



Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option?

Konstantinos Farsalinos¹ · Anastasia Barbouni¹ · Raymond Niaura²

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Abstract

The effects of smoking on Corona Virus Disease 2019 (COVID-19) are currently unknown. The purpose of this study was to systematically examine the prevalence of current smoking among hospitalized patients with COVID-19 in China, considering the high-population smoking prevalence in China (26.6%). A systematic review of the literature (PubMed) was performed on April 1. Thirteen studies examining the clinical characteristics of hospitalized COVID-19 patients in China and presenting data on the smoking status were found. The pooled prevalence of current smoking from all studies was calculated by random-effect meta-analysis. To address the possibility that some smokers had quit shortly before hospitalization and were classified as former smokers on admission to the hospital, we performed a secondary analysis in which all former smokers were classified as current smokers. A total of 5960 patients were included in the studies identified. The current smoking prevalence ranged from 1.4% (95% CI 0.0–3.4%) to 12.6% (95% CI 10.6–14.6%). An unusually low prevalence of current smoking was observed from the pooled analysis (6.5%, 95% CI 4.9–8.2%) as compared to population smoking prevalence in China. The secondary analysis, classifying former smokers as current smokers, found a pooled estimate of 7.3% (95% CI 5.7–8.9%). In conclusion, an unexpectedly low prevalence of current smoking was observed among patients with COVID-19 in China, which was approximately 1/4th the population smoking prevalence. Although the generalized advice to quit smoking as a measure to reduce health risk remains valid, the findings, together with the well-established immunomodulatory effects of nicotine, suggest that pharmaceutical nicotine should be considered as a potential treatment option in COVID-19.

Keywords SARS-CoV-2 · COVID-19 · ACE2 · Inflammation · Smoking · Nicotine · Hospitalization

Introduction

There is a lot of speculation about the effects of smoking on Corona Virus Disease 2019 (COVID-19). Media reports suggest that it may increase the risk of being infected with acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19. SARS-CoV-2 is known to use the angiotensin converting enzyme 2 (ACE2) as a receptor for cell entry [1]. There is a complex and unclear

interplay between COVID-19 and the renin–angiotensin–aldosterone system [2]. Until recently, smoking and nicotine were found to down-regulate ACE2 expression in the lung and other tissues [3, 4]. In the last few weeks, studies suggest that up-regulation of ACE-2 caused by smoking could be detrimental for COVID-19 [5–7]. However, it seems that up-regulation of ACE2 may in fact be protective against disease severity [2]. Experimental data suggest that infection with SARS-CoV and SARS-CoV-2 leads to down-regulation of ACE2, and this could be detrimental due to uncontrolled ACE and angiotensin II activity, leading to inflammation, and organ damage [1, 8]. It has been observed that decreased ACE2 availability contributes to lung injury and ARDS development [9–11]. Therefore, up-regulation of ACE2 does not necessarily imply increased susceptibility or disease severity and in fact could be beneficial.

According to the 2018 Global Adult Tobacco Survey, China has a high prevalence of smoking (26.6%), much

✉ Konstantinos Farsalinos
kfarsalinos@gmail.com

¹ Department of Public and Community Health, School of Public Health, University of West Attica, Leoforos Alexandras 196A, 11521 Athens, Greece

² Departments of Social and Behavioral Science and Epidemiology, College of Global Public Health, New York University, New York, USA

higher among males (50.5%) than females (2.1%) [12]. Thus, it is expected that a high prevalence of current smoking would be observed among hospitalized COVID-19 patients in China. However, it was recently suggested that there is no strong evidence for a link between smoking and COVID-19 due to the low prevalence of smoking among COVID-19 patients in 2 studies [13]. The purpose of this study was to systematically examine the prevalence of current smoking among all published case series of hospitalized patients with COVID-19 in China, and compare it with the population prevalence of current smoking.

Methods

A literature search was conducted on PubMed, using the terms “(SARS-CoV-2 OR COVID-19 OR 2019-nCoV) AND Clinical” in the title or the abstract on April 1. Out of a total of 432 studies, 13 studies which included data about the smoking status were identified [14–26]. The pooled prevalence of current smoking from all studies was calculated by random-effects meta-analysis using JASP Version 0.11.1 (JASP Team 2019, University of Amsterdam, The Netherlands). To address the possibility that some smoker had quit shortly before hospitalization and were classified as former

smokers on admission to the hospital, we performed a secondary analysis in which all former smokers were classified as current smokers. Additionally, because two studies were performed from the same group of researchers (China Medical Treatment Expert Group for Covid-19) and could involve overlap of patients [14, 15], we performed an additional analysis by removing the study with the lower prevalence of current smoking from the calculations [14].

Results

The studies analyzed are presented in Table 1. A total of 5960 hospitalized COVID-19 patients from China were presented in all studies. The majority (55.1%) were males. The mean or median age ranged from 38 to 68 years, with some studies presenting mean age in different subgroups. One study presented patients divided into two subgroups according to age (< 60 years and ≥ 60 years) [16] while another one reported cases according to the presence or absence of gastrointestinal symptoms. [17] In both studies, the 2 subgroups were combined and treated as one sample. Two studies reported the smoking status as “history of smoking” or “smoking”. [23, 25] Although it was unclear if this included both current and former smokers, we analyzed the

Table 1 Gender and smoking prevalence among hospitalized COVID-19 patients in China

	Hospitalized cases <i>N</i>	Age Mean(SD)/median(IQR)	Males <i>n</i>	Females <i>n</i>	Hospitalized current smokers <i>n</i>	Hospitalized current smokers % (95% CI)	Hospitalized former smokers <i>n</i>
Guan, Liang et al. [14]	1590	49 (16)	904	674	111	7.0 (5.7–8.2)	NR
Guan, Ni et al. [15]	1085	47 (35–58)	637	459	137	12.6 (10.6–14.6)	21
Lian et al. [16] ^a	788	41 (11) 68 (7)	407	381	54	6.9 (5.1–8.7)	NR
Jin et al. [17] ^b	651	46 (14) 45 (14)	331	320	41	6.3 (4.4–8.2)	NR
Chen et al. [18]	274	62 (44–70)	171	103	12	4.4 (2.0–6.8)	7
Zhou et al. [19]	191	56 (46–67)	119	72	11	5.8 (2.5–9.1)	NR
Mo et al. [20]	155	54 (42–66)	86	69	6	3.9 (0.9–6.9)	NR
Zhang et al. [21]	140	57 (25–87)	71	69	2	1.4 (0.0–3.3)	7
Wan et al. [22]	135	47 (36–55)	72	63	9	6.7 (2.5–10.9)	NR
Liu et al. [23]	78	38 (33.57)	39	39	5	6.4 (0.1–11.8)	NR
Huang et al. [24]	41	49 (41–58)	30	11	3	7.3 (0.0–15.3)	NR
Guo et al. [25]	187	59 (15)	91	96	18	9.6 (5.4–13.9)	NR
Cai et al. [26] ^c	645	35 (14) 47 (14)	328	317	41	6.4 (4.5–8.2)	NR

In Ling et al., data on sex was presented for 1578 patients. In Ni et al., data on sex was presented for 1096 patients

NR not reported

^aAge was presented separately for patients aged < 60 years and ≥ 60 years

^bAge was presented separately for those with and without gastrointestinal symptoms

^cAge was presented in separately for those with normal and abnormal imaging findings

data assuming they were all current smokers. In most studies, former smokers were not reported (Table 1).

The current smoking prevalence ranged from 1.4 to 12.6%. The random effects pooled prevalence of current smoking was 6.5% (95% CI 4.9–8.2%). Findings from the random-effects meta-analysis are presented in Fig. 1. The observed outcome is the estimated prevalence of current smoking among those who were hospitalized with COVID-19. The forest plot depicts the fractional prevalence of smokers in each study. The size of the dark squares is proportional to the weight each study has in determining the combined effect size estimate. The combined effect estimate is depicted via the dark diamond (RE Model), with the 95% confidence interval corresponding to the width of the diamond. The meta-analysis also indicated statistically significant heterogeneity between studies ($p < 0.001$).

Only three studies reported the prevalence of former smoking among hospitalized COVID-19 patients [13, 16, 19]. When considering these patients as current smokers, the pooled estimate of smoking prevalence was 7.3% (95% CI 5.7–8.9%).

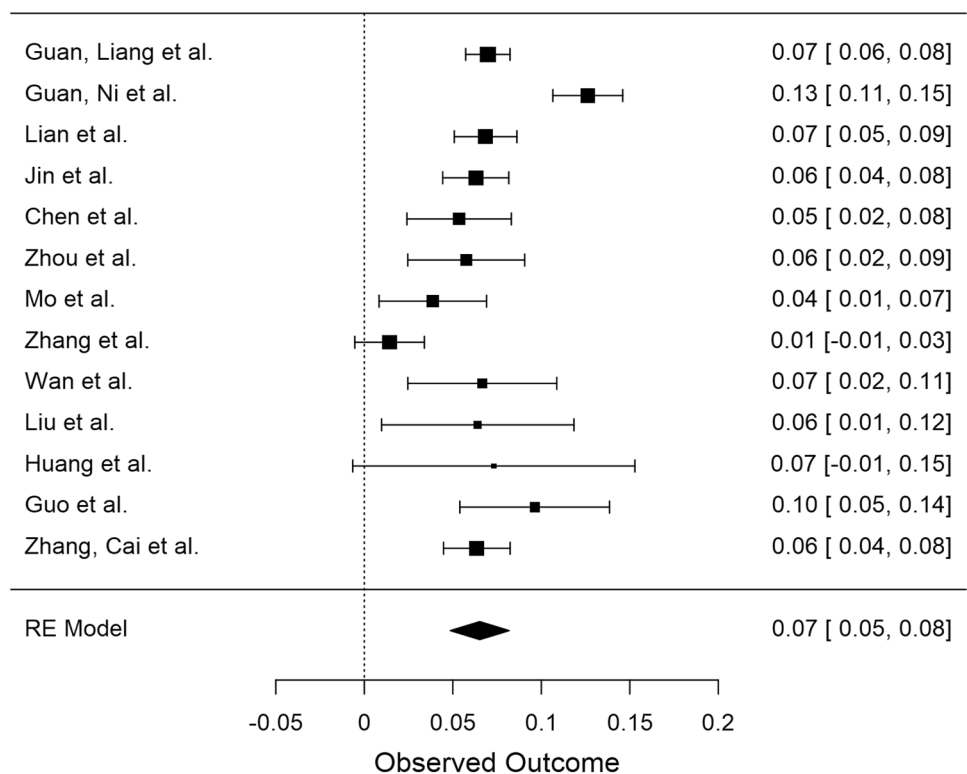
By removing the study by Liang et al. [14] due to potential overlap with patients presented in the Ni et al. study, [15] the pooled estimate of smoking prevalence was 6.5% (95% CI 4.5–8.4%).

Discussion

This study calculated for the first time the prevalence of current smoking among hospitalized patients with COVID-19 in China. The estimated prevalence of current smoking was unexpectedly low, approximately 1/4th the most recently estimated population smoking prevalence in China.

This preliminary analysis, assuming that the reported data are accurate, suggests that current smoking does not appear to be a predisposing factor for hospitalization for COVID-19. However, there are limitations that cannot be addressed with currently available evidence and data. Confounding factors, such as socioeconomic status, should be considered in examining if access of Chinese smokers with COVID-19 to hospital care may be different as compared to the non-smoking population. While the pooled prevalence of smoking was not adjusted for gender, gender distribution of the patients included in the studies was similar to population estimates (51.1% males). [27] At this time, it is impossible to perform a multivariate analysis or examine the prevalence of COVID-19 hospitalization according to the smoking status in a population-representative sample. The consistency and accuracy of the recorded smoking status are also unknown. Considering the emergency of the epidemic, it is possible that the smoking status of patients was not accurately recorded or some patients were unable to report their smoking status. It is also possible

Fig. 1 Random effects pooled prevalence of current smoking observed from 13 studies of hospitalized COVID-19 patients in China. The forest plot depicts the fractional prevalence of smokers in each study. The size of the dark squares is proportional to the weight each study has in determining the combined effect size estimate. $P < 0.001$ for heterogeneity



that some patients may have been in critical condition at the time they were hospitalized, which would compromise their communication capacity and their ability to report their smoking status. One study reported that the group of never smokers included patients with unknown smoking status, but the authors did not report the number of patients with unknown smoking status. [14] One study mentioned that “few patients had a current or former cigarette smoking history of at least 30 pack years”, but it was unclear if only patients with 30 pack years or more were presented in the study table [19]. At the same time, two studies may have included former smokers into the groups referred to as “smoking” or “smoking history” [23, 25]. In any case, the large difference between smoking prevalence among patients and population smoking prevalence is difficult to be fully explained by missing data on the smoking status. The smoking status was not objectively assessed, but this is common and expected practice in case series of hospitalized patients. Another possibility is that some patients may have quit smoking shortly after disease initiation and before admission to hospital; these patients would be registered as former smokers. However, the secondary analysis, which classified former smokers as current smokers, also found a low pooled smoking prevalence. While only 3 out of the 13 studies reported former smoking and 2 studies reported smoking without clarifying if they were current or former smokers, a study by Lui et al. found that only 8.4% of males and 0.8% of females in China were former smokers [28]. Consider the low prevalence of former smoking in the Chinese population, it is possible that none of the patients were former smokers in some of the studies. Another limitation is that differences in population smoking prevalence may exist between age groups, considering that age is a predisposing factor for severe COVID-19 and hospitalization would be more likely for older people. A study by Liu et al. reported that the highest smoking prevalence in China was observed in males aged 40–59 years [28]. The median age in all the studies analyzed herein was < 59 years. Additionally, high smoking prevalence was observed among older Chinese males by Liu et al. Specifically, the prevalence of current smoking in males was: 46.5% in 18–29 years, 57.6% in 30–39 years, 60.3% in 40–49 years, 59.5% in 50–59 years, 52.2% in 60–69 years and 41.5% in 70+ years. In females, the highest smoking rates were observed in those aged 50 years or higher (4.7–8.7%) compared to younger age groups (1.7–2.6%) [28]. Moreover, the 2018 GATS reported that prevalence of current smoking was 57.7% and 2.7% in males and females, respectively, in age groups 45–64 years, and 44% and 4.1%, respectively, in age group ≥ 65 years [12]. Thus, it is unlikely that age was a factor that substantially affected the present analysis. In any case, the calculated pooled prevalence of current smoking was approximately

1/4th the population smoking prevalence in China. Such a difference could only be explained by massive under-reporting of current smoking.

The study may also have implications when examining the effect of smoking status on disease progression, complications and death among hospitalized COVID-19 patients. Two recent studies performed univariate analyses and found an association between smoking and adverse outcome among hospitalized COVID-19 patients, although it was not always statistically significant [29, 30]. Smokers are more likely than non-smokers to suffer from comorbidities, such as cardiovascular disease, which appear to be implicated in COVID-19 mortality. Thus, it is possible that at least some of the smokers hospitalized for COVID-19 may have suffered from comorbidities that adversely affected disease severity. In fact, due to the higher prevalence of these comorbidities among current smokers, it would have been expected for smokers to be over-represented among hospitalized COVID-19 cases as compared to the general population; however, the reverse is true. The recent evidence from the US CDC is in agreement with the data from Chinese studies. [31] From a total of 7162 patients in the US, only 1.3% were current smokers. Low smoking prevalence was also observed among hospitalized non-ICU (2.1%) and ICU cases (1.1%), while the population smoking prevalence in the US is 13.8%. Additionally, a small case series from Germany presented 50 COVID-19 patients of whom only 3 (6.0%) were current smokers. [32] It is possible that the risk for hospitalization for COVID-19 may be different for otherwise healthy smokers as compared to smokers with smoking-related disease. This is an important reason for not recommending smoking as a measure to reduce risk for severe COVID-19. The well-established elevated risk for cancer, cardiovascular, and respiratory disease due to smoking would not make it an appropriate and sustainable protective measure.

Although no firm conclusion can currently be made concerning the specific effects of smoking on the risk of hospitalization for COVID-19, tobacco cigarette smoke contains several toxins and other chemicals that are not known to have any potentially protective effects against COVID-19 through immunomodulatory or antiviral properties. However, one of the main components of tobacco cigarette smoke is nicotine. Nicotine has been found to prevent acute lung injury in an animal Acute Respiratory Distress Syndrome (ARDS) model and to inhibit TNF expression in airway epithelial cells *in vitro* [33, 34]. It has also exhibited anti-inflammatory properties *in vivo* in humans exposed to endotoxins [35]. Nicotine is an agonist of the cholinergic anti-inflammatory pathway that regulates host immune and inflammatory responses [36–39]. It inhibits the production of pro-inflammatory cytokines, such as TNF, IL-1, and IL-6, without inhibiting the production of anti-inflammatory

cytokines, such as IL-10 [36, 40–42]. Such an effect has been found to protect against cytokine-mediated diseases, such as sepsis and endotoxemia, which lead to organ damage and death. “Cytokine Release Syndrome” (also known as “cytokine storm”) is a phenomenon characterized by an increased release of pro-inflammatory cytokines that may occur in response to infections and can progress to ARDS. This phenomenon seems to be important in the pathophysiology of severe COVID-19 and could explain the postmortem histopathological findings in a COVID-19 patient [43–46]. SARS-CoV-2 activates the innate immune system and the accompanying release of a large number of cytokines, including IL-6, which can increase vascular permeability, cause migration of fluid and blood cells into the alveoli and result in dyspnea and respiratory failure [44]. IL-6 was a predictor of mortality in a case series of 160 COVID-19 patients [47] and it was elevated in non-survivors as compared to survivors in another study of 191 patients [19]. As a result, the use of medications targeting pro-inflammatory cytokines, such as IL-1 or IL-6 inhibitors, has been recommended and is already being tested in clinical trials, in an effort to treat patients with severe COVID-19 by neutralizing these key inflammatory mediators [43, 44, 47, 48]. The US FDA recently approved a phase III clinical trial of an IL-6 inhibitor for the treatment of COVID-19 [49]. Other anti-inflammatory therapeutic options that have been proposed to be tested include anti-TNF medications [50]. Therefore, the cytokine storm is a therapeutic target in clinical trials conducted on COVID-19 patients, and nicotine has effects on the immune system that could be beneficial in reducing the intensity of the cytokine storm.

Concerning the renin–angiotensin–aldosterone axis, ACE2 counteracts the adverse effects of angiotensin II by cleaving angiotensin I and angiotensin II to angiotensin (1–7). The latter has well-established vasodilatory, anti-inflammatory and antioxidant properties. In smokers, the recently-observed ACE2 up-regulation is probably induced as a defense mechanism to counteract the effects of angiotensin II. ACE2 has been found to protect mice from developing ARDS [10, 51]. Tobacco cigarette smoke caused enhanced damage to the lungs of ACE2 knockout mice as compared to wild-type mice, providing further support that ACE2 up-regulation is an important and beneficial defense mechanism [52]. Data from SARS experimental studies suggest that continuous SARS-CoV-2 infection and replication induces down-regulation of ACE2 which may be implicated in organ damage and disease severity [2]. Thus, up-regulation of ACE2, though seemingly paradoxical, may in fact protect patients from severe disease and lung injury [11]. Currently, there is no evidence to suggest that up-regulation of ACE2 is associated with increased COVID-19 susceptibility or severity. In fact, estrogens appear to up-regulate ACE2 while children and younger adults have higher ACE2

levels as compared to older people, which could explain the milder COVID-19 in women and younger people and suggest a protective effect [53, 54]. Moreover, the contradictory findings about smoking in the literature, with studies published before the COVID-19 pandemic reporting that smoking and nicotine down-regulate ACE2 [3, 4] and other studies published during the pandemic reporting that they up-regulate ACE2 [5–7], do not allow for solid conclusions regarding the effects of nicotine or smoking on ACE2. These findings may also represent an indication of the dynamic balance between ACE and ACE2, which may be continuously changing depending on stressors and stimuli. Thus, there is uncertainty on whether nicotine affects COVID-19 progression through the renin–angiotensin–aldosterone axis.

The potential benefits of nicotine through its immunomodulatory effects and complex interactions with the renin–angiotensin system suggested with this hypothesis could explain, at least in part, the increased severity or adverse outcome among smokers hospitalized for COVID-19 since these patients inevitably experience abrupt cessation of nicotine intake during hospitalization. Comorbidities that are associated with smoking, such as cardiovascular diseases and COPD, also represent risk factors for adverse outcome in COVID-19. Therefore, the presence of these comorbidities would confound the clear interpretation of nicotine effects.

It is important to emphasize that the present analysis examined only hospitalized cases. Thus, no conclusion can be drawn about the prevalence of current smoking among patients with less severe COVID-19 that would not require hospitalization. Nicotine is unlikely to have direct antiviral properties, thus it is not expected to act as chemoprophylaxis. Therefore, it is unlikely that nicotine could prevent infection with SARS-CoV-2. However, the above-mentioned hypothesis is relevant to experiencing a milder form of COVID-19, reducing the risk for being hospitalized.

In conclusion, the observations of a consistently low prevalence of smoking among COVID-19 cases in China and the US, together with the potential mechanisms through which nicotine interacts with the inflammatory process and the renin–angiotensin–aldosterone axis, warrant an investigation of the clinical effects of pharmaceutical nicotine on COVID-19 susceptibility, progression, and severity through clinical trials. This may be feasible through repurposing already approved (for other indications) pharmaceutical nicotine products such as nicotine patches, or even by using these products as already indicated (i.e. as smoking substitutes). These products are relatively safe and have been administered therapeutically in non-smokers for neurological conditions and inflammatory bowel disease for longer periods than would be needed for COVID-19 [55–57]. Nicotine could also be administered through inhalation, with the use of a nebulizer or other aerosol systems, if needed, for

an added local effect [58]. Additionally, nicotine administration would not substitute for other treatment regimens and could be added to antiviral or other therapeutic options for COVID-19. The potential need to provide pharmaceutical nicotine products to smokers and users of other nicotine products who experience an abrupt cessation of nicotine intake when hospitalized for COVID-19 or aim to follow medical advice to quit smoking should also be examined. In that case, the use of pharmaceutical nicotine products would represent an “on-label” use since they would be used based on their official indication (as smoking substitutes). In fact, the Addiction Prevention Network in France (RES-PADD) officially recommends the use of nicotine replacement therapies for smokers when hospitalized for any illness [59]. Finally, our findings could have implications for users of other nicotine products, such as electronic cigarettes or snus, who may also experience nicotine withdrawal if hospitalized. No studies recording electronic cigarette or snus use or among COVID-19 have been published until now.

Author contributions KF conceived the study. KF, AB, and RN performed the analysis. All authors have read and approved the manuscript.

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Availability of data and material The study presents an analysis of data published in other studies.

Compliance with ethical standards

Conflict of interest The authors report no competing interests for the past 36 months. For the past 60 months, two of his studies were funded by the non-profit association AEMSA and one study was funded by the non-profit association Tennessee Smoke-Free Association. AB reports no conflict of interest. AB has nothing to report. RN receives funding from the Food and Drug Administration Center for Tobacco Products via contractual mechanisms with Westat and the National Institutes of Health. Within the past three years, he has served as a paid consultant to the Government of Canada and the FDA via contracts with Industrial Economics Inc., and has received an honorarium for a virtual meeting from Pfizer Inc.

Statements on human and animal rights Not applicable. The present study is an analysis of published studies using anonymized data.

Informed consent Not applicable.

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