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Smoking Association with Transmission and Mortality of COVID-19

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Abstract

Introduction: Given the unclear evidence about smoking in COVID-19 infected patients, we conducted a comprehensive review to determine the association between smoking and disease severity in COVID-19 infected patients by including all eligible studies. Systematic searching of databases for available evidence and careful definition of disease severity was performed for a rigorous summary of the conclusions.

Methods: To find relevant studies, scientific databases including Embase, PubMed, Science Direct, Google Scholar and Cochrane Library databases were systematically searched. All relevant articles that reported clinical characteristics and epidemiological information on smoking among COVID-19 infected patients were included in the analysis. All articles with any design (randomized controlled trials and observational studies) were included. The primary outcome was disease severity among COVID-19 patients with a history of smoking. The secondary outcome was death among COVID-19 patients with a history of smoking.

Results: Studies reporting a low rate of smoking have been criticized for the poor quality and retrospective collection of smoking status data, the comparison of smoking of subjects covid-19 to smoking of the general population sometimes without taking into account sex and age and for having included only symptomatic or in-hospital subjects, creating possible selection bias. In this context, it is important to further explore the relationships between smoking and covid-19, and to determine whether these relationships could reflect an effect of nicotine or smoke itself. Among 8910 patients hospitalized for covid-19 (low smoking rate, 6% smokers) researchers observed a greater risk of death for current smokers than non-smokers or former smoker.

Conclusions: Smoking is confirmed to be a risk factor for the negative progression of COVID-19, particularly on disease severity and death. Both current and former smokers have higher odds of disease severity than never smokers. Given the well-established harm associated with tobacco use, smoking cessation is recommended for all smokers and avoidance of second-hand smoke by non-smokers.

Keywords: *Smoking, Nicotine, Risk, COVID-19, Transmission, Mortality.*

Introduction

The challenge for studies of covid-19 is to have large enough sample sizes to allow correction for confounders, such as hypertension, diabetes, obesity, race, sex, and chronic obstructive pulmonary disease (COPD), all of which might be associated with tobacco smoking and poor outcomes. To determine the effect smoking might have on infection, it is essential that every person tested for covid-19, and for other respiratory infectious diseases, should be asked about their smoking history.. For covid-19, data are also scarce; one review did not report on smoking as a risk factor for infection, but did report an increased risk of severe disease for current smokers [1].

The sharing behavior associated with the smoking is common social habit in Middle East countries. Furthermore, due to the use of flavorings, shisha smoking leaves a pleasant smell, unlike cigarettes. It becomes more and more prevalent among the young adult and teenage population in many western countries [2]. It seems to be more socially acceptable than cigarette smoking. In Saudi Arabia, it was found that a half of high school students believe smoking shisha was less harmful than smoking cigarettes, 61% of which thought that harmful substances were purified by water filtration [2]. However, there is a substantial risk of infection with herpes, hepatitis and tuberculosis (TB) after smoking shisha. Often, shisha is smoked in large groups, rather than as individuals [3]. By sharing mouthpieces, various commensal and pathogenic organisms may be transmitted between the smokers through saliva. The risk of infectious disease also increases due to the moist nature of shisha molasses, creating an environment that promotes growth of many different microorganisms. For example, TB may grow and survive on the internal surface of the shisha pipe and water, significantly increasing risk of transmission [4, 5]. Some previous

individuals do not change the water in the shisha for each smoking session and its structure make difficult washing of all its parts, for these reasons, the pipe smokers may be exposed to different microorganisms that may be harmful to health.

Studies reported that a risk factor for transmission of hepatitis C virus in the shisha smoking community practice, because sharing the mouthpiece between individuals with gingivitis or any other type of lesion in the oral cavity makes them likely to transmit or be infected. [6, 7] Other viruses such as herpes and human papilloma viruses can be found on the surface of the lips, the lining of the mouth, on the tongue, and so on. Therefore, as an infected person places a smoking device on their lips, they simultaneously deposit viral particles on the device. They could remain there until another user places the same area of the smoking device onto their lips. When water-pipes are shared, pathogens may spread from one host to another person through interactions with the pipe or smoking materials. The water-pipe sharing behavior also creates a social context in which airborne or droplet transmission due to proximity may occur with contacts not otherwise a part of an individual's social network [8]. Associations between smoking status and confirmed covid-19 differed significantly by level of education. Odds of confirmed covid-19 were 3.5 times higher among current smokers with no post-16 qualifications than never smokers after adjustment for covariates, but they did not differ significantly by smoking status among participants with post-16 qualifications [9]. The association between smoking and worry about catching covid-19 was stronger for smokers without than those with post-16 qualifications, but there was no interaction with education for associations between smoking status and other worry/stress variables. Among smokers with

post-16 qualifications, smoking less was also associated with not being a key worker and experiencing significant stress about becoming seriously ill from covid-19 (table 5). Smoking more than usual was independently associated with being a heavy smoker (≥ 10 cigarettes per day), younger, female sex and experiencing significant stress about becoming seriously ill from covid-19 [10]. Among smokers with no post-16 qualifications, smoking more was also associated with not being a key worker, having comorbid health conditions and having confirmed or suspected covid-19. Among smokers with post-16 qualifications, smoking more was also associated with not having confirmed or suspected covid-19. Associations of smoking more with female sex and experiencing significant stress about becoming seriously ill from covid-19 were stronger for smokers without post-16 qualifications than those with. Among current smokers, we used logistic regression to analyse unadjusted and multivariable associations of socio-demographic characteristics, comorbid health conditions, confirmed/suspected covid-19, significant stress about becoming seriously ill from covid-19 and survey date with recent changes in smoking [11].

Given the unclear evidence about smoking in COVID-19 infected patients, we conducted a comprehensive review to determine the association between smoking and disease severity in COVID-19 infected patients by including all eligible studies. Systematic searching of databases for available evidence and careful definition of disease severity was performed for a rigorous summary of the conclusions.

Methods

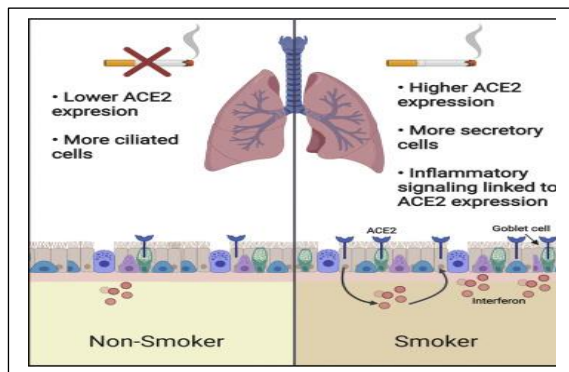
To find relevant studies, scientific databases including Embase, PubMed, Science Direct, Google Scholar and Cochrane Library databases were systematically searched from their inception to December 2021. Medical Subject Headings (MeSH) were used whenever applicable. Bibliographic lists of related articles were explored. The search strategy was carried out with the following keywords: [tobacco OR smok*] AND [covid OR coronavirus OR sars cov*] with slight adjustments depending on the database. There was no study design and language restriction. Additionally,

extra searches were performed in the reference lists of included studies to avoid missing any article. All relevant articles that reported clinical characteristics and epidemiological information on smoking among COVID-19 infected patients were included in the analysis. All articles with any design (randomized controlled trials and observational studies) were included. Animal studies, reviews, commentaries, editorials, expert opinions, letters, conference meeting abstracts, case reports, case series, systematic reviews and meta-analyses were excluded. Studies with the same participants that did not include effect estimates or had insufficient data to measure effect estimates were also eliminated. Articles with explicit involvement with the tobacco industry were excluded.

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".. 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 databases. The primary outcome was disease severity among COVID-19 patients with a history of smoking. The secondary outcome was death among COVID-19 patients with a history of smoking. The term 'disease severity' includes clinical presentations based on physical examinations and laboratory results, and other medical records, as diagnosed and described by physicians. The following information was extracted from each study: setting, region, design, sample size, demographic characteristics of participants (age, sex), details of intervention/exposure (smoking status: current or former smoker), and details of outcomes (disease severity: severe or critical vs non-severe; death), and number of COVID-19 patients. The quality of individual studies was appraised independently by two independent authors.

Results and discussion

Studies reporting a low rate of smoking have been criticized for the poor quality and retrospective collection of smoking status data, the comparison of



smoking of subjects covid-19 to smoking of the general population sometimes without taking into account sex and age and for having included only symptomatic or in-hospital subjects, creating possible selection bias. In this context, it is important to further explore the relationships between smoking and covid-19, and to determine whether these relationships could reflect an effect of nicotine or smoke itself [12]. Among 8910 patients hospitalized for covid-19 (low smoking rate, 6% smokers) Mehra et al. observed a greater risk of death for current smokers than non-smokers or former smokers (adjusted odds ratio, 1.79 [95% CI, 1.29-2.47]). According to univariable analyses, current smoking was significantly associated with covid-19 compared to former and non-smokers and subjects >50 years old were at significantly higher risk of catching covid-19. smoking status did not delay covid-19 onset, as new symptomatic infections peaked between April 6 and 8 for smokers and non-smokers. Among covid-19 patients, current smoking was associated with less frequent fever >38°C, dyspnea, coughing, myalgias, diarrheas, and headache [13].

These findings are in contrast with two systematic reviews of 19 and 47 studies of covid-19 patients which came to the conclusion that there is a significant association between smoking and progression of covid-19 amongst infected patients. This highlights that the study of the association between smoking and covid-19 morbidity and mortality is complex and requires further investigations. There are currently several pressing issues related to smoking and covid-19 that need to be resolved. First, there is a need to disentangle the risks of smoking and covid-19 morbidity and mortality. To assess the modification

effect of age and sex on the association between smoking exposure and covid-19 outcomes, we added multiplicative interaction terms to the unadjusted models [14]. In the full cohort (covid-19 naïve cohort), 224,451 (55.7%), 139,056 (34.5%), and 39,471 (9.8%) reported that they were never smoking, previous smoking and current smoking, respectively. Current smoking was associated with greater risk of covid-19 infection compared to never smoking across unadjusted and socio-demographics adjusted models. Previous smoking was similarly associated with an increased risk of covid-19 infection. There was an interaction effect of sex ($P < 0.001$) and age ($P < 0.001$) with smoking status on the risk of covid-19 infection. Smokers under the age of 69 years were nearly twice as likely to become infected with covid-19 than never smokers [adjusted IRR 1.88 (1.49-2.38)] whereas there was no differential risk associated with smoking for participants aged above 69 [15]. In the 1591 individuals who tested positive for covid-19 or had a death certificate with a covid-19 cause, the proportion of smokers was slightly different from the covid-19 naïve cohort, 771 (48.5%), 628 (39.5%) and 192 (12%) reported that they were never, previous smoking or current smoking, respectively [16]. These data suggest a smoking paradox for covid-19, with current smokers being at a lower risk for infection but at a significantly greater risk for worse outcomes. The smoking-related comorbidities (cardiovascular disease, chronic obstructive pulmonary disease [COPD]) provide the most coherent connection between smoking and covid-19 severity [17].

Clearly, measurements of the activity of RAS processing enzymes and the resultant product peptides in smoking and non-smoking patients with covid-19 would provide some guidance for pilot therapeutic studies. The possible opposing effects of nicotine on the SARS-CoV-2 infection/ morbidity axis create a strong incentive to dissect this complex relationship of smoking and covid-19 pathogenesis. By combining careful cohort phenotyping for tobacco product exposures and disease expression with informative preclinical studies, the complex relationship between smoking and covid-19 can be better elucidated and ultimately serve public health objectives [18]. 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. 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. 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. 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), in addition to the possible role of squamous cell metaplasia, which is commonly associated with smoking [19].

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. At this time, it is impossible to estimate the prevalence of smoking status among covid-19 patients in a population representative sample. A Brazilian study on 10 covid-19 patients found that both smoking and pulmonary disease increased the risk of hospitalization [20]. 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. 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 [21]. 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. 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. Smoking and comorbidities suggested mechanisms DM may aggravate the risk of severe covid-19 and mortality because it increases the surface expression of ACE2 through hyperinsulinemia, in addition to other synergistic

mechanisms. These data provide a potential model for the increased susceptibility of smoking patients to covid-19. 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. Risk factors for covid-19, such as cardiovascular disease, chronic obstructive pulmonary disease, and diabetes, are all strongly associated with smoking habits. Thus, the probability of a beneficial effect of smoking on covid-19 outcomes is manifestly unlikely [22]. This may be particularly exploited by tobacco industry to promote smoking as not only safe activity but as preventive agent from covid-19 complications [22].

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. 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 with those of covid-19 with those of covid-19, and may present for testing more frequently than non-smokers. 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 [23]. This will promote smoking cessation as a lead practice, contributing to the mitigation of the covid-19 pandemic. Similarly, an ecological study found a statistically significant negative association between smoking prevalence and the prevalence of covid-19 across the European nations, after controlling for confounding factors. However, it could not demonstrate a direct association between smoking prevalence and covid-19 mortality ($P = .626$). 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%. Furthermore, a systematic review of reviews also showed a significant association between covid-19 infection and current or ever smoking [24].

A study among 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 smoke [25]d. 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). 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 [26]. 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). 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 [27].

It is therefore likely that the true effect of smoking on covid-19 severity reported in these analyses is clouded by considerable bias. This led to the World Health Organization releasing a statement on May urging caution with regards to these claims, and emphasizing the lack of evidence confirming a link between smoking or nicotine in the prevention or treatment of covid-19 [28]. Consequently, there remains a distinct lack of clarity and high-quality evidence regarding the relationship between smoking and the severity of covid-19. Our finding that current smoking is associated with increased disease severity in covid-19 patients validates previous findings from several smaller meta-analyses in a much larger patient population, achieved through a more rigorous, prospectively registered methodology.

Conclusions

Smoking is confirmed to be a risk factor for the negative progression of COVID-19, particularly on disease severity and death. Both current and former smokers have higher odds of disease severity than never smokers. Given the well-established harm

associated with tobacco use, smoking cessation is recommended for all smokers and avoidance of second-hand smoke by non-smokers. Well-designed longitudinal population-based studies are needed to address questions about the risk of infection by SARS-CoV-2 and the risk of hospitalization with COVID-19. Stronger evidence coming from smoking status data that are systemically recorded and analyzed among COVID-19 patients are needed. Some factors such as number of cigarettes smoked, nicotine addiction level, and the length of time after quitting until COVID-19 infection should be collected.

Conflict of interests

The authors declared no conflict of interests.

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