COVID-19 and smoking

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COVID-19 is mainly a disease of the respiratory tract characterized by a severe acute respiratory syndrome; the causative agent is SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2). The virus main entrance way is through mucosal tissues: nose, mouth, upper respiratory tract and less frequently conjunctival mucosa. Tobacco smoke exposure results in inflammatory processes in the lung, increased mucosal inflammation, expression of inflammatory cytokines and tumor necrosis factor α ([TNF]-α), increased permeability in epithelial cells, mucus overproduction and impaired mucociliary clearance (1). Knowledge about host factors, and in particular avoidable host factors such as smoking, may be of importance in reducing viral contamination and the severity of the disease.

The SARS-CoV-2 pandemic started in Wuhan, China towards the end of 2019. To the best of our knowledge, 6 published case series reported the prevalence of smoking among individuals with COVID-19 (Table 1). The study with the highest number of patients compared severe (N=173) to non-severe (N=926) cases. The percent of current and former smokers were higher among the severe cases: 17% and 5%, respectively, than among the non-severe cases (12%, and 1%, respectively) (2). More importantly, among those with the primary composite end point (admission to an intensive care unit, the use of mechanical ventilation, or death), the proportion of smokers was higher with than among those without this end point (26% vs 12%) (2). Another case series also showed more smokers among the severe (N=58) than among the non-severe (N=82) cases (3). The single modifiable host factor associated with progression of COVID-19 pneumonia was current smoking in a multivariable logistic analysis (OR = 14.3, 95% CI: 1.6 to 25.0) (4). Among those who died the number of smokers was also been found to be somewhat higher (9%, 5/54)) than among survivors (6%, 9/137) (5).

Vardavas and Nikitara's recent systematic review (8) identified 5 studies (2, 3, 4, 5, 6) and concluded that "smoking is most likely associated with negative progression and adverse outcomes of COVID-19". Conversely, Lippi and Henry's short meta-analysis reported no association of smoking status with severity of COVID-19 (9). However, the number of cases in most studies to date is very low, and consequently the 95% CIs very wide.

These case series reports are descriptive and do not allow to draw firm conclusions about the association of severity of COVID-19 with smoking status. Underlying health conditions such as COPD, diabetes, coronary heart disease are more prevalent among severe cases (2, 5). Although these can causally be associated with smoking, the specific effect of smoking on COVID-19 severity cannot be disentangled.

However, the nicotine and tobacco research and health care community cannot ignore these signals. We know that tobacco smoke exposure is a major risk factor for lung disease (1) and cigarette smoking is a substantial risk factor for bacterial and viral infections (10). In addition, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) that caused a small coronavirus epidemic in 2012-215 presented the same clinical features as the current COVID-19, and reports also indicated an association between smoking status and fatality rate (11), with current smoking also more frequent among cases than among controls (37% vs 19 %, OR=3.14, 95% CI 1.10 to 9.24, N=146) (12).

MERS-CoV infection involves the dipeptidyl peptidase IV (DPP4) receptor while SARS-CoV-2 involves the ACE2 receptor (angiotensin II conversion enzyme-2 receptor). Both are abundant in mucosal epithelial cells and lung alveolar tissue and have multiple physiological functions. To infect the host, both viruses attach to its receptor: MERS-CoV to DPP4 and SARS-CoV-2 to ACE2, a probably key step for coronavirus infections.

DPP4 mRNA and protein expressions are significantly higher in smokers compared to never smokers without airflow limitation and are inversely correlated with lung function (13). It has recently been reported that *ACE2* gene expression is higher in ever smokers (both current and former) compared to never smokers in normal lung tissue in a sample of patients with lung adenocarcinoma, after adjustment for age, gender and ethnicity. *ACE2* gene expression was also higher in small and large airway epithelia of healthy ever smokers compared to never smokers: current smokers had the highest expression, never smokers had the lowest expression; recent former smokers (≤15 years) had higher *ACE2* gene expression than non-smokers but not long-term former smokers (>15 years) (14).

The similar upregulation associated with smoking of two different virus receptors observed with two different coronaviruses suggests that smoking contributes to the higher number of viral receptors and may support the findings of the recent case series observations.

It is also worth noting that smoking behavior is characterized by inhalation and by repetitive hand-to-mouth movements which are strongly advised against to reduce viral contamination. Public health interventions, such as lockdown, may increase the exposure of family members to secondhand smoke. Lockdown may be an opportune moment to quit to reduce not only the smoker's health risk but also that of his/her family members. Finally, risk factors of COVID-19 severity (lung and cardiovascular disorders, diabetes etc.) are more frequent among smokers. Smoking cessation by any means should be a priority among smokers with comorbidities.

Future research directions

The nicotine and tobacco research community should explore the role of tobacco and in the current COVID-19 pandemic. We need stronger evidence about the association of smoking with COVID-19. Databases should be identified and analyses focused on the role of this association in virus contamination, severity of the illness, ability to recover, and so on. Smoking status data should be systematically recorded and analyzed among COVID-19 patients. We need data about the immediate and short-term benefit of quitting smoking among symptomatic COVID -19 smokers. Laboratory studies should focus on quantifying the viral contamination of tobacco products with particular attention to shared products such as waterpipes. We also need data about alternative nicotine delivery systems and their risk/benefit ratio in relation to COVID-19.

Public health challenges/opportunities

We suggest that ongoing public health campaigns should include reference to the importance of smoking cessation during the pandemic. Healthcare providers should be involved in

offering evidence-based pharmacological and behavioural smoking cessation interventions by remote support. Quit lines should promote contacts with smokers with or without COVID-19, symptomatic or asymptomatic. Lockdown may result in social isolation and mental distress both increasing the need for smoking; smoking is more prevalent among economically less-advantaged groups, and they are potentially at higher risk for COVID-19. Large scale interventions should be targeted at these populations in particular.

References

1. Strzelak A, Ratajczak A, Adamiec A, Feleszko W. Tobacco smoke induces and alters immune responses in the lung triggering inflammation, allergy, asthma and other lung diseases: A mechanistic review. *Int J Environ Res Public Health*. 2018;15(5):1033. Published 2018 May 21. doi:10.3390/ijerph15051033

2. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of coronavirus disease 2019 in China [published online ahead of print, 2020 Feb 28]. *N Engl J Med*. 2020;10.1056/NEJMoa2002032. doi:10.1056/NEJMoa2002032

3. Zhang JJ, Dong X, Cao YY, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China [published online ahead of print, 2020 Feb 19]. *Allergy*. 2020;10.1111/all.14238. doi:10.1111/all.14238

4. Liu W, Tao, ZW, Lei W, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chinese Medical Journal*: February 28, 2020 - Volume Publish Ahead of Print - Issue -doi: 10.1097/CM9.0000000000000775

5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published online ahead of print, 2020 Mar 11] [published correction appears in Lancet. 2020 Mar 12;:]. *Lancet.* 2020;S0140-6736(20)30566-3. doi:10.1016/S0140-6736(20)30566-3

6. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:]. *Lancet.* 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5

7. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study [published online ahead of print, 2020 Feb 24] [published correction appears in Lancet Respir Med. 2020 Feb 28;:]. *Lancet Respir Med*. 2020;S2213-2600(20)30079-5. doi:10.1016/S2213-2600(20)30079-5

8. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. *Tob Induc Dis*. 2020 Mar 20;18:20. doi: 10.18332/tid/119324. eCollection 2020.

9. Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). *Eur J Intern Med*. 2020 Mar 16:S0953-6205(20)30110-2. doi: 10.1016/j.ejim.2020.03.014. Online ahead of print.

10. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med. 2004;164(20):2206–2216. doi:10.1001/archinte.164.20.2206

11. Nam HS, Park JW, Ki M, et al.. High fatality rates and associated factors in two hospital outbreaks of MERS in Daejeon, the Republic of Korea. *Int J Infect Dis*. 2017;58:37–42. doi:10.1016/j.ijid.2017.02.008

12. Alraddadi BM, Watson JT, Almarashi A, et al. . Risk factors for primary Middle East Respiratory Syndrome Coronavirus illness in humans, Saudi Arabia, 2014. *Emerg Infect Dis*. 2016 Jan;22(1):49-55. doi: 10.3201/eid2201.151340.

13. Seys LJM, Widagdo W, Verhamme FM, et al. DPP4, the Middle East Respiratory Syndrome Coronavirus Receptor, is upregulated in lungs of smokers and chronic obstructive pulmonary disease patients. *Clin Infect Dis*. 2018;66(1):45–53. doi:10.1093/cid/cix741

14. Cai G. Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ACE2, the receptor of 2019-nCov. *medRxiv* 2020.02.05.20020107; https://doi.org/10.1101/2020.02.05.20020107; Posted February 28, 2020

Table 1. Frequency of smoking and former smoking among COVID-19 patients. N (%)

Guan et al. (2)	Nonsevere, N=926	Severe, N=173	Primary Composite End Point (admission to an intensive care unit, the use of mechanical ventilation, or death)
Never smoked	793/913 (86.9)	134/172 (77.9)	Yes 44/66 (66.7%) No 883/1019 (86.7%)
Former smoker	12/913 (1.3)	9/172 (5.2)	Yes 5/66 (7.6%) No 16/1019 (1,6%)
Current smoker	108/913 (11.8)	29/172 (16.9)	Yes 7/66 (25.8%) No 120/1019 (11.8%)
Zhang et al. (3) Hospitalized for COVID-19	Nonsevere, N=82	Severe, N=58	
Current smokers	0/82	2/58 (3.4)	
Past-smokers	3/82 (3.7)	4/58 (6.9)	
Cigarettes smoked per day × years of smoking <400 ≥400	 1/82 (1) 2/82 (2)	 2/58 (3.4) 4/58 (7)	
Liu et al. (4) COVID-19 induced pneumonia	Improvement/stabilization, N=67	Progression, N=11	
Smokers	2/67 (3)	3/11 (27.3)	
Zhou et al. (5) Inpatients, laboratory confirmed COVID-19	Survivor, N=137	Non-survivor, N=54	
Smokers	9/137 (6)	5/54 (9)	

Huang (6) Inpatients, laboratory confirmed COVID-19	ICU care not needed, N=28	ICU needed, N=13	
Smokers	0	3 (23)	
Yang et al. (7) Admitted to ICU unit	Survivor, N=20	Non-survivor, N=32	
Smokers	2 (10)	0	