Research Article

Smoking, vaping and hospitalization for COVID-19

Konstantinos Farsalinos[1], Anastasia Barbouni[1], Raymond Niaura[2]

1. University of West Attica, Athens, Greece; 2. New York University, United States

The study presents an analysis of the current smoking prevalence among hospitalized patients with COVID-19 in China, compared to the population smoking prevalence in China (52.1% in males and 2.7% in females). Through a systematic research of the literature (PubMed) we identified 7 studies examining the clinical characteristics of a total of 2352 hospitalized COVID-19 patients that presented data on the smoking status. The expected number of smokers was calculated using the formula Expected smokers = (males x 0.521) + (females x 0.027). An unusually low prevalence of current smoking was observed among hospitalized COVID-19 patients (8.7%, 95%CI: 7.6-9.9%) compared to the expected prevalence based on smoking prevalence in China (30.3%, 95%CI: 28.4-32.1%; z-statistic: 22.80, P < 0.0001). This preliminary analysis does not support the argument that current smoking is a risk factor for hospitalization for COVID-19, and might even suggest a protective role. The latter could be linked to the down-regulation of ACE2 expression that has been previously known to be induced by smoking. However, other confounding factors need to be considered and the accuracy of the recorded smoking status needs to be determined before making any firm conclusions. As a result, the generalized advice on quitting smoking as a measure to improve health risk remains valid, but no recommendation can currently be made concerning the effects of smoking on the risk of hospitalization for COVID-19. No studies recording e-cigarette use status among hospitalized COVID-19 patients were identified. Thus, no recommendation can be made for e-cigarette users.

Keywords. SARS-CoV-2, COVID-19, ACE2, expression, susceptibility, smoking, hospitalization, electronic cigarette.

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

Introduction

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There is a lot of speculation about the effects of smoking on Corona Virus Disease 2019 (COVID-19). Smoking increases susceptibility to respiratory infections and 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, and there is evidence that smoking down-regulates ACE2 expression in the lung and other tissues.[1] China has a high prevalence of smoking (27.7%), much higher among males (52.1%) than females (2.7%).[2] It was recently suggested that there is no strong evidence between smoking and prevalence of COVID-19 due to the low prevalence of smoking among COVID-19 patients in 2 studies compared to the population smoking prevalence in China.[3] The purpose of this study was to examine the prevalence of current smoking among Chinese hospitalized cases with COVID-19 relative to the population prevalence of current smoking in China.

Methods

To examine how the prevalence of smoking among hospitalized COVID-19 compares to the smoking prevalence of the population, we systematically searched on PubMed using the terms "(SARS-CoV-2 OR COVID-19 OR 2019-nCoV) AND Clinical" in the title or the abstract. Out of a total of 341 studies published until March 29, 7 studies which included data about the smoking status were identified.[4-10] Prevalence of smoking among hospitalized patients was compared with the expected prevalence that was calculated based on the population smoking prevalence and gender of hospitalized cases using the formula:

Expected smokers = (males x 0.521) + (females x 0.027)

The expected prevalence was calculated separately for each study and for the sum of all cases from the 7 studies examined. The comparison between the prevalence of smoking among hospitalized COVID-19 patients and the expected prevalence was performed using the test for one proportion (z-statistic).

Results

Findings are presented in **Table 1**. From a total 2352 hospitalized COVID-19 cases analyzed in the 7 studies, 55.8% were males and 44.2% were females. One study presented patients divided into two subgroups according to the presence or absence of gastrointestinal symptoms.[5] The two subgroups were presented separately in the table. One study reported the smoking status as "history of smoking".[9] While it was unclear if this included both current and former smokers, we analyzed the data assuming they were all current smokers.

The overall prevalence of current smoking was 8.7% (95%CI: 7.6-9.9%). However, the calculated expected

prevalence of current smoking, considering the population prevalence in China, was 30.3% (95%CI: 28.4-32.1%). The difference was statistically significant for each study and for the sum of all cases (z-statistic: 22.80, P < 0.0001).

Table 1. Gender and smoking prevalence among hospitalized COVID-19 patients, and expected number of smokers based on population prevalence of smoking in males (52.1%) and females (2.7%) in China.

	Hospitalized cases	Age	Males	Females	Expected current smokers (1)	Expected current smokers	Hospitalized Current smokers	Hospitalized Current smokers	z-statistic
	N	median (IQR) or mean (SD)	n	n	n	% (95%CI)	n	% (95%CI)	P (value)
Guan et al.	1096	47 (35-58)	637	459	344	31.4 (28.7-34.1)	137	12.5 (10.5-14.5)	13.48 (< 0.001)
Jin et al. (2)	577	45 (14)	294	283	161	27.9 (24.2-31.5)	38	6.6 (4.6-8.6)	11.40 (< 0.001)
Jin et al. (3)	74	46 (14)	37	37	20	27.4 (17.5-37.9)	3	4.1 (0.0-8.5)	4.49 (< 0.001)
Zhou et al.	191	56 (46-67)	119	72	64	33.5 (26.8-40.2)	11	5.8 (2.5-9.1)	8.11 (< 0.001)
Mo et al.	155	54 (42-66)	86	69	47	30.3 (23.1-37.5)	6	3.9 (0.9-6.9)	7.15 (< 0.001)
Zhang et al.	140	57 (25-87)	71	69	39	27.8 (20.4-35.2)	2	1.4 (0.0-3.3)	6.97 (< 0.001)
Liu et al.	78	38 (33.57)	39	39	21	27.4 (17.5-37.3)	5	6.4 (0.1-11.8)	4.16 (< 0.001)
Huang et al.	41	49 (41-58)	30	11	16	38.8 (16.9-45.3)	3	7.3 (0.0-15.3)	4.15 (< 0.001)
Total	**2352**		**1313**	**1039**	**712**	**30.3 (28.4-32.1)**	**205**	**8.7 (7.6-9.9)**	**22.80 (< 0.001)**

(1) Expected number of smokers was calculated based on the prevalence of smoking in China, using the formula:
Expected smokers = (males x 0.521) + (females x 0.027)
(2) Subgroup of patients without gastrointestinal symptoms.
(3) Subgroup of patients with gastrointestinal symptoms.

Figure

Discussion

The current study examined for the first time the prevalence of current smoking among hospitalized patients with COVID-19 in China and compared it with the expected prevalence based on the population smoking prevalence. Care was taken to consider the large difference between genders, with current smoking being substantially more prevalent among Chinese males than females. An unusually low prevalence of current smoking among hospitalized COVID-19 cases in China was observed when considering the population smoking prevalence. The prevalence observed in the 7 studies analyzed was less than one-third the expected prevalence.

This preliminary analysis, assuming that the reported data are accurate, does not support the argument that current smoking is a risk factor for hospitalization for COVID-19, and might even suggest a protective role. The latter could be linked to the down-regulation of ACE2 expression that has been previously known to be induced by smoking. However, other 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 compared to the non-smoking population. At this time, it is impossible to perform a multivariate analysis or examine the prevalence of COVID-19 infection and hospitalization according to the smoking status of the whole population. The accuracy of the recorded smoking status also needs to be determined. It is possible that some patients may have quit smoking shortly after disease initiation and before admission to hospital, and thus would be registered as former smokers. Only two of the studies reported the proportion of former smokers among patients, which was particularly low (1.9% and 5.0%).[4,8] Another limitation is that differences in smoking prevalence exist between age groups, particularly considering that hospitalization for COVID-19 may 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.[12] The median age in all the study 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 rats were observed in those aged 50 years or higher (4.7-8.7%) compared to younger age groups (1.7-2.6%).[12] Thus, it is unlikely that age was a factor that substantially affected the present analysis. Finally, the present analysis examined only hospitalized cases. Thus, no conclusion can be drawn on the susceptibility of smokers to less severe COVID-19 that would not require hospitalization.

The study also has implications when examining the effect of smoking status on disease progression, complications and death among hospitalized COVID-19 patients. Smokers are more likely than non-smokers to suffer from comorbidities, such as cardiovascular disease, which are risk factors for adverse COVID-19 outcomes. It has been reported that medications such as ACE-inhibitors, which are commonly used in patients with hypertension and cardiovascular disease, up-regulate ACE2.[11] It remains unclear whether smoking *per se* or other factors related to comorbidities may be responsible for an adverse outcome. Considering the above-mentioned uncertainties, the generalized advice on quitting smoking as a measure to improve health risk remains valid but no recommendation can be currently made concerning the effects of smoking on the risk of hospitalization for COVID-19. An important issue that also needs to be addressed is the effect of e-cigarette use on COVID-19 risk, particularly for Europe and the US where prevalence of use is higher compared to China. No studies recording e-cigarette use status among hospitalized COVID-19 patients in China were identified. Thus, no recommendation can be made for e-cigarette users.

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