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Review article

Tobacco use as a well-recognized cause of severe COVID-19 manifestations

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ABSTRACT

Introduction: The Coronavirus disease (COVID-19) infection is caused by the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) primarily affecting the lungs. All tobacco-related illnesses including asthma, chronic obstructive pulmonary disease (COPD), and coronary artery disease are known to reduce the lung capacity and impair the immune system of the body and can greatly influence the ability to fight the novel coronavirus. The purpose of this state-of-the-art literature review is to summarize the evidence of the association of tobacco use with the severity of the COVID-19 manifestations.

Method: Articles describing the association of tobacco use with the severity of COVID-19 manifestations were searched on PubMed, MEDLINE, and Google. This review covers the relevant studies on the subject published from January 1, 2020 to September 10, 2020.

Results: Tobacco use in all forms, whether smoking or chewing, is significantly associated with severe COVID-19 outcomes. Pre-existing comorbidities in tobacco users such as cardiovascular diseases, diabetes, respiratory diseases and hypertension were found to further aggravate the disease manifestations making the treatment of such COVID-19 patients more challenging due to their rapid clinical deterioration.

Conclusions: Current review indicates that nicotine exposure is linked to cardiopulmonary vulnerability to COVID-19 and tobacco use can be a potential risk factor for not only getting the viral infection but also its severe manifestations. The current pandemic provides a teachable moment to break the cycle of nicotine addiction and accelerate national tobacco control programs to achieve a tobacco-free world.

1. Introduction

Tobacco is a prime cause of potentially preventable global morbidity and mortality, leading to about 8 million deaths in a year, mainly due to lung and heart diseases [1]. Low and middle-income countries have 80% of the world's 1.3 billion tobacco users, many of whom are reeling under the heavy burden of tobacco-related illness and death [2]. 71% of all lung cancer deaths and 42% of chronic obstructive pulmonary disease (COPD) and 10% of cardiovascular disease are attributable to tobacco use [3].

Tobacco products are found to contain about 4000 toxic chemicals with 36 known carcinogens [4,5]. They mainly include tobacco-specific nitrosamines, volatile aldehydes, polycyclic aromatic hydrocarbons, pesticides, and heavy metals [6]. Due to non-standardization and heterogeneity in formulation and packaging, a diverse variety of tobacco products both smoking and smokeless, are available in the market [7]. Smokeless tobacco (SLT) mainly includes chewing tobacco, in the form of loose-leaf, plug or twist, snus, snuff, and dip [8]. Electronic nicotine delivery systems (ENDS) are battery operated non-combustible products, designed for direct nicotine delivery to the lungs. Newer variants of ENDS like electronic cigarettes, vaping devices, hookah pens, or vape pens have now flooded the market and all of them contain many toxicants including highly addictive nicotine [9,10]. Tobacco smoke is known to induce and alter immune responses in the lungs, triggering inflammation, allergy, asthma, and other lung diseases [11]. Nicotine constricts blood vessels and limits the amount of blood flows to internal organs. It also stimulates the sympathetic nervous system by increasing the levels of catecholamines leading to increased heart rate and stroke volume in the user [1]. Cigarette tar, produced during the burning of tobacco, can paralyze and eventually kill cilia in the lungs or reduce the

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contact surface area between oxygen and pulmonary capillaries, thereby decreasing the capacity of the arteries to transport oxygenated blood [12]. Carbon monoxide, a by-product of incomplete carbon combustion, has a hemoglobin-binding affinity 200 times higher than that of oxygen, which diminishes the oxygen-carrying capacity of the blood [13].

The novel SARS-CoV-2 virus is mainly known to affect lungs and induces severe acute respiratory syndrome in humans [14] and is highly contagious infecting nearly 31 million people in a short span of time causing more than 9,61,733 deaths worldwide [15]. The entire human race is reeling under tremendous pressure as there is no known treatment or vaccine for the COVID-19 yet and limited knowledge on its pathogenesis due to the lack of long-term data [16].

2. Methodology

2.1. Electronic searches

An extensive literature search was performed in September 2020, the strategy for which is depicted in Fig. 1. The period included for this search was from January 1, 2020 to September 10, 2020, and was done on PubMed, MEDLINE and Google using a combination of key words, such as tobacco, smoking, COVID-19, Coronavirus disease-19, SARS-CoV-2.

2.2. Selection of studies

Two authors (AKG, STN) independently extracted data through this literature search, identified studies, and assessed their eligibility. Titles and abstracts of papers identified through the search strategy were reviewed and articles potentially fulfilling the inclusion criteria were retrieved in full text.

2.3. Inclusion criteria

All original study types (i.e. randomized control trials, case-control studies, cohort studies) published in full-text and primarily aimed at discussing the association of tobacco use with the severity of COVID-19 outcomes, and those written in English were included.

2.4. Exclusion criteria

Studies that did not fulfil all the inclusion criteria i.e. with differing and/or contradictory objectives/results; providing incomplete information; reviews, letters to editors or commentaries; repetition of the same data; or those not written in English, were excluded.

3. Results

As shown in Fig. 1, a total of 398 published articles were found in the initial literature search, among which screening of records was done from 356 articles after removing duplicates and 42 articles were assessed for eligibility; the final 23 studies were included in the current review.

Most studies indicated that COVID-19 patients with COPD or smokers have an increased expression of ACE2 in bronchial epithelial cells in the respiratory tract as compared with healthy subjects [17–23]. As nicotine, present in tobacco products, acts on nicotinic acetylcholine receptors (nACE), it can possibly, promote SARS-CoV-2 entry and

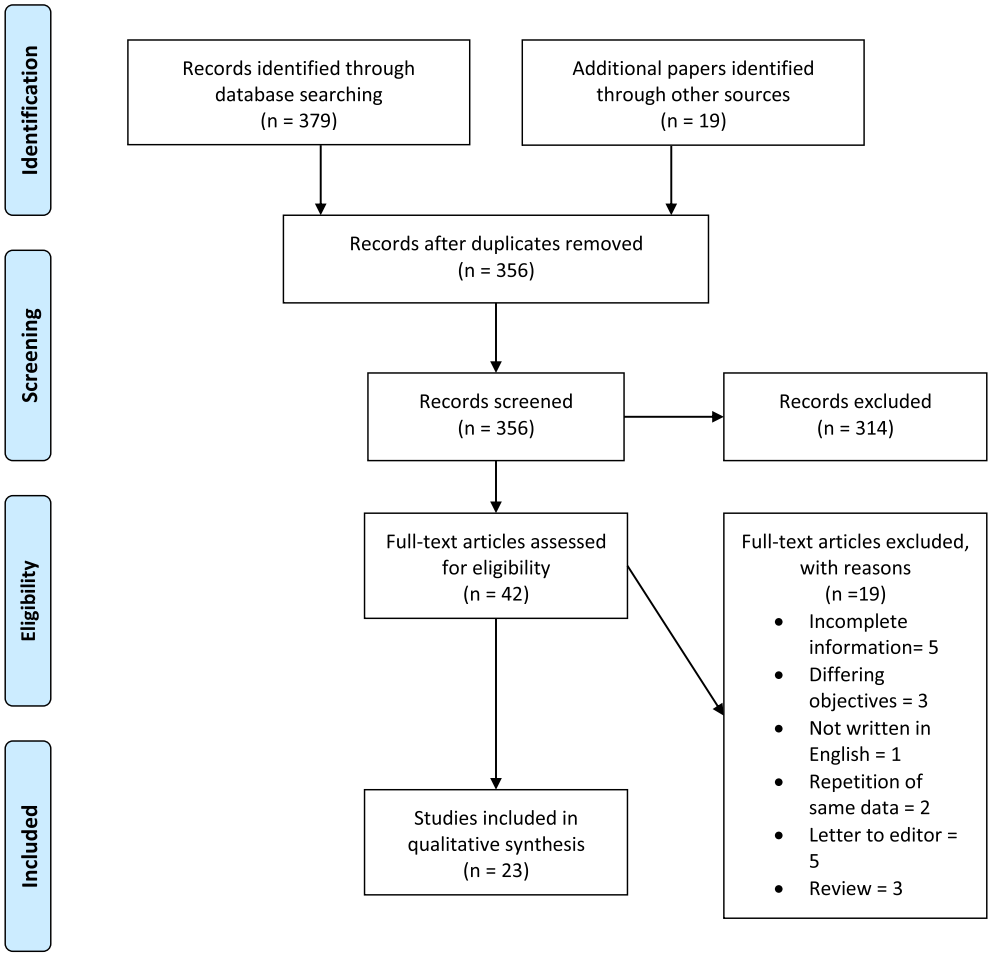

Fig. 1. Search strategy flow-chart.

proliferation in epithelial cells through co-expression of ACE2 [24]. Smoking status was found to increase the majority of COVID-19 related genes in the lower airways, which was associated with a significant increase in the predicted proportion of goblet cells in bronchial samples of smokers [25]. Smoking-mediated upregulation of the androgen pathway also leads to an increased SARS-CoV-2 susceptibility [26]. Acute smoke exposure allows for more severe proximal airway epithelial disease from SARS-CoV-2 by reducing the mucosal innate immune response and ABSC proliferation and has implications for disease spread and severity in people exposed to cigarette smoke [27]. The radiological manifestation of COVID-19 is mainly peripheral ground-glass opacity while age, smoking and hypertension were used to predict the severity of COVID-19 disease [28].

A cross-sectional, observational follow-up for 284 COVID-19 infected persons indicated that multiple comorbidities are closely related to the severity of COVID-19 disease progression and the higher mortality rate was seen in smokers as compared with healthy patients [29]. A study on 10,713 COVID-19 patients in Espírito Santo State, Brazil, reported that older age, male gender, Asian, indigenous or unknown race, comorbidities like smoking, kidney disease, obesity, pulmonary disease, diabetes, and cardiovascular disease, as well as fever and shortness of breath, increased the risk of hospitalization and mortality due to COVID-19 [30]. A retrospective review of three studies done at a different time at Wuhan, China showed that old age and smoking were the major covariates associated with the risk of in-hospital death in persons with COVID-19 [31–33].

A study in Iran showed that among 193 confirmed COVID-19 patients, more than half of cigarette smokers and 40% of waterpipe smokers reported their COVID-19 symptoms as severe compared to 22% of never-smokers [34]. In a retrospective study, an observational cohort study of 112 in-patient adults, diagnosed with COVID-19, between March 12 and April 16, 2020, in Los Angeles, smoking history along with obesity and elevated inflammatory markers was associated with an increased need for invasive mechanical ventilation in patients with COVID-19 [35]. Another retrospective cohort study, conducted between February 24, 2020 and April 20, 2020 in Kuwait indicated that asthma, smoking and elevated procalcitonin levels correlated significantly with mortality in COVID-19 patients [36]. A study of critically ill 59 covid-19 patients, hospitalized in ICU in Japan, clearly predicted that patients with older age and smoking history have a higher incidence of multiple organ injuries, more deteriorative lymphopenia and thrombocytopenia, remarkably impaired cellular immune response, and strengthened cytokine release [37]. A community-based cohort study of 387,109 adults in the UK reported smoking as a lifestyle risk factors for cardiovascular disease in relation to covid-19 hospitalization [38], however, smokers have reported to have a lower adherence to WHO recommendations to prevent the spread of the virus [39].

4. Discussion

4.1. Role of ACE2 receptors in COVID-19 severity in tobacco users

COVID-19 infections begin at the ACE2 receptor, a neurotransmitter protein present on the surface of the cells and tissues in the lungs, heart, blood vessels, kidneys, liver, intestines, and epithelial cells in the upper and lower respiratory tracts [40]. ACE2 is a critical mediator of the renin-angiotensin system (RAS) signaling throughout the body and its dysfunction leads to critical congestive heart failure, acute lung disease, and cardiorenal metabolic syndrome [41] which closely resemble the symptoms associated with SARS-CoV-2 infection [42]. Nicotine is known to disrupt the homeostasis of the RAS in multiple organs, which can lead to the development of cardiovascular and pulmonary diseases [43].

Because a SARS-CoV-2 virus contains spike-like coat proteins, it can plug into human ACE2 receptors, inject its genetic material, replicate itself, rupture the host cell, then spread further [44]. Lungs exposed to cigarette smoke are shown to accumulate abnormally large numbers of ACE2 receptors in the human respiratory tract, making it more vulnerable to damage [45,46]. Thus, prolonged active tobacco use can provide a cellular mechanism for viral susceptibility and disease severity during the course of the infection in the lungs [47,48]. The viral entry in the human body has been shown to cause a 'cytokine storm' involving elevated levels of inflammatory cytokines which get augmented in smokers [49]. Smokers infected with COVID-19 are seen to have more severe infections than individuals who are non-smokers mainly due to an increased risk for the virus binding and entry into the lungs of tobacco users [50–54].

Based on the hypothesis that SARS-CoV-2 virus is a nicotinic agent which competes with nicotine for the receptor, some studies from France, have alarmed the public health community by reporting that smoking or nicotine products could reduce the risk of COVID-19 infections [55] and daily smokers could have a lower probability of developing symptomatic or severe SARS-CoV-2 infection [56]. But these studies were found inconsistent with the broader emerging literature on the links between smoking and COVID-19. The main limitation of these studies was the potential of under-reporting of smoking history among COVID-19 patients.

Possibly, an exogenous supplement of recombinant human (Rh) ACE2 in soluble form might be utilized in the prevention and treatment of COVID-19 as ACE2 may act as the bait to neutralize the spike protein on the surface of the SARS-CoV-2 [57].

4.2. Tobacco use in the vulnerable population, including adolescents

Pre-existing comorbidities in tobacco users such as cardiovascular diseases, diabetes, respiratory diseases, and hypertension are found to further aggravate the disease manifestations [58–60]. Being an important immune modulator, tobacco significantly suppresses the immune system by reducing antibody responses and T-cell proliferation, thereby increasing the susceptibility of tobacco users towards acute viral infections [61]. A population vulnerability analysis done in Europe indicated that elderly people and those with low immunity are at higher risk of developing severe health consequences from COVID-19 [62]. Severe COVID-19 infection causes critically low levels of blood oxygen (i.e. hypoxemia) due to damage and inflammation of the alveoli in the lungs and they are unable to transfer oxygen to the small blood capillaries [63]. This severe decrease in oxygen saturation occurs without any visible symptoms of hypoxia and causes rapid deterioration of the patient's clinical condition. The elevated level of hemoglobin is found to be a strong predictor of acute respiratory distress syndrome (ARDS), a severe outcome in COVID-19. Thus, a patient with pre-existing COPD mortality rate is four times greater than for a normal COVID-19 patient, smoking increases the chances of death from COVID-19 by a staggering 80%. Smokers were 1.4 times more likely to have severe symptoms of COVID-19 and 2.4 times more likely to be admitted to an ICU, requiring mechanical ventilation, or to die compared to non-smokers. Thus, all tobacco-related ailments viz. asthma, COPD, and coronary artery disease are known to reduce the lung capacity, impair the immune system of the body and thereby greatly hinder the ability to fight the coronavirus, SARS-CoV-2 [64,65]. The risk of tobacco users being infected by SARS-CoV-2 or requiring hospitalization needs more detailed well-designed population-based studies taking into consideration the age, history of tobacco use and underlying risk factors, there is clear evidence to indicate that smoking is associated with the severity of disease and death in hospitalized COVID-19 patients [66].

Adolescents are highly vulnerable to tobacco addiction [67]. The COVID-19 pandemic can adversely affect the vulnerable population who can take up smoking as a sort of mental health 'therapy' to relieve depression and anxiety associated with the social isolation resulting from extended quarantine [68]. Smoking when co-occurs with mental illness or any other addictive disorder can make a young person more vulnerable to the potential for a gateway effect. Smoking is viewed as a

means of reversing negative mood, anxiety, and irritability associated with nicotine withdrawal [69].

Epidemiological data show that SARS-CoV-2 is highly infectious and its' transmission route and mode are largely unknown due to virus mutation and other factors [70]. SARS-CoV-2 can spread through human-to-human transmission by direct means i.e. small droplets from the nose or mouth, which are spread when an infected person coughs or exhale [71,72] or by indirect contact with contaminated objects and airborne contagion where the virus can survive for a few hours to several days [73]. Smokers have a higher risk of getting coronavirus because they are constantly putting their hands to their lips while tobacco chewers often touch their mouths with their fingers during product use [74]. Smoking products such as water pipes often involve the sharing of mouthpieces and hoses, which could facilitate the transmission of COVID-19, especially in communal and social gatherings [75]. Cigarette and bidis butts are often discarded in open after use can also be a means of virus transmission. Chewing tobacco products, paan masala and areca nut (supari) increase the production of saliva followed by a very strong urge to spit and the virus can be spread when the user spits out the excess saliva produced during the chewing process [76].

In the current scenario, depression from the mental health burden due to social isolation, work from home, and fear of job loss may become a cue to revert to smoking especially in young population [77]. Anxio-depressive disorders or post-traumatic stress disorder during COVID-19 can be the cause of an increase in tobacco consumption or a relapse of smoking after smoking cessation [78,79]. Some reports show that during the COVID-19 pandemic, sale of pharmaceutical preparations of nicotine replacement therapies (NRTs), including gum, lozenges, patches, nasal sprays, mouth sprays, and inhalers, is seeing an increase [80].

4.3. Right time to quit tobacco

Many countries in the world are fighting against the global tobacco epidemic and a recent WHO report states that substantial progress has been made in developing evidence-based and cost-effective tobacco control strategies over the last decade [81]. The banning of public smoking; prohibition of tobacco product advertising, promotion, and sponsorship, display of warnings on product packaging; and increasing product prices and taxes have reduced the affordability and availability of tobacco products to the general public. All of these efforts have significantly contributed to a reduction in demand for tobacco products and have also increased awareness among existing tobacco users and also their intention to quit [82]. However, only 30% of the world's population has adequate cessation support available at the present time [81], so there is an urgent need for suitable training of health practitioners, as it is anticipated that the number of patients motivated to tobacco cessation may increase after COVID-19 pandemic [83]. At the same time, it becomes even more important for the government and the public to be more watchful about tobacco industry gimmicks as big tobacco and e-cigarette companies are exploiting the COVID-19 crisis to sell their addictive products on social media especially luring youngsters.

Given the adverse effect on respiratory health, the COVID-19 pandemic could serve as a message to all tobacco users (both smokers and chewers) to quit promptly and take immediate action to reduce their risks of viral transmission [84]. The crisis should be seen as a blessing in disguise for tobacco users. The increased control and scrutiny of the movement of goods and people at this time could make tobacco cessation easier at this time [85]. While the effects of smoking can last for years, the benefits of quitting tobacco begin almost immediately. Within 24 h of quitting, the body starts to recover and repair tobacco-related damage. The act of quitting smoking leads to a normalization of respiratory epithelial architecture as cilia in the lungs and the airways improve as mucus and debris are cleared. Lung function improves and respiratory symptoms of chronic bronchitis, such as chronic cough, mucus production, and wheezing decrease rapidly. Also, among people with asthma or COPD symptoms become less severe. These benefits become obvious within months of quitting and the improvement is sustained with long-term abstinence. Primary care doctors and other healthcare workers need to play their role in public health by helping the tobacco-dependent population to quit [86,87]. The use of proven interventions such as toll-free Quitline, mobile text-messaging cessation programs, and NRTs should be encouraged for quitting tobacco use alongside COVID-19 public health programs amid the pandemic crisis.

5. Conclusions

There is a very close association between tobacco use and severe COVID-19 manifestations. As nicotine exposure is linked to cardiopulmonary vulnerability to COVID-19, tobacco use could be a potential risk factor for, not only contracting the viral infection but also making the treatment of such COVID-19 patients more challenging. Hopefully, the COVID-19 pandemic could just prove to be the game-changer and a teachable moment that we have been waiting for, to ultimately achieve a tobacco-free world.

Credit author statement

Alpana K. Gupta (AKG): Conceptualization, Writing- Original draft preparation and Reviewing.
Suzanne T. Nethan (STN): Reviewing and Editing.
Ravi Mehrotra (RM): Writing- Reviewing and Editing.

Declaration of competing interest

Authors Dr. Alpana K Gupta, Dr. Suzanne T Nethan and Dr. Ravi Mehrotra hereby state that they have no conflict of Interest regarding the submitted manuscript entitled " Tobacco Use: A Potential Risk Factor for Severe COVID-19 Manifestations".

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