# Smoking and COVID-19: A Scoping Review

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**ABSTRACT:** Smoking affects a person's overall health and damages nearly every organ of the body. Since smoking tobacco affects and damages the lungs, it increases the risk of respiratory infections and makes it easier for the coronavirus disease (COVID-19) to invade the lung tissue, causing more severe symptoms and increasing the risk of death. However, debates are still ongoing as to the effect of cigarette smoking on vulnerability to COVID-19. Some studies, where active smokers were underrepresented among patients with COVID-19, claimed that a "smoker's paradox" may exist in COVID-19 and that smokers are protected from infection and severe complications of COVID-19. However, other studies reported the opposite trend. The objective of this study is to review the findings of epidemiological and in vitro studies about the association between smoking and the risk of contracting COVID-19, taking into account disease severity. Several epidemiological studies have found a higher smoking prevalence among COVID-19 infected patients. Also, studies had shown that people with respiratory diseases caused by tobacco use are at higher risk of developing severe COVID-19 symptoms. Studies have shown that in vitro, the acute exposure allows for more severe proximal airway epithelial disease from SARS-CoV-2 by reducing the mucosal innate immune response and the proliferation of airway basal stem cells and has implications for disease spread and severity in people exposed to cigarette smoke, with a more severe viral infection and cell death. Smoker patients with different comorbidities are at higher risk of contracting the COVID-19 virus and have a worse prognosis for the virus as well as for their comorbidities. Further investigations of the interaction between smoking and COVID-19 are warranted to accurately assess the risk of contracting COVID-19 among smokers, and the progression to mechanical ventilation or death in patients who suffer from it.

**KEYWORDS:** Smoking, tobacco waterpipe, coronavirus disease, epidemiologic studies, cigarette smoking

## Introduction: Smoking in the Context of COVID-19 Pandemic

The COVID-19 pandemic has imposed on humans a new way of living: restricted movements, confinement in closed spaces, fear of being infected, and strict hygiene measures for endless periods. Psychologically, this era is considered as a "transition" phase and seems to require a search for a new balance. While boredom and confinement might have stimulated smoking among some, the threat of contracting COVID-19 and becoming severely ill might have motivated others to improve their health by quitting smoking; this is particularly true for individuals with moderate to severe stress.[1]

Studies have reported mixed findings regarding changes in tobacco use during the pandemic. Indeed, in the United States, far more participants reported increasing their tobacco use since COVID-19 started (40.9%) versus decreasing their tobacco use (17.8%).[2] In Italy, most exclusive cigarette smokers have considered quitting, but most exclusive e-cigarette users have not considered stopping the use of e-cigarettes. In the group of former smokers, about one-third of participants reported having thoughts about smoking again, and in the group of never smokers, few participants declared the intention to start smoking.[3] In China, relapses from smoking abstinence were relatively common during the pandemic (25%). Similarly, 20% of regular smokers increased their usage amount.[4] In England, a study have found that increased smoking among smokers and relapsed smoking among former smokers were a result of social isolation and potential stress.[5] A study done by Chertok[6] among 810 adults from Ohio have found a change in smoking behavior among current smokers since COVID-19 were 36.7% having attempted to quit since the outbreak.

Debates are still ongoing as to the effect of cigarette smoking on vulnerability to COVID-19. Although it is well established that smoking is associated with morbidity and mortality in several respiratory infections, some studies, where active smokers were underrepresented among patients with COVID-19, claimed that a "smoker's paradox" may exist in COVID-19 and that smokers are protected from infection and severe

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complications of COVID-19. However, other studies reported the opposite trend. Therefore, the need of a scoping review to provide an overview of the available research evidence. The objective of this study is to review the findings of epidemiological and in vitro studies about the association between smoking and the risk of contracting COVID-19, taking into account disease severity.

*Method and research design*

A comprehensive literature review was conducted using the MEDLINE/PubMed database and references cited in relevant articles were also searched. Included studies were recently published about the effect of COVID-19 on smoking from January 1st, up till the end of September, 2020. Also, studies about the mechanisms by which smoking affects the body were included from December 2001 up till May 2018. No restrictions were placed on language of publication or study origin. Limitations were placed on the type of publication when using the PubMed database and included all of the following: case reports, clinical studies, clinical trials, comparative studies, controlled clinical trials, journal articles, meta-analyses, observational studies, systematic reviews, and books and documents. Whenever possible, peer-reviewed randomized clinical trials (RCTs) and placebo controlled trials were preferred over case reports, case studies and commentaries, while review articles and meta-analyses were also included whenever relevant. Similarly, books and book chapters on the topic of smoking were also reviewed for eligibility.

To ensure retrieval of the largest number of articles covering the topic of smoking, the following key search terms were used: "smoking," "tobacco," "nicotine," "covid-19," "coronavirus disease," "hookah" and "waterpipe," "cigarette," "smoker," "epidemic," "SARS-CoV-2," "virus," and "respiratory function". The search term "smoking" was included in the initial run of the online databases but resulted in over 315 133 articles, the majority of which were irrelevant. Consequently "smoking" as a search term was eliminated from the primary searches conducted.

Then we used the term "Smoking and covid-19" and "effect of smoking on the body" and we obtained a total of 20 188 articles using the MEDLINE/PubMED database. Of the 20 188 article, 557 articles were about 'smoking and COVID-19" and 19 631 were about "harmful effect of smoking." Title and abstract screening resulted in the elimination of articles that were not relevant or did not cover the topic of smoking; did not meet the initial inclusion criteria related to article type; focused primarily on other disease and disorders other than smoking; or primarily focused on psycho-social aspects and risk factors related to smoking. This resulted in 200 articles that required in-depth analysis, of which 50 were eliminated due to irrelevance, and 48 were not found to be focused on smoking and COVID-19. This resulted in 107 articles which were included in the final version of the article.

## Modes of COVID-19 Transmission Using a Tobacco Smoking

Viral transmission through tobacco smoking might first occur through contact since smoking involves regular contact between saliva, hands, and devices.[7] Moreover, smoking tobacco (cigarettes, e-cigarettes, or waterpipe) produces exhaled smoke and aerosols, and causes coughing or sneezing, thus contaminating surroundings and surfaces with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).

Additionally, SARS-CoV-2 survives in aerosols and surfaces (plastic, paper, and steel) for several hours to days[8] after oral/nasal release (coughing, sneezing, smoking).[9,10] Also, the virus is actively found for 4 hours up to 2 to 3 days on shared surfaces of smoking devices.[7] Thus, touching contaminated surfaces of smoking devices can actively harm smokers and non-smokers, even when people practice social distancing.[7]

*The act of cigarette smoking and virus transmission*

The COVID-19 is transmitted from hand to mouth as smoking cigarettes implies that fingers and contaminated cigarettes are in contact with the lips or comes close to the mouth, which increases the risk of transmission.[11,12] The latter also depends on whether hands are contaminated and how the packet is prepared and handled.[12] Indeed, infected hands can contaminate a clean packet and the cigarettes it contains, thus it is no longer clean during the remaining time of its use.[12]

*The act of waterpipe smoking and virus transmission*

Waterpipe smoking is the process of inhaling tobacco smoke after it has passed through a chilled water chamber, with a hose capped with a plastic mouthpiece.[13] Virus transmission through the waterpipe is high since smokers might cough and contaminate the inner side of the hose. The moisture in tobacco smoke and the use of cold water in the water chamber promote the survival of viruses and bacteria.[13,14] Also, uncontrolled manual preparation of waterpipe could spread infectious diseases.[14] Another factor of contamination is that most cafés prefer not to clean the waterpipe upon each smoking session, since it is labor-intensive and time-consuming to wash and clean pieces, including the cold water jar, ideal for virus transmission.[13,15] Moreover, the waterpipe tobacco smoke contains many dangerous chemicals that damage the respiratory tract and predispose the smoker to viral infection.[15]

On the other hand, smoking waterpipe is an activity typically performed within groups in public settings.[16] Social gatherings encourage the transmission of the COVID -19 virus.[17] The risk may be higher when waterpipe is used indoors.[18] Participants usually pass the hose from person to person and may use the same mouthpiece[16] during smoking sessions that last from 45 to 60 minutes but can also be up to several hours.[14] Even if only 1 customer uses the pipe and mouthpiece at a

time, other customers might reuse uncleaned waterpipes chambers and hoses on the same day.[14]

It is noteworthy to mention that until now no studies have directly examine the mode of transmission of COVID-19 through cigarette or waterpipe use. The abovementioned studies are most often prospective envisioning or predicting the COVID-19 transmission based on facts about waterpipe and cigarette use. Further studies and evidence are needed in order to understand the transmission way of COVID-19 through smoking and measures should be implemented within the community to limit its direct and indirect effects.[7]

## Mechanisms Through Which Smoking may Increase the Risk of Infection with COVID-19

Mechanistic studies indicate that the enhanced susceptibility to infection could be attributed to angiotensin converting enzyme 2 (ACE2) receptor upregulation, the key receptor used to gain entrance into the host mucosa and induce active infection by the acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an apparently unique mechanism for this virus. Smoking contributes to a worse disease state and increased vulnerability to SARS-CoV-2 infection via the activation of peripheral nicotinic acetylcholine receptors (nAChRs) expressed in many organ systems. Nicotine affects homeostasis of the renin angiotensin system (RAS)[19] and contributes to the up-regulation of the angiotensin-converting enzyme (ACE)/angiotensin (ANG)-II/ANG II type 1 receptor axis, leading to the development of cardiovascular and pulmonary diseases.[19]

In parallel, coronaviruses have distinctive crown-shaped features due to the presence of large type 1 transmembrane spike (S1 and S2) glycoproteins mediating entry of the virus into the host cell. The S1 domain is responsible for first stage host cell entry and contains the angiotensin-converting enzyme-2 (ACE2) receptor. Recent evidence suggests that the SARS-CoV-2 modified S protein exhibited a significantly higher affinity for ACE2 and is 10- to 20-fold more likely to bind to ACE2 in human cells, enabling an easy person-to-person spread of the virus.[20] So the action of nicotine on nAChRs facilitates the SARS-CoV-2 host entry.[21]

### Smoking and the respiratory function

The lung RAS is involved in the pathogenesis of different lung diseases other than blood pressure and fluid balance, like pulmonary arterial hypertension (PAH)[22] lung infection/inflammation,[23] acute respiratory distress syndrome,[24] Chronic Obstructive Pulmonary Disease (COPD),[25] and pulmonary fibrosis.[26]

Bronchial epithelial cells absorb inhaled nicotine and smoke components. The gas mixture generated by smoking contains hundreds of components including carbon monoxide, nicotine, oxidants, fine particulate matters (PM), and aldehydes associated with the onset of COPD.[27] Inhaled smoke is responsible for the destruction of the matrix, shortage of blood supply, and

death of epithelial cells. It leads to the infiltration of inflammatory cells to mucosa and glandular tissue.[27]

Furthermore, acrolein, a smoke component, impairs the alveolar-capillary barrier function, resulting in lung inflammation and increased susceptibility to acute respiratory distress disorder (ARDS).[28]

Chronic smoking significantly decreases pulmonary function, that is, Forced Expiratory Volume (FEV1), Forced Vital Capacity (FVC), Forced Expiratory Flow (FEF), and Fractional Exhaled Nitric Oxide (FeNO).[29] The latter is associated with decreased NO and its conversion to peroxynitrite (ONOO) due to oxidative stress.[30]

### Smoking and the immune system

Smoking is a cause of the release of many inflammatory mediators (pro-inflammatory and anti-inflammatory cytokines).[31] Many studies have demonstrated the association of smoking with chronic systemic inflammation and autoimmune diseases (rheumatoid arthritis, psoriasis, COPD, and systemic lupus erythematosus).[32]

Nicotine interacts with nAChRs α7 on the surface of immune cells like macrophages and lymphocytes T and B,[33] and induces an immunosuppressive effect, modulating innate and adaptive immune responses.[34,35] Therefore, smoking alters the development and function of innate (dendritic cells, macrophages, and natural killer cells) and adaptive immune cells (cytotoxic CD8+ T cells, CD4+ T helper cells (Th), regulatory T cells, and B cells), leading to pro-inflammatory responses, thus worsening smoking-associated COPD.[32]

### Smoking and oxidative stress

Oxidative stress is the result of an imbalance between the production of reactive oxygen species (ROS) and the antioxidant capacity of the organism. ROS are essential for some signaling pathways, but their excess leads to proteins, lipids, and DNA oxidation, which is involved in some diseases.[36] Tobacco smoke constituents induce oxidative stress via different mechanisms, including the direct effects of nicotine (neutralized by N-acetylcysteine) and the abundance of PM.[37] Oxidative stress and inflammation lead to the increased production of superoxide anion ($O2^{\cdot-}$) via the NADPH oxidase and nitric oxide synthase (iNOS) as principal sources of ROS.[38] Furthermore, carbon monoxide released by smoking is directly absorbed in the lungs. It forms a tight but reversible bond with hemoglobin and leads to tissue hypoxia. But once eliminated, oxygen reperfusion occurs, thus increasing ROS.[39]

Waterpipe is also a source of heavy metals such as Pb, Cr and arsenic that lead to free radicals formation.[40] Acrolein, a toxic unsaturated aldehyde produced by cigarette and waterpipe, binds to proteins and DNA, and induce oxidative stress and inflammation. Acrolein decreases antioxidant enzyme promoting ROS production, oxidizes lipids and produces more

acrolein in a vicious circle.[41] Acute and high dose exposures to acrolein suppresses immune response while in the case for repetitive waterpipe smoking, (chronic exposure with low doses) enhances inflammatory response.[42]

*Smoking and the cardiovascular function*

Chronic exposure to nicotine (through the activation of nAChRs, widely expressed in the heart)[43] exacerbates pathological changes in the heart. Cigarette smoke accelerates the progression of cardiac hypertrophy and heart failure.[44] Previous findings demonstrated a possible cardiotoxic interaction between nicotine and the RAS.[45] Nicotine was shown to exacerbate cardiovascular remodeling induced by ANG II, which included increased heart rate, and increased thickening of the aortic wall.[45] Both nicotine and RAS are involved in the pathogenesis of vascular calcification and abdominal aortic aneurysms (AAA).[41] Thus, smoking is a considerable risk factor associated with the development, expansion, and rupture of AAA.[46]

*Smoking and the endocrine system*

The activation of nAChRs affects many organ systems, including the endocrine system. Prolactin levels are directly related to dopamine secretion, while the hypothalamic-pituitary-adrenal (HPA) axis stimulation is associated with the stress level controlled by nicotine administration.[47] Furthermore, smoking worsens insulin resistance and diabetes mellitus (DM) via many proposed mechanisms, including but not limited to the activation by the nicotine of a macrophage $\alpha$7-nAChR associated anti-inflammatory pathway and the exacerbation of nicotine-associated inflammation and insulin resistance.[48] Another mechanism may be the increased ROS due to the increased expression of tumor necrosis factor-$\alpha$ (TNF-$\alpha$),[49] in addition to maternal smoking during pregnancy and breastfeeding, causing insulin resistance later in childhood.[50]

## A Known Fact: Harmful Effects of Smoking

In addition to the increased risk of virus transmission, smoking affects a person's overall health and damages nearly every organ of the body.[51,52] When tobacco toxins enter the body through the mouth and nose, they cause tissue and cells damage up to the lungs,[53] including upper lung airways and alveoli, resulting in lung inflammation and reduced lung and immune function.[53] Consequently, cigarette smoking causes lung diseases such as bronchiolitis, chronic bronchitis, pulmonary emphysema, tuberculosis, and lung cancers, in addition to an increased risk of respiratory infections.[53] While the lung has initial ways to protect itself from damage caused by inhalation agents, these defenses are gradually overwhelmed as tobacco smoke is repeatedly inhaled over time.[53] After years of smoking, the lung tissue becomes severely damaged, loses its elasticity, and can no longer easily exchange air.[53] Similar to cigarettes, waterpipe

smoke harms pulmonary cells and damages alveoli, causing tissue inflammation and undermining the capacity of the lungs to fight off infection.[54] Indeed, after a single session, cell damage and lung inflammation have been detected among waterpipe users.[54] Thus, smoking reduces the ability of the lung to absorb oxygen and release carbon dioxide, storing up mucus, which leads to excessive coughing and difficulties in breathing.[53]

Since smoking tobacco affects and damages the lungs, it makes it easier for the SARS-CoV-2 to invade the lung tissue, causing more severe symptoms and increasing the risk of death.[18] Smoking also requires high respiratory volumes, deep inhalation, progressive cooling and drying of the mucous respiratory tract, and changes in nose-to-mouth breathing. It reduces the mobility of ciliated cells and raises the viscosity of the mucous membrane, which impairs the filtration of microorganisms from the upper respiratory tract system.[53]

## Smoking and COVID-19: Current Clinical Findings

Based on these mechanisms, smoking is hypothesized to increase risks associated with COVID-19. Several epidemiological and clinical studies conducted to confirm this hypothesis found conflicting results.

*Lower prevalence of smoking in COVID-19 infected patients*

A spatial analysis involving 175 countries showed that the percentage of the total smoking population was inversely associated with COVID-19 at the global level.[55] In Mexico, among 89 756 laboratory-confirmed positive cases (retrospective case series used a publicly available nation-level dataset released on May 31, 2020, by the Mexican Ministry of Health), current smokers were 23% less likely to be diagnosed with COVID-19 compared to non-smokers. However, having COPD (among other comorbidities) was associated with hospitalization and adverse outcomes. Current smoking was not linked to unfavorable outcomes.[56] Similarly, an ecological study found a statistically significant negative association between smoking prevalence and the prevalence of COVID-19 across the 38 European nations, after controlling for confounding factors. However, it could not demonstrate a direct association between smoking prevalence and COVID-19 mortality ($P$ = .626).[57] A preliminary study that analyzed the data available in published articles showed a lower prevalence of smoking in COVID-19 patients compared to the regional average.[58]

It is noteworthy that statistical associations do not imply causation: they might be explained by several facts, such as an interfering dose-effect relationship (whenever the number of packs, the duration, and the timing of smoking, are not measured), reverse causation (some people had stopped smoking during the pandemic), or a residual confounding (additional confounding factors not taken into account). Likely, the low prevalence of smokers among COVID-19 hospitalized patients is partly due to the fact that many smokers were misclassified

as nonsmokers.[59] Researchers have also identified information and selection biases, in addition to knowledge gaps, which may give the false impression that smoking is protective against COVID-19.[60]

Plausible biologic mechanisms by which smoking might be protective against COVID-19 include an anti-inflammatory effect of nicotine, a blunted immune response among smokers (reducing the risk of a cytokine storm in COVID-19), and increased nitric oxide in the respiratory tract (which may inhibit replication of SARS-CoV-2 and its entry into cells),[60] in addition to the possible role of squamous cell metaplasia, which is commonly associated with smoking.[61] As of now, however, the data supporting the smoker's paradox claims are limited and questionable The claims of a protective effect must be viewed with extreme caution by both the general population and clinicians.[60]

### Higher prevalence of smoking in COVID-19 infected patients

Several epidemiological studies have found a higher smoking prevalence among COVID-19 infected patients. In a systematic review including thirteen studies the prevalence of current smoking among 5960 hospitalized COVID-19 patients in China ranged from 1.4% to 12.6%.[61] The random effects pooled prevalence of current smoking was 6.5% (95% confidence interval [CI]: 4.9%-8.2%).[61] Another, meta-analysis done by Emami et al.[62] analyzed data for 2986 patients and found a pooled prevalence of smoking of 7.6% (CI: 3.8%-12.4%). In a cross sectional study done among 53 002 adults from United Kingdom found that the prevalence of confirmed COVID-19 was higher among current smokers (0.56% [CI: 0.41%-0.75%]) as compared with never smokers.[63] Data from a hospital in France also indicate that while prevalence of current smoking was lower in hospitalized COVID-19 patients than the general population, prevalence of former smoking was much higher.[64] In a cross-sectional study among adolescents and young adults, COVID-19 diagnosis was 5 times more likely among ever-users of e-cigarettes only (95% CI: 1.82-13.96), 7 times more likely among ever-dual-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). Symptoms were also 4.7 times more likely among past 30-day dual-users (95% CI: 3.07-7.16).[65] Furthermore, a systematic review of reviews also showed a significant association between COVID-19 infection and current or ever smoking.[66]

At this time, it is impossible to estimate the prevalence of smoking status among COVID-19 patients in a population-representative sample.[61] The accuracy and consistency of the reported smoking status is also unknown. Given the emergency of the outbreak, the patient's smoking status could not have been properly reported or certain patients have been unable to register their smoking status.[61] It is also possible that some patients may also have been in critical condition at the time

they were hospitalized, affecting their communication capacity and their capacity to disclose their smoking status.[61]

### Smoking and COVID-19 progression, severity, and mortality

Numerous studies had shown that people with respiratory diseases caused by tobacco use are at higher risk of developing severe COVID-19 symptoms.[67-69] A study among 1099 Chinese COVID-19 patients found that 32% of patients with a history of smoking (smokers and ex-smokers) had a severe form of COVID-19 pneumonia at the time of hospitalization, compared with 15% of patients who had never smoked.[67] Another study among 78 patients with COVID-19-induced pneumonia found that 27% of smokers worsened within 2 weeks of hospitalization, compared to 3% of non-smokers.[68] A meta-analysis based on 15 studies showed that 22% of current smokers and 46% of ex-smokers had severe complications of the COVID-19.[69]

During a follow up of 28 days among 720 patients, 71.50% had recovered or were symptomatically stable, COPD was a risk factor of progression, while smoking was inversely related to it.[70] A meta-analysis found that smoking is a risk factor for COVID-19 progression, with smokers having higher odds of COVID-19 progression than never smokers (OR = 1.91).[71] In Kuwait, among 1096 consecutive COVID-19 patients, the risk factors found to be significantly associated with admission to intensive care were age above 50 years old, a qSOFA score above 0, smoking, elevated CRP, and elevated procalcitonin levels. Smoking and elevated procalcitonin levels also correlated significantly with mortality.[72] In a study to characterize a large cohort of patients with COVID-19 (n = 4536) and their outcomes, several factors were involved with increased hospitalization risk, including former smoking history, shortness of breath, and certain medications (NSAIDs, immunosuppressive treatment).[73] A Brazilian study on 10 713 COVID-19 patients found that both smoking and pulmonary disease increased the risk of hospitalization.[74] Other smaller studies showed similar results.[75] Among patients with lung cancer, determinants of COVID-19 severity got largely patient-specific features, including smoking status and COPD (odds ratio for severe COVID-19 = 2.9).[76] Moreover, there is a possible role of smoking and vaping on cerebrovascular and neurological dysfunction in COVID-19 patients, along with potential pathogenic mechanisms associated with it.[77]

When assessing clinical characteristics and risk factors for mortality of patients with COVID-19 from Mexico, smoking was found to increase the risk of death. Less frequent comorbidities, such as COPD, chronic kidney disease, and immunosuppression, also showed a significant risk for death (*P* < .0001).[78] Common independent factors associated with an increased risk of death were older age, history of smoking status, number of comorbidities, more advanced performance status, and active cancer.[79] Moreover, a pooled meta-analysis

showed that the prevalence of respiratory diseases, specifically COPD (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.[80] Another meta-analysis also showed that current smokers were more likely to have an adverse outcome compared with non-current smokers (odds ratio [OR]: 1.53, 95%CI: 1.06-2.20, $P$ = .022) but less likely compared with former smokers (OR: 0.42, 95% CI: 0.27-0.74, $P$ = .003).[81] An older meta-analysis also found similar results: current smokers were 1.45 times more likely (95% CI: 1.03-2.04) to have severe complications compared to former and never smokers. Current smokers also had a higher mortality rate of 38.5%.[69]

COVID-19 disease state worsening by smoking is evidence based, despite some studies claiming a reduced SARS-CoV-2 infection risk in smoker population. In fact, a review assessing the relationship between smoking status and some COVID-19 disease outcomes (infection, hospitalization, disease severity, and mortality), showed no important association between being a smoker and hospitalization or mortality and that current smokers were at lower risk of getting infected with SARS-CoV-2 compared to never smokers. But the authors related these results to study specific factors that complicated the interpretation, including inverse causality.[82] In all cases, it is impossible to prove causality through observational studies or to conduct interventional studies, except for smoking cessation trials in the general population and among patients after COVID.

## Confirmation of Smoking as a Risk Factor for COVID-19 in vitro

Even if smoking may not necessarily increase one's risk for contracting COVID-19, the biological and inflammatory cascade that occurs upon SARS-CoV-2 infection may be particularly devastating for a smoker.[83]

### Smoking and demographics suggested mechanisms

Evidence has shown that smoker patients with different comorbidities (DM, cardiovascular diseases (CVD), COPD, cancer etc.) are at higher risk of contracting SARS-CoV-2. They also have a worse prognosis for COVID-19 as well as for their comorbidities, especially for higher age patients. Older men are in particular at higher risk of testing positive for COVID-19 because smoking rates are highest for men, and older male smokers will have smoked for most of their lives (causing maximum damage to their respiratory and cardiovascular systems In fact the SARS-CoV-2 viral capsid binds to surface ACE2 and activates a cellular serine protease *TMPRSS2* (an androgen-responsive gene highly expressed in men[84]) for protein priming.[85] Therefore, the higher expression of *TMPRSS2* in men could increase their vulnerability to COVID-19,[84] thus explaining the higher morbidity and mortality associated with older age and male gender.[86]

### Smoking and comorbidities suggested mechanisms

DM may aggravate the risk of severe COVID-19[87] and mortality because it increases the surface expression of ACE2 through hyperinsulinemia,[88] in addition to other synergistic mechanisms. DM is associated with immunodeficiency due to reduced TNF-α and impaired Treg cells, which facilitates infections.[88,89]

CVD patients are also predisposed to an increased risk of more severe disease for many reasons. Hypertension is associated with a dysregulation in the immune system, manifested by elevated IL-17 levels and abnormal T-cell function.[90] Other factors include overactive sympathetic drive and elevations in angiotensin II, a pro-inflammatory peptide.[91] ACE2 modulators (ACE1 inhibitors, angiotensin receptor blockers, and thiazolidinediones), frequently used to treat hypertension, upregulate ACE2 expression.[29]

Furthermore, the expression of ACE-2 receptors is increased in COPD, leading to severe COVID-19 symptoms, including structural damage to lungs, lower immunity, and increased mucous production and airway blocking.[92] Consequently, higher morbidity and mortality are associated with chronic lung diseases.[86]

Patients suffering from any malignancy, exacerbated by smoking, are also at a higher risk of developing COVID-19 infection due to the weak immunity providing an efficient viral replication environment.[93]

### Additional smoking suggested mechanisms

The impact of the toxic constituents of tobacco products on endothelial function has been thoroughly discussed. Studies have shown that smoking (cigarettes, waterpipe, and e-cigarette) may have contributed to an increased burden of COVID-19 symptoms and severe health consequences.[94] In vitro, the acute exposure allows for more severe proximal airway epithelial disease from SARS-CoV-2 by reducing the mucosal innate immune response and the proliferation of airway basal stem cells and has implications for disease spread and severity in people exposed to cigarette smoke, with a more severe viral infection and cell death.[95] Furthermore, the viral entry has been shown to cause cytokine storm involving excessive production of pro-inflammatory cytokines/chemokines, including IL-6, TNF-α, IFN-γ, IL-2, IL-7, IP-10, MCP-3, or GM-CSF, which is increased by smoking.[96] Also, the expression levels of *TMPRSS4*, a gene coding for a protease that primes SARS-CoV-2 for cell entry similarly to *TMPRSS2*, were elevated in bronchial epithelial cells from current smokers compared with never smokers, suggesting that higher bronchial *TMPRSS4* levels in smokers might put them at higher risk for SARS-Cov-2 infection.[97]

Chronic smoke exposure triggers the expansion of this cell population and a concomitant increase in ACE2 expression. In contrast, quitting smoking decreases the abundance of these

secretory cells and reduces ACE2 levels. Thus, ACE2 expression is responsive to inflammatory signaling and can be upregulated by viral infections or interferon treatment. Taken together, these results may partly explain why smokers are particularly susceptible to severe SARS-CoV-2 infections. Furthermore, ACE2 was identified as an interferon-stimulated gene in lung cells, suggesting that SARS-CoV-2 infections could create positive feedback loops that increase ACE2 levels and facilitate viral dissemination.[98] This biological phenomenon could also apply to new electronic smoking devices such as electronic cigarettes and "heat-not-burn" IQOS devices.[20] In the same line, smoking may upregulate ACE2 expression through the upregulation of the androgen pathway. These data provide a potential model for the increased susceptibility of smoking patients to COVID-19.[99]

Finally, increased age, comorbidities, smoking status, and recent chemotherapy were associated with higher viral load. In turn, a high viral load (OR = 6) was linked to an increased need for intubation (OR = 3) and in-hospital mortality.[100]

## Future Perspectives

Further investigations of the interaction between smoking and COVID-19 are warranted to accurately assess the risk of contracting COVID-19 among smokers, and the progression to mechanical ventilation or death in patients who suffer from it. Also, further systematic review and meta-analysis studies are needed that could provide a critical analyses of the available data suggesting Covid19 susceptibilities amongst smokers. Risk factors for COVID-19, such as cardiovascular disease, chronic obstructive pulmonary disease, and diabetes, are all strongly associated with smoking habits.[101] Thus, the probability of a beneficial effect of smoking on COVID-19 outcomes is manifestly unlikely. Future investigation should focus on homogenizing variables' definitions, leading to less heterogeneity and easier results interpretation.

Authors of potentially controversial articles should thus restrain from promoting their results before the peer-review process is complete,[102] given all the limitations and biases that they could include, and the false message they could convey. This may be particularly exploited by tobacco industry to promote smoking as not only safe activity but as preventive agent from COVID-19 complications. Furthermore, given the likely benefits of smoking cessation in vulnerable populations, the current pandemic should provide an opportunity to enforce smoking cessation in health facilities (including mental health) and encourage nicotine replacement therapy alongside smoking cessation counseling, to increase the rate of quitting.[103-105] For instance, studies aiming at assessing smokers' attitude toward quitting smoking during the pandemic, showed increased motivation to quit and decreased quantity of smoking.[106] This may offer for policy makers a strong justification for implementing strong antismoking campaigns while making quitting practices available and affordable for the general public. Moreover, nicotine, nicotinic agonists, or modulators of nicotinic receptors may play a potential therapeutic role in COVID-19, owing to their varied effects, including mood regulation, anti-inflammatory, as well as purported interference with SARS-CoV-2 entry and/or replication.[107] The hypothesis that nicotine may have a protective effect against COVID-19, partially masked by smoking-related toxicity and abrupt cessation of nicotine consumption when smokers are hospitalized, need to be explored in laboratory studies using nicotine-based pharmaceutical products.[81] Additionally, its role in the prevention and treatment of COVID-19 should be evaluated in appropriate placebo-controlled trials.[104]

### *Limitations of epidemiological data*

Smoking contributes to COVID-19 morbidity and mortality as explained by several biological mechanisms, while epidemiological data is not conclusive whether smoking is associated with increased odds of infection as well as worse disease state. The inconclusive results may be due to some limitations. First data was not collected directly from the participants (due to the applied social distancing policies). These were rather provided by data banks (like the European bank or the WHO data. . .), so questions about smoking habits may not have adequately reported. Also some hospitalized COVID-19 patients may also have been unable to communicate and disclose their smoking habits because of their critical condition. Some inflated results may be due to the fact that current smokers, negative for COVID-19, confusing their chronic smoking symptoms (cough, increased sputum, altered sense of smell or taste) with those of COVID-19) with those of COVID-19, and may present for testing more frequently than nonsmokers.[82] Studies taking into consideration potential confounders, selection and information biases are recommended. Finally, tobacco industry may have exploited some investigations drawbacks to diffuse falsified studies about the benefits of smoking as a protective agent against COVID-19.

In conclusion, physicians and public health professionals should adequately collect detailed data from trusted sources on smoking as part of clinical management to draw useful conclusions for policy makers to adopt. This will promote smoking cessation as a lead practice, contributing to the mitigation of the COVID-19 pandemic.[71] Further studies, including systematic reviews and meta-analyses, and studies with appropriate assessment of potential confounders and bias minimization, are necessary to conclude about the association of smoking with CIVID-19 severity and fatality.

## ORCID iDs

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