

Smoking Enigma in Coronavirus Disease 2019: A Tug of War between Predisposition and Possible Way Out

Nadira Naznin Rakhi¹ and Ritu Biswas

Department of Biotechnology and Genetic Engineering, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj-8100, Bangladesh.

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ABSTRACT

BACKGROUND: The recent global inclination for smoking during the Coronavirus Disease 2019 (COVID-19) pandemic has drawn attention to the impact of smoking on COVID-19. While smoking increases susceptibility to common respiratory pathogens including the closely related coronaviruses, COVID-19 causing Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2) being a respiratory pathogen intrigues the possible association between smoking and viral pathogenicity.

SMOKING AND COVID-19: The gender dependence of COVID-19 infection rates and a higher prevalence of smokers among males made the scientific world assume smoking to be a confounding variable in sex predisposition to COVID-19. Conversely, the controversial findings of discrepant morbidity and mortality rates of COVID-19 among smokers questioned the credibility of this hypothesis. More importantly, nicotine in smoking has been hypothesized to downregulate Interleukin-6 (IL-6) which plays a role in COVID-19 severity and to interfere with the Angiotensin-Converting Enzyme 2 (ACE2), the receptor of SARS-CoV-2 led the scientists to experiment nicotine patch prophylactically against COVID-19. Besides, interaction between spike protein and nicotinic acetylcholine receptors (nAChRs) supports the nicotinic cholinergic system dysregulation hypothesis in COVID-19 pathophysiology leading to its therapeutic use. However, despite the contradictions in the direct impact of smoking, it surely acts as fomites for viral transmission.

CONCLUSION: Irrespective of the role nicotine in COVID-management, compassionate use of smoking against SARS-CoV-2 cannot be recommended until the therapeutic value gets proved and therapeutic form becomes available.

KEYWORDS: Smoking, nicotine, COVID-19, SARS-CoV-2, Angiotensin-Converting Enzyme 2, nicotinic acetylcholine receptor

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CORRESPONDING AUTHOR: Nadira Naznin Rakhi, Lecturer, Department of Biotechnology and Genetic Engineering, Bangabandhu Sheikh Mujibur Rahman Science and Technology University, Gopalganj 8100, Dhaka, Bangladesh. Email: nadiranrakhi@gmail.com

Background

The inertia effect of Coronavirus Disease 2019 (COVID-19) management is raising concerns globally, which is now noticeably reflected in the behavioral response to the pandemic along with global public health and economy. Even relapse of smoking among the ex-smokers has already been spiked in the United Kingdom along with a higher inclination to smoking among the current smokers.¹ But this trend urges immediate attention, as the significant correlation between smoking and higher incidences of diverse respiratory diseases such as colds, influenza, pneumonia, tuberculosis², and even lung cancer³ intrigues the possible effects of smoking on COVID-19 susceptibility. Besides, exposure to tobacco smoke was found to reduce the innate immunity of respiratory cells to other respiratory viral pathogens such as rhinovirus and influenza, especially H1N1.^{4,5} On top of that, the mortality rate was noticed higher among smokers during the previous outbreak of Middle East respiratory syndrome-related coronavirus (MERS-CoV), the close relative to COVID-19 causing Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2).⁶ So, the current literature available on this association was investigated to determine the role of smoking in COVID-19.

Mortality and morbidity of COVID-19 among smokers

Earlier research claimed that the risk of COVID-19 severity is higher among both current and former smokers compared to non-smokers (Odds Ratio = 14.2 CI 1.57-24, $P = .018$).⁷ Also, the gender bias in COVID-19 infection in China was partially explained by the fact that the rate of smoking is higher among males (48%) than females (3%).⁸ However, despite the insufficient data, the effect of smoking on the mortality rate of COVID-19 has mostly been denied since the beginning.⁹ On the other hand, the recent meta-analyses on risk assessment are conjecturing of no significant impact of smoking on COVID-19 severity and mortality,^{10,11} while the other recent meta-analyses reported that smokers being hospitalized with COVID-19 showed higher odds for adverse outcomes.^{12,13} However, the prevalence of current or former smokers among the COVID-19 patients is so far strikingly lower than the population smoking rates in either China, Israel, USA, or Italy.¹⁴⁻¹⁶ Even Evidence showed that 72.2% of the SARS-CoV-2 negative test results came from individuals with smoking history rather never smokers.¹⁷



Possible protective potential of nicotine against COVID-19

Nicotine in tobacco and cigarette showed promising results in preventing lung injury in an animal Acute Respiratory Distress Syndrome (ARDS) model¹⁸ along with developing in vivo anti-inflammatory response in humans exposed to endotoxins.¹⁹ Moreover, nicotine was reported to inhibit the production of pro-inflammatory cytokines, including TNF, IL-1, IL-6 without disrupting the production of anti-inflammatory IL-10,^{20,21} while elevated IL-6 has recently been introduced as the mortality indicator among COVID-19 severe cases.^{22,23} So, nicotine can be of therapeutic potential in counterbalancing cytokine storm produced in response to SARS-CoV-2 by an increased release of pro-inflammatory cytokines such as Interleukin-6 (IL-6), which enhances vascular permeability thus migration of fluid and blood cells into the alveoli resulting into dyspnea and respiratory failure.²⁴ On the other hand, nicotine has been hypothesized to block the docking site of Angiotensin-Converting Enzyme 2 (ACE 2), the receptor of SARS-CoV-2 preventing viral entry into the host cell thus lowering susceptibility to SARS-CoV-2.^{25,26} So, the French researchers have planned to examine the nicotine patch as prophylaxis for COVID-19.²⁷ But interestingly, the protective effect of nicotine by blocking ACE2 was controverted by the observation that dysfunction of ACE2 regulated renin-angiotensin system (RAS) pathway can result in congestive heart failure, acute and chronic lung diseases, and cardiorenal metabolic syndrome, which coincided with COVID-19 related complications.²⁸⁻³⁰

The regulation of ACE 2 expression has been the other contradictory fact in literature with reports of down-regulation of ACE 2 before the pandemic,^{31,32} but up-regulation during COVID-19 pandemic,^{33,34} which makes the prediction of its role in both pathogenesis and treatment of COVID-19 more difficult at this stage. However, the study reporting the highest ACE2 expression among current smokers and even elevated expression among recent former smokers (≤ 15 years) compared to nonsmokers advocated in support of increased COVID-19 susceptibility among smokers through receptor mediated cellular entry.³⁴ But paradoxically, other studies reported that ACE 2 prevented ARDS development in mice and also an enhanced damage to the lungs of ACE2 knockout mice by smoking, which possibly suggests its role in defense mechanism.^{35,36} Nevertheless, the correlation between the up-regulation of ACE 2 and increased COVID-19 susceptibility or severity has yet not been proved.

However, the hypothesis of the nicotinic cholinergic dysregulation in COVID-19 pathophysiology suggests the therapeutic potential of nicotine considering COVID-19 as the consequence of the immunological response to viral invasion and failure to restore the immune homeostasis and the function of the cholinergic anti-inflammatory pathway through direct

interaction between SARS-CoV-2 spike protein and nicotinic acetylcholine receptors (nAChRs) rather than the cellular entry of SARS-CoV-2 through ACE 2.³⁷ So, according to this proposed mechanism, nicotine can be administered prophylactically to control the cytokine storm by blocking nAChRs, particularly $\alpha 7$ nAChRs from interacting with SARS-CoV-2 causing the restoration of the function of the nicotinic cholinergic system,³⁸ while the cholinergic anti-inflammatory pathway is considered an important regulator of the inflammatory response contributing in the control of immune dysregulation and cytokine storm which play major roles in COVID-19 severity.^{39,40}

Indirect negative impacts of smoking in COVID-19 susceptibility

Although we will have to wait longer to answer if smoking has a direct effect on COVID-19 pathophysiology, the human genome sequencing and analyzing initiative by Genomics England and the GenOMICC (Genetics of Mortality in Critical Care) consortium targeting initially 35 000 COVID-19 patients may offer an unprecedented insight into the interaction between nicotine thus smoking and SARS-CoV-2.⁴¹ But it has been evident that contaminated cigarettes, electronic devices, waterpipes (commonly known as hookahs) or marijuana cigarettes can act as fomites (vector) for the transmission of SARS-CoV-2 increasing the chance of getting infected through the mouth while smoking or “vaping.”⁴² Besides, tobacco use and exposure to second-hand smoke lead to cardiovascular damage⁴³ which is directly associated with COVID-19 severity.⁴⁴ Moreover, tobacco smoke also impairs defense mechanisms of the respiratory system, cellular and humoral immunity and non-specific defense mechanisms such as mucociliary clearance mechanism, while it produces inflammation as well increasing the susceptibility to diverse diseases.⁴⁵

Conclusion

The health consequence of nicotine and smoking is long established in developing disease severity, especially in case of respiratory diseases, while some recent studies showed the therapeutic potential of smoking. But, even if nicotine gets proved to be effective against SARS-CoV-2, public health advocacy in favor of smoking for recreational use can never be recommended.

Author Contributions

NNR wrote the manuscript and supervised the whole work, while RB helped in manuscript drafting and literature mining.

ORCID iD

Nadira Naznin Rakhi  <https://orcid.org/0000-0003-2253-7071>

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