



EDITORIAL

Tobacco and COVID-19: A position from Sociedade Portuguesa de Pneumologia



The impact of smoking on the transmission of the novel coronavirus SARS-CoV-2 and on the severity and mortality of COVID-19 is not yet fully understood. It is well established that tobacco consumption is an important risk factor for several chronic illnesses, such as respiratory and cardiovascular diseases, diabetes, cancer and others, and these patients are at greater risk for serious disease and death by COVID-19.^{1,2}

Tobacco smoke has a known immunosuppressive effect, making smokers more vulnerable to infection. Biochemical analysis of induced sputum in healthy smokers has shown a higher ratio of CD4+/CD8+ T cells and a lower rate of T CD8+ lymphocytes, whose activity is crucial to the rapid resolution of acute viral infections. This suggests a cell-mediated immune deficit and a greater susceptibility to viral infections.³ Smoking (and vaping) also increase epithelial permeability and cause oxidative stress and inflammation responses, leading to more susceptibility to viral and bacterial infections.⁴

Previous studies have demonstrated that smokers have a 34% higher probability of influenza-like illness compared to non-smokers, a five-fold increase in risk of laboratory-confirmed influenza and a higher risk of hospital admission.⁵ They also have a higher mortality risk from other coronaviruses, as was seen in the previous outbreak of MERS-Cov (Middle Eastern Respiratory Syndrome).⁶ This susceptibility probably includes the new coronavirus by additional mechanisms: Brake et al. have shown that smoking has the potential to up-regulate the angiotensin converting enzyme-2 receptor (ACE-2) in the respiratory epithelium, which is the receptor for both SARS-coronaviruses (SARS-CoV-1 and SARS-CoV-2) and for human coronavirus NL6384.⁷ Besides smokers, this expression is also increased in patients with COPD, suggesting this group could be more susceptible to COVID-19 and turning this receptor into a potential therapeutic target.⁸ Also Cai G. reported a higher expression of ACE-2 gene on samples from smokers compared to non-smokers⁹ and Zhao et al. have shown that ACE-2 protein is expressed on the surface of a small population of type-2 pneumocytes, where

genes regulating viral replication and transmission also have a high expression.¹⁰

Furthermore, the smokers' frequent and repeated hand-to-mouth contact represents a known infection pathway. Additionally, sharing tobacco products is associated with increased risk of transmission and the use of cigarettes, electronic cigarettes and waterpipes can contribute to SARS-Cov-2 dissemination through exhalation of aerosols that may contain the virus.¹¹ A recent study among teenagers and young adults showed that 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).¹²

Despite being scarce and sometimes contradictory, the scientific evidence available suggests an association between smoking and severity of COVID-19. A systematic review by Vardavas and Nikatara evaluated outcomes of 5 Chinese studies and using data published by Guan et al.,¹³ estimated a 1,4 higher risk for severe COVID-19 presentation in smokers compared to non-smokers and a 2,4 higher risk of intensive care admission, mechanical ventilation or death.¹⁴ The multivariate logistic regression analysis of another study by Liu et al.¹⁵ showed that smoking history represents a 14 times greater risk of disease progression (OR: 14.28; IC95%: 1.58–25.0; $p=0.018$).^{14,15}

A meta-analysis by Patanavanich and Glantz including 19 studies with 11,590 COVID-19 patients established a significant association between smoking and progression of COVID-19 (OR 1.91, 95% [CI] 1.42–2.59, $p=0.001$), and suggested that quality limitations in some studies may actually underestimate this effect.¹⁶

A recent review paper including 8 systematic reviews or meta-analysis revealed growing evidence on the association between smoking status and COVID-19 severity and poor clinical outcomes.¹⁷ This is also the conclusion of the WHO panel of experts, stating on May 11th that "smokers are at higher risk of developing severe disease and death".¹⁸

Although linked to severity of the disease and death, it is difficult to assess if smokers are at higher risk of contract-

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ing SARS-Cov-2 infection. Observations in different cohorts of relatively low rates of smokers among patients may be related to poor quality of records or lack of smoking status reports; well-designed population studies, controlled for other risk factors, are needed to address this question.^{19,20}

WHO also warned researchers to “be cautious about amplifying unproven claims that tobacco or nicotine could reduce the risk of COVID-19”, in view of recent non-peer reviewed studies with allegations that nicotine or tobacco might have a protective effect, due to low rates of smokers in COVID-19 patients.^{18,21,22} These publications make claims with serious public health implications, with a complete lack of good evidence to support them and with unacceptable ethical conflicts, including one of the authors having been financed by the tobacco industry.²³ Although some studies point out biologically plausible pathways through which nicotine may impact SARS-CoV-2, the clinical significance of these is entirely unclear and there is no evidence to support the use of nicotine replacement therapy in COVID-19.²⁴

It is important to note that there is a clear lack of good quality information concerning smoking status in most studies, challenging the investigation of the relation between tobacco and COVID-19. A recent living review and meta-analysis²⁵ found that only 26% of 256 studies reported current, former and never smoking status, and a high proportion did not distinguish between missing data and never smokers.

Beyond all well-known benefits, it is highly likely that smoking cessation can help reduce the transmission and severity of COVID-19 in the community, so reducing tobacco and related products should be part of pandemic control measures.

Taking into account what has been said above, smoking cessation programs should be a priority, especially in this Pandemic phase. Carbon monoxide (CO) measurement in the exhaled breath is a useful tool in smoking cessation programs; however, without specific disposable filters, adequate disposable mouthpieces and proper personal protective equipment,²⁶ it should not be used in clinical practice during Covid-19 pandemic.

With this in mind, the Portuguese Pulmonology Society has issued recommendations addressing tobacco use during the pandemic.²⁷ In the present text we update these recommendations, urging health authorities and policy-makers to:

- 1 Record smoking history in all COVID-19 patients.
- 2 Promote smoking cessation programs for patients and health care workers, including CO analysis only with adequate protective measures.
- 3 Facilitate the use of nicotine replacement therapy by health care workers who smoke, during work shifts.
- 4 Warn against sharing any tobacco products.
- 5 Warn smokers to only smoke in isolated, designated areas with ventilation.
- 6 Prioritize smokers as a risk group for infection.
- 7 Promote smoking cessation in the community.
- 8 Further advance tobacco control measures, such as raising taxes, smoke-free laws, publicity and marketing bans, including alternative tobacco products.

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Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Wang X, Fang X, Cai Z, Wu X, Gao X, Min J, et al. Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients: a systemic review and meta-analysis. *Research* (Wash DC). 2020;(April):2402961, <http://dx.doi.org/10.34133/2020/2402961>.
2. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging* (Albany NY). 2020;12(7):6049–57, <http://dx.doi.org/10.18632/aging.103000>.
3. Zhou Z, Chen P, Peng H. Are healthy smokers really healthy? *Tob Induc Dis*. 2016;14:35, <http://dx.doi.org/10.1186/s12971-016-0101-z>.
4. Kaur G, Lungarella G, Rahman I. SARS-CoV-2 COVID-19 susceptibility and lung inflammatory storm by smoking and vaping. *J Inflamm*. 2020;17:21, <http://dx.doi.org/10.1186/s12950-020-00250-8>.
5. Lawrence H, Hunter A, Murray R, Lim WS, McKee T. Cigarette smoking and the occurrence of influenza—systematic review. *J Infect*. 2019;79:401–6, <http://dx.doi.org/10.1016/j.jinf.2019.08.014>.
6. Park JE, Jung S, Kim A. MERS transmission and risk factors: a systematic review. *BMC Public Health*. 2018;18:574, <http://dx.doi.org/10.1186/s12889-018-5484-8>.
7. Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. Smoking upregulates angiotensin-converting enzyme-2 receptor: a potential adhesion site for novel Coronavirus SARS-CoV-2 (Covid-19). *J Clin Med*. 2020;9:841, <http://dx.doi.org/10.3390/jcm9030841>.
8. Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, et al. ACE-2 expression in the small airway epithelia of smokers and COPD patients: implications for COVID-19. *Eur Respir J*. 2020;55:2000688, <http://dx.doi.org/10.1183/13993003.00688-2020>.
9. Cai G. Bulk and single-cell transcriptomics identify tobacco-use disparity in lung gene expression of ACE2, the receptor of 2019-nCov. Preprints. 2020:2020020051, <http://dx.doi.org/10.20944/preprints202002.0051.v2>.
10. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. *Am J Respir Crit Care Med*. 2020;202(September (5)):756–9, <http://dx.doi.org/10.1164/rccm.202001-0179LE>.
11. Ahmed N, Maqsood A, Abduljabbar T, Vohra F. Tobacco smoking a potential risk factor in transmission of COVID-19 infection. *Pak J Med Sci*. 2020;36:S104–7, <http://dx.doi.org/10.12669/pjms.36.COVID19-S4.2739>.
12. Gaiha SM, Cheng J, Halpern-Felsher B. Association between youth smoking, electronic cigarette use and coronavirus disease 2019. *J Adolesc Health*. 2020;67:519–23, <http://dx.doi.org/10.1016/j.jadohealth.2020.07.002>.
13. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708–20, <http://dx.doi.org/10.1056/NEJMoa2002032>.

14. Vardavas C, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. *Tob Induc Dis.* 2020;18:20, <http://dx.doi.org/10.18332/tid/119324>.
 15. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J.* 2020;133(9):1032–8, <http://dx.doi.org/10.1097/CM9.0000000000000775>.
 16. Patanavanich R, Glantz SA. Smoking is associated with COVID-19 progression: a meta-analysis. *Nicotine Tob Res.* 2020;22:1653–6, <http://dx.doi.org/10.1093/ntr/ntaa082>.
 17. Grundy E, Suddek T, Filippidis FT, Majeed A, Coronini-Cronberg S. Smoking, SARS-CoV-2 and COVID-19: a review of reviews considering implications for public health policy and practice. *Tob Induc Dis.* 2020;18:58, <http://dx.doi.org/10.18332/tid/124788>.
 18. World Health Organization (WHO). WHO statement: tobacco use and COVID-19; 2020. Available at: <https://www.who.int/news/item/11-05-2020-who-statement-tobacco-use-and-covid-19>. [Date accessed: 16 October 2020].
 19. World Health Organization (WHO). Smoking and COVID-19—scientific brief; 2020,. [Date accessed: 16 October 2020] <https://www.who.int/news-room/commentaries/detail/smoking-and-covid-19>
 20. van Zyl-Smit RN, Richards G, Leone FT. Tobacco smoking and COVID-19 infection. *Lancet Respir Med.* 2020;8:664–5, [http://dx.doi.org/10.1016/S2213-2600\(20\)30239-3](http://dx.doi.org/10.1016/S2213-2600(20)30239-3).
 21. Miyara M, Tubach F, Pourcher V, Morelot-Panzini C, Pernet J, Haroche J, et al. Low rate of daily active tobacco smoking in patients with symptomatic COVID-19. *Qeios;* 2020, <http://dx.doi.org/10.32388/WPP19W.4> (prepublication).
 22. Changeux JP, Amoura Z, Rey F, Miyara M. A nicotinic hypothesis for Covid-19 with preventive and therapeutic implications. *Qeios;* 2020, <http://dx.doi.org/10.32388/FXGQSB.2> (prepublication).
 23. STOP Stopping Tobacco Organizations and Products. Studies that suggest smoking and nicotine protect against COVID-19 are flawed; 2020. Available at: exposetobacco.org/news/flawed-covid19-studies/. [Date accessed: 16 October 2020].
 24. Hartmann-Boyce J, Lindson N. The role of nicotine in COVID-19 infection. *Centre for Evidence-Based Medicine;* 2020. Available at: <https://www.cebm.net/covid-19/nicotine-replacement-therapy/>. [Date accessed: 16 October 2020].
 25. Simons D, Shahab L, Brown J, Perski O. The association of smoking status with SARS-CoV-2 infection, hospitalisation and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 8). *Qeios;* 2020, <http://dx.doi.org/10.32388/UJR2AW.9>.
 26. Munarinia E, Veronese C, Ogliari AC, Allegri F, Bolchi MG, Boffi R. COVID-19 does not stop good practice in smoking cessation: safe use of CO analyzer for smokers in the Covid era. *Pulmonology.* 2020, <http://dx.doi.org/10.1016/j.pulmoe.2020.08.008> (article in press).
 27. Matos CP, Boléo-Tomé JP, Rosa P. Recomendações da SPP sobre tabaco e COVID-19—Documento da Comissão de Trabalho de Tabagismo da Sociedade Portuguesa de Pneumologia; 2020. Available at: <https://www.sppneumologia.pt/uploads/subcanais conteudos ficheiros/tabaco-e-covid19.pdf>. [Date accessed: 2 October 2020].
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