoxical Relationship Between Nicotine and SARS-CoV-2 Infection: A Systematic Review

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Abstract

Across the board, smoking is considered to be negative toward our health. While this information has been known for a relatively long time, the COVID-19 pandemic has stirred up a controversial idea: that smokers are protected from severe COVID-19 relative to non-smokers. This suggests that smoking is a helpful agent in the evolving fight against SARS-CoV-2, and impressionable individuals are at risk of starting to smoke as a means of protecting themselves from the virus. To address the validity of this claim, a systematic review was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed was searched for relevant articles and the results were screened according to inclusion criteria. Our search yielded a total of 81 results and after removal of duplicates, non-English papers, and a quality appraisal a total of 16 papers were included in this review. We found that while smokers were more likely present with a less severe disease due to downregulation of severe cytokine storm, they were overall more likely to contract COVID-19 due to upregulation of ACE-2 receptors which SARS-CoV-2 uses to enter the cells of the respiratory epithelium. Also, long time smokers who develop COPD are more likely to have fatal outcomes from COVID-19 infection. Further, these results were due to the effects of nicotine and not cigarettes themselves. Since cigarettes contain numerous carcinogens, they are not recommended as a prophylaxis for COVID-19. However, we recommend that nicotine should be a topic for further research as potential therapy.

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INTRODUCTION

COVID-19 is a disease that is extremely contagious. While it usually causes a mild respiratory infection, severe pneumonia is possible, which is exacerbated by the intense release of cytokines, which can lead to multiple organ failure and, eventually, death [1]. SARS-CoV-2 is a single-stranded RNA virus related to viruses that cause Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [2].

Although SARS-CoV-2 has a much lower mortality rate (3.8%) when compared to SARS (10%) or MERS (37.1%), the infection rate is ten times higher. It can spread from asymptomatic people through inhaled respiratory droplets [3].

SARS-CoV-2 then enters the body via the angiotensin-converting enzyme 2 (ACE2) receptors found on lung alveolar epithelial cells [4].

People who are older or have comorbidities may be

more likely to develop serious infection complications [3]. Cigarette smoking is a significant risk factor. Because smoking has such a negative impact on lung health, it's no surprise that it's associated with more severe disease and a poor prognosis [5]. In contrast, smoking rates among hospitalized patients are significantly lower [6].

When it comes to the impact of current smokers and COVID-19 hospitalization, some studies have found conflicting results. A meta-analysis of 6515 patients discovered that, while current smokers were more likely to have a negative outcome than non-smokers, current smokers were less likely to have a negative outcome than past smokers [7].

Given that smoking is associated with a number of negative health outcomes, including the destruction of lung parenchyma [8], the goal of this study is to look into the seemingly contradictory relationship between smoking and COVID-19 outcomes.

Review

A review of the literature was done in the PubMed database for articles from 2016 to 2021 with the keywords (Covid* OR coronavirus OR "SARS Cov-2") AND (smok* OR tobacco) on June 18, 2021. Non-English articles not relevant to COVID-19 or to smokers were not included as they were not relevant to the study objectives. Studies that explored the effects of smoking on COVID-19 infection and disease progression are included in [Figure 1] [9].

RESULTS

Our search yielded 81 results, of which 16 articles were included for the effects of smoking on COVID-19 infection [Table 1]. In these papers, a total of 246,392 patients were studied. Smoking was found to be correlated with more severe disease compared to never smokers).

However, when comparing current smokers to past smokers, there was decreased prevalence of current smokers in the ICU as well as a decreased mortality in this population).

Effects of Smoking on the Body

Smoking doubles the risk of most cardiovascular diseases (CVDs), including myocardial infarction and heart failure [10]. According to a retrospective study [11], smoking increased the risk of death in males aged 15 to 74 by 1.5 times. The number of cigarettes smoked can also influence disease rates.

According to a systematic review of the relationship between the number of cigarettes smoked and lung cancer, the relative risk of lung cancer increased from 2.89 percent to 6.42 percent as the number of cigarettes smoked per day increased from about 5 per day to about 45 per day [12]. There is an unmistakable link between smoking and cardiovascular disease. With a pooled odds ratio of 1.61, current smokers had a higher risk of stroke than nonsmokers [13].

In the same study, a dose-dependent relationship was also discovered. The relative risk of stroke increases by 12% for every additional 5 cigarettes smoked per day.

Other than the cardiovascular system, smoking has been shown to have a negative impact on many other systems. According to a systematic review of the occurrence of rheumatoid arthritis [14], smokers had significantly higher values on the Disease Activity Score and a simple erosion narrowing score than nonsmokers. Other effects, such as bone density, can be seen in male smokers.

Current smokers had significantly higher hip fracture rates when compared to never smokers and nonsmokers [15]. An increase in current smokers has also been linked to post-surgical complications. Smoking is a significant risk factor for complications in patients who had shoulder arthroscopy with subacromial decompression [16].

Effects of Quitting Smoking on the Body

Quitting smoking has been shown to have significant and immediate health benefits, as well as lower mortality rates. Former heavy smokers who had quit smoking for five years had significantly lower CVD rates than current heavy smokers [17].

According to the same study, former heavy smokers had essentially the same risk of developing CVD as never smokers after 16 years of smoking abstinence. Some of the health benefits of quitting smoking can be felt even after being diagnosed with cancer. Patients who quit smoking after receiving a positive cancer diagnosis reduced their risk of death by 30% to 40% [18]. Not only does quitting smoking improve one's health, but it also improves one's overall quality of life. When compared to smokers, quitting smoking resulted in higher total and physical quality of life scores [19].

Mechanism of SARS-CoV-2 Infection and COVID-19 Effects on the Body

While it is well known that cigarette smoke is a carcinogen and that smoking causes a wide range of cancers and diseases, the relationship between COVID-19 and smoking is more complicated. Former smokers are more likely to develop COVID-19 extreme cases and complications requiring critical care.

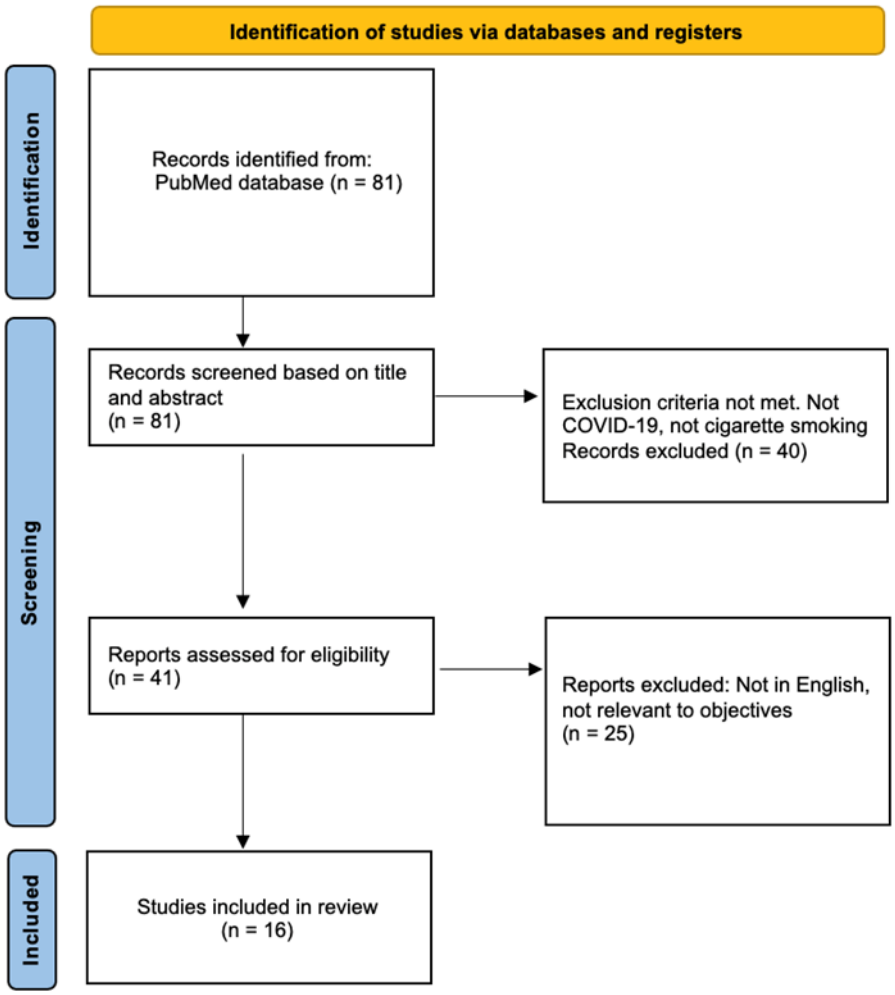

Figure 1: PRISMA flowchart of the literature screening for the prevalence of smoking among COVID patients. Literature screening has been done as described in the PRISMA statement

Only 24% of current smokers experienced severe complications, compared to 48% of ex-smokers. This could be due to the increased exposure time of former smokers as well as the prevalence of highly morbid conditions such as COPD in this group [8].

Furthermore, former smokers may experience an elevated inflammatory response as well as an active immune system for some time after quitting smoking.

During this time, they are more vulnerable to respiratory infections like COVID-19 and have a higher risk of contracting infections like community-acquired pneumonia [20].

The virus's entry into the body is the first step in COVID-19 infection. The most common method of transmission is inhalation of small particle droplets from an infected person. Once in the respiratory tract, SARS-CoV-2 enters the cell via the ACE-2 receptor and begins its infection [8].

SARS-CoV-2 primarily targets ACE-2 receptors on airway epithelial cells and type II alveolar cells, but it can also be found in extrapulmonary locations such as the gastrointestinal tract, heart, endothelial cells, testes, and kidney [21].

SARS-viral CoV-2's envelope binds to the host cell and is internalized via clathrin-mediated endocytosis [22].

Nicotine increases the ACE/angiotensin II/angiotensin II receptor pathway while decreasing the protective ACE2/Angiotensin 1-7/Mas receptor pathway [23].

While nicotine is the primary active ingredient in cigarettes, they also contain over 5000 other chemicals, including polycyclic hydrocarbons, carbon monoxide, and other toxins.

These components interfere with normal function, resulting in conditions like COPD, and they may be involved in severe COVID-19 cases [22].

Table 1: Studies on COVID-19 infection in the smoking population

S. No.	Author	Country	Study Population	Findings	Conclusion
1.	[24]	China	12 studies, 2,445 patients	Severe (ICU) disease was associated with a smoking history (P = .003) and comorbidities including chronic obstructive pulmonary disease (OR = 5.08, P < .001)	A history of smoking could be a high-risk factor for serious illness.
2.	[25]	China	13 studies, 3,027 patients	Male, older than 65, and smoking were risk factors for disease progression in patients with COVID-19. P < 0.00001; current smoking: OR =2.51, 95% CI(1.39, 3.32), P = 0.0006	Male smokers over the age of 65 may have a higher risk of developing a critical or fatal condition.
3.	[26]	USA	19 studies, 11,590 patients	The meta-analysis showed a significant association between smoking and progression of COVID-19 (OR 1.91, 95% confidence interval [CI] 1.42-2.59, p = 0.001).	COVID-19 progression is more likely in smokers than in nonsmokers.
4.	[27]	China	11 case series, 2,002 cases	The pooled OR of COPD and the development of severe COVID-19 was 4.38 (fixed-effects model; 95% CI: 2.34-8.20), while the OR of ongoing smoking was 1.98 (fixed-effects model; 95% CI: 1.29-3.05)	Active smoking doubles the risk of developing severe COVID19. COPD and a history of smoking contribute to COVID-19's poor progression and outcome.
5.	[2]	UK	2,473 patients	Results showed that 22% (31/139) of current smokers and 46% (13/28) of ex-smokers had severe complications.	Current smokers had a higher risk of severe complications and a higher mortality rate than former and never smokers.
6.	[28]	Italy	12 studies, 2,794 patients	Smoking (OR: 1.54, 95% CI 1.07-2.22) was associated with severe disease.	Characteristics linked to the severity of SARSCoV2 infection may aid in the early detection and management of the virus.
7.	[29]	Iran	10 studies, 76,993 patients	SARS-CoV-2 infection was found in 7.63 percent of hospitalized smokers, according to the combined data.	Coronavirus infections are more common in smokers, especially the most recent species.

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Table 1 continued

S. No.	Author	Country	Study Population	Findings	Conclusion
8.	[8]	Germany	16 studies, 11,322 patients	There is an association between the current smoking status and severe COVID-19 (OR = 1.51; 95% CI: 1.12-2.05; P < .008). In 10.7% (978/9067) of non-smokers, COVID-19 was severe, while in active smokers, severe COVID-19 occurred in 21.2% (65/305) of cases.	Severe COVID-19 is clearly linked to active smoking and a history of smoking.
9.	[1]	Spain	18 studies, 7,671 patients	Smokers were statistically less likely to be hospitalised (OR = 0.18, 95% CI: 0.14-0.23, p < 0.01)	According to an analysis of data from 18 studies, the percentage of current smokers in hospitals is much lower than expected.
10.	[30]	Canada	13,184 patients	Pooled analysis showed that prevalence of respiratory diseases (OR 4.21; 95% CI, 2.9-6.0) and smoking (current smoking OR 1.98; 95% CI, 1.16-3.39 and former smoking OR 3.46; 95% CI, 2.46-4.85) were significantly associated with severe COVID-19 outcomes.	The findings suggested that underlying respiratory diseases, particularly COPD, and smoking were linked to poor COVID-19 results.
11.	[7]	Greece	18 studies, 6,515 patients	Current smokers were more likely than non-current smokers to suffer a negative outcome in the study. [odds ratio (OR): 1.53, 95%CI: 1.06-2.20, p = 0.022] but less likely compared with former smokers (OR: 0.42, 95% CI: 0.27-0.74, p = 0.003).	In this meta-analysis of retrospective observational case series, current smoking was found to be uncommonly low among COVID-19 hospitalized patients.
12.	[31]	Spain	60 studies, 51,225 patients	The following predictors were more markedly associated with mortality in studies with patients with a mean age $\leq$60 years: dyspnoea (p-OR = 4.3), smoking (p-OR = 2.8), kidney disease (p-OR = 3.8)	All of the comorbidities studied had a higher mortality risk in the study.

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Table 1 continued

S. No.	Author	Country	Study Population	Findings	Conclusion
13.	[20]	China	16 studies, 3,975 patients	While former smokers were more common in severe cases, there was no difference between the two groups of "current smokers."	Radiologic findings, some symptoms such as dyspnea and hemoptysis, some laboratory indicators, and smoking history, particularly in ex-smokers, can all be used to determine the severity of COVID-19.
14.	[32]	USA	38,906 patients	Compared to never smokers, patients with smoking history had higher relative risk of death [sRR: 1.28; 95% CI: 1.06–1.55; I2 = 68%; n = 13] and severe COVID-19 disease [sRR: 1.29; 95% CI: 1.18–1.42; I2 = 33%; n = 27]	Upregulation of pulmonary Angiotensin Converting Enzyme 2 (ACE2) gene expression and, as a result, pulmonary ACE2 receptors in smokers, implying that smoking has a direct effect on COVID-19 susceptibility and disease progression.
15.	[7]	China	13 studies, 5,960 patients	Current smoking prevalence ranged from 1.4% (95% CI 0.0-3.4%) to 12.6% (95% CI 10.6-14.6%). An unusually low prevalence of current smoking was observed from the pooled analysis (6.5%, 95% CI 4.9-8.2%) as compared to population smoking prevalence in China.	In China, patients with COVID-19 had a low prevalence of current smoking, about a quarter of the population's smoking prevalence. The findings, combined with nicotine's well-known immunomodulatory effects, suggest that pharmaceutical nicotine could be a viable treatment option for COVID-19.
16.	[33]	Greece	18 studies, 6,310 patients	Overexpression of the ACE2 receptor gene24 has a potentially harmful effect, while attenuation of the excessive immune response seen in critically ill patients with COVID-19 infection has a potentially protective effect.	Smoking may have a negative impact on disease severity and mortality in COVID-19 patients who are hospitalized, which is more pronounced in younger patients without diabetes.

Smokers have higher levels of ACE2 gene expression, which codes for ACE-2 [34]. Nicotine exposure causes upregulation by stimulating the alpha 7 types of nicotinic acetylcholine receptors (alpha 7-nAChR) [34]. According to Leung et al. [34], increasing nicotine doses resulted in a stepwise increase in ACE-2 levels. Nicotine alters the normal Renin-Angiotensin System (RAS) homeostasis, with ACE-2 acting as a key mediator [35]. ACE-2 degrades angiotensin II into angiotensins (1-7) and angiotensin II (2-7), (1-9). These metabolites are potent vasodilators that counteract the vasoconstrictive and proinflammatory properties of angiotensin II [32, 34]. ACE-2 is thought to have both a protective and pathogenic mechanism in the lung in mice [22]; studies show that ACE-2 protects against severe lung injuries caused by aspiration and sepsis [36]. As a result, the paradoxical effects of smoking emerge. Although ACE-2 upregulation facilitates SARS-CoV-2 entry into host cells, ACE-2's protective mechanism prevents severe disease.

Impact of e-cigarette usage on COVID-19

E-cigarettes and waterpipes have become increasingly popular in recent years due to their perceived lower risk of harm than traditional cigarettes [37]. The heated liquid in cartridges or tanks is then aerosolized and inhaled by the e-cigarette delivery system. The addition of flavoring chemicals to the liquid improves the taste of the vapor, which has caught the attention of the younger generation (18-24) [37]. The aerosol can contain a variety of harmful components, including humectants (such as glycerin and propylene glycol), contaminants (such as heavy metals), flavoring agents, and harmful solvent byproducts (such as formaldehyde and acrolein), in addition to tobacco-specific nitrosamine [38]. The belief that e-cigarettes aren't as dangerous as they appear shifted dramatically in mid-2019 as a result of this new research, when reports emerged about the traumatic, inflammatory lung injuries they were causing chronic users. Given the lack of knowledge, ability to diagnose, etiology, and treatment for e-cigarette, or vaping, product use associated with lung injury (EVALI), as well as the demographics of those affected [39], this was especially concerning. Since there is increased pulmonary toxicity associated with e-cigarette use, e-cigarette users are at risk of enhancing respiratory disease caused by COVID-19. The aerosols and vapor created by e-cigarette devices could also assist in the spread of COVID-19 [40]. An online national survey of individuals from the ages of 13 to 24 years found that COVID-19 diagnosis was five times more likely in e-cigarette users only (95% confidence interval [CI]: 1.82–13.96), seven times more likely among dual-e-cigarette-users (95% CI: 1.98–24.55), and 6.8 times more likely among past 30-day dual-users (95% CI: 2.40–19.55) [41]. In past 30-day dual-users, testing was nine times more likely (95% CI: 5.43–15.47) and 2.6 times more likely among past 30-day e-cigarette only users (95% CI: 1.33–4.87). Among past 30-day dual-users, symptoms were 4.7 times more likely (95% CI: 3.07–7.16). These data indicate a significant risk of COVID-19 diagnosis associated with e-cigarette usage. While the data may be scarce and at times conflicting, the potentially devastating effects of e-cigarette usage should not be ignored, and more research should be conducted.

DISCUSSION

Overall, the paradoxical protective effect of smoking in the presence of SARS-CoV-2 infection can be attributed to nicotine's effects on lung parenchyma rather than smoking itself [34]. Because smoking is carcinogenic and causes systemic inflammation, it causes a destructive immune response in the body [42]. Cigarettes contain over 5000 chemicals and toxins, including carbon monoxide and polycyclic hydrocarbons [23], as previously stated. Lung carcinoma is thought to be caused by polycyclic hydrocarbons in particular. Other toxins have been linked to additional negative effects in the body, including alterations in cardiovascular, immune, and pulmonary system function [22]. Further research is needed to see if these toxins are involved in the progression or outcome of COVID-19 disease. Furthermore, because COVID-19 begins with SARS-CoV-2 infecting lung epithelial cells via ACE-2 receptors, upregulation of these receptors makes it easier for smokers to become infected [8]. Once infected, nicotine's protective effects aid recovery in all but the most serious cases; however, this does not mean that smokers are immune to severe disease [6]. Moreover, this is based on the assumption that the patient is a healthy smoker. Smokers with a long history of smoking are more likely to have comorbidities like COPD. Upregulated ACE-2, as well as altered cytokines and severely damaged lung tissue, can result in a fatal COVID-19 infection in these patients [34]. Most smokers cut down on their smoking once infected with COVID-19, at least for the duration of their infection. This is even more likely if you are admitted to the hospital. Given nicotine's 120-minute half-life, its effects may begin to wear off, reducing nicotine's protective effects [43]. In these cases, a nicotine patch may help with the patient's withdrawal symptoms while also providing protection [8]. It could also be used as a treatment, but more research is needed. Individuals should not begin smoking in order to protect them-

selves from COVID-19, as upregulated ACE-2 would result in a more manageable infection. Furthermore, the risks of smoking far outweigh the benefits. Fortunately, COVID-19 has been found to have caused about half of smokers to consider quitting. Although few have done so, it would be the most beneficial option in the long run.

CONCLUSION

We are learning more about how SARS-CoV-2 affects different people as the pandemic progresses. According to a much larger body of evidence, smoking is not a protective measure against COVID-19 infection. Small studies that showed COVID-19 reduced disease severity clashed with a much larger body of evidence that showed the opposite. Even in studies that found a minor protective effect, the risks of smoking are widely acknowledged to outweigh any benefits. ACE-2 has been suggested as one of COVID-19's primary infection routes based on these findings. More research into the interaction of COVID-19 and ACE-2 receptors is needed, but current understanding suggests an upregulation of ACE-2 receptors in the bodies of smokers which increases the likelihood of infection. Potential treatment options include agents that could modulate the expression of the ACE-2 receptors and thus limit the severity of SARS-CoV-2 infection through reduced entry. Further research would be needed on such agents. Also, nicotine's downregulatory effects on host cytokine production has potential to be used as therapy in severe cases. During the global COVID-19 pandemic, it became clear that certain demographics were more vulnerable than others to negative consequences. Hospitalization and death rates are higher when pre-existing health conditions are combined with unhealthy lifestyle choices like smoking. Public health initiatives must target vulnerable groups, such as current smokers, to encourage smoking cessation in pandemic situations, in order to reduce the health-care burden.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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