1 INTRODUCTION : COVID risk / Vaping

WHO's Latest Error: The Link Between Vaping and COVID

Over the last few years, the World Health Organization (WHO) has made a grotesque number of tragic mis-steps that have cost lives all around the world. Most recently they have been supporting the statement that vaping and smoking lead to contracting COVID-19. According to a report from The Coalition of Asia Pacific Tobacco Harm Reduction Advocates (CAPHRA), their review of global medical research into the relationship between vaping and contracting COVID-19 has shown no such relationship, and in its quest to rid the world of smoking the WHO has once again sought to knowingly and deliberately prevent millions of adult cigarette smokers from getting access to safer vaping products.

CAPHRA found that studies around the world have been reporting three key observations - a noticeably low percentage of smokers among COVID-19 patients; a theory that nicotine may in fact be a potential deterrent to COVID-19; and that the link between COVID-19 and vaping is currently considered inconclusive at best, with researchers calling for more study to clarify the situation.

According to CAPHRA Executive Coordinator Nancy Loucas, "This vaping/COVID link is just their latest dangerous lie. For years the WHO has created a steady stream of anti-vaping claims, which has had dire consequences for adult smokers seeking to quit. It has also led to many governments passing legislation that bans vaping and all related products. By going this route the WHO has chosen to support deadly cigarette consumption over a healthier alternative and in the process has forced vaping into the waiting hands of the black market – and they do this with the full knowledge of the consequences of their actions. The lack of legislation means that these unregulated products end up in the hands of minors, courtesy of the WHO."

The WHO's own findings support the position that there is no established link to COVID. In *Smoking and COVID-19* , published in June 2020 by the WHO's Western Pacific Division, a review of 34 studies concluded that no evidence of a link existed between smoking and the likelihood of catching COVID-19, and that further, direct research was needed. In their May 2020 Q&A report the WHO again said "There is no evidence about the relationship between e-cigarette use and COVID-19."

Research into the role of nicotine has provided some surprising results. In May 2019 a report by Riccardo Polosa and Grazia Caci entitled "*COVID-19: counter-intuitive data on smoking prevalence and therapeutic implications for nicotine"* it was reported that the incidence of smokers contracting COVID-19 was unexpectedly low, stating, "Intuitively, one vulnerability to severe illness from COVID-19 would be assumed to be cigarette smoking because it is known to increase the risk of serious respiratory infections. But is this in fact true? In this issue of Internal and Emergency Medicine, Farsalinos et al. explore the hypothesis that smokers are at higher risk and unexpectedly found data that point to the opposite and counter-intuitive conclusion that smoking may actually have a protective effect." These findings have been replicated in numerous subsequent research reports.

The WHO's continued demonization of vaping bears significant and severe consequences. A 2012 study (Global economic cost of smoking-attributable diseases by Mark Goodchild, Nigar Nargis, Edouard Tursan d'Espaignet) showed that the total economic cost of smoking was roughly US$422 billion, equivalent to 5.7% of global health expenditures, or 1.8% of global GDP.

The WHO and the anti-vaping community has justified its untenable position on the back of its outrage over an imagined "youth vaping epidemic", insisting that vaping poses a grave risk to minors. Thy have now dragged COVID-19 into their dialogue without scientific evidence to back it up. Tragically, the good intentions of these groups has ensured that unregulated and uncontrolled products will be left to the black market, who will sell to anyone willing to buy.

The one area of complete agreement between the vaping community and the anti-vaping community is that neither cigarettes nor ecigarettes should be in the hands of minors and that vaping should be sensibly legislated. Sadly, governments following the WHO's directives simply choose to deny vaping to all while supporting cigarette smoking, which is known to result in a roughly 50% death rate.

There are three main areas where the pro-vaping community and the WHO agree:

1. To eliminate cigarette smoking
2. ENDS and ENNDS are not 100% safe and must not be available to minors
3. ENDS and ENNDS are different from cigarettes and must be regulated sensibly

Across Asia Pacific, an estimated 5 million adults vape, with most of them being former smokers who have either quit smoking completely or have cut down significantly using their preferred devices and liquids.

Literally, millions of former Asian smokers have already made the switch, and in almost every case they did so against the advice and in defiance of the highly restrictive, disproportionate regulations that continue to be imposed on safer nicotine products and the punitive treatment of adult consumers, under the guidance and advice of the World Health Organisation and supporters of the "quit or die" school of tobacco control.

If the World Health Organisation and governments globally can be so reliant on the science around COVID-19, why won't they take the same approach to the smoking pandemic that kills someone every 10 seconds? Half of all smokers who cannot stop, WILL DIE from smoking related illnesses. That is over 8 million deaths per year.

The response to COVID has been firmly rooted in science, there is a disconnect between the science and the regulatory frameworks being applied to safer nicotine products and the concept of Tobacco Harm Reduction. To the detriment of the health and rights of not only smokers and consumers, but also of society as a whole, who are being negatively impacted by the disconnect between science and policy.

This begs the question "If governments trust the science around the COVID pandemic, why are they not trusting the science on Tobacco Harm Reduction to mitigate the long standing smoking pandemic?"

2 Report: COVID risk / Vaping

In its mission to reduce cigarette smoking around the world the WHO has refused to identify vaping as a viable harm-reduction option, causing a cascading effect of many governments banning it outright, without consideration of creating protective, sensible, and fiscally responsible legislation. The effects are devastating, allowing black marketers to sell to minors while robbing the government of revenues.

One of the statements to emerge from the WHO and anti-vaping groups has been an unsupported declaration that smoking and vaping increases the likelihood of catching COVID-19.

This report reviews a selection of literature that examines whether currently available scientific research provides clear evidence of a relationship between smoking cigarettes and/or Heat-Not-Burn (HNB), and/or electronic nicotine delivery systems (ENDS/ENNDS) and contracting COVID-19? It also examines the role of nicotine.

The available evidence suggests a that while much more research is needed, smoking cigarettes and/or Heat-Not-Burn (HNB), and/or electronic nicotine delivery systems (ENDS/ENNDS) are not a factor in contracting COVID-19, and moreover, nicotine may have a protective effect against contracting COVID-19.

Here are the key findings:

#1 : There is not enough research or evidence to state that vapers and smokers are more likely to catch COVID-19

Multiple studies, state that no relationship between smoking or vaping and catching COVID-19 have yet been established and that further research is needed.

Most notable among these reports is the Scientific Brief of 30 June 2020 from the World Health Organization's Western Pacific Division (WHO) which states that "*There are currently no peer-reviewed studies that have evaluated the risk of SARS-CoV-2 infection among smokers. This research question requires well-designed population-based studies that control for age and relevant underlying risk factors".* With regards to vaping, they add, "*There is no evidence about the relationship between e-cigarette use and COVID-19."*

#2 : Smokers were less likely to be diagnosed with COVID-19 compared to non-smokers.

A study by Farsalinos et al. had begun with the hypothesis that smokers are at higher risk, but came away with evidence to the contrary, stating that "*smoking may actually have a protective effect. Their systematic review observed that smoking is vastly protective for hospitalized COVID-19 based on the surprisingly low prevalence of smoking in patients hospitalized with COVID-19.*"

Farsalinos' findings have been supported by studies in the US, Germany, Mexico, Iceland, Israel, and France. In the US, the Centers for Disease Control and Prevention (CDC) reported an unusually low prevalence of current smoking among COVID-19 cases at 1.3% compared to population smoking prevalence in US of 16.5%.

The study *"Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory–confirmed COVID-19 cases"* (Section 3.15), is the largest study ever undertaken on laboratory-confirmed COVID-19 patients, and the first of this size from a Low and Middle Income Country (LMIC), and the results have shown that smokers are less likely to test positive for COVID-19 than the general population. It goes on to state that "*very few smokers relative to the population smoking rates appear to be hospitalised for COVID-19".*

#3 : Smoking as a Risk Factor

Numerous studies reviewed here have identified common risk factors, and smoking is not among them. Age, male gender, hypertension, obesity, and diabetes are the main culprits in study after study. However, while very few smokers relative to the population smoking rates appear to be hospitalised for COVID-19, if a

smoker does catch the virus, the risk of adverse outcomes is higher. Recent meta-analyses reported that hospitalised smokers with COVID-19 had higher odds for adverse outcomes.

#4 : The role of Nicotine is currently inconclusive

The findings that smokers are under-represented among COVID-19 patients has presented a hypothesis that nicotine may exert protective effects, but the science is currently in opposing camps, and it is currently impossible to state the role of nicotine one way or the other, as there is disagreement over interpreting the science.

For example, a number of studies suggest that nicotine can prevent acute lung injury (which is similar to COVID-19 pneumonia) and that nicotine inhibits the production of pro-inflammatory cytokines, it has been established that SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as a receptor for cell entry and viral replication. While this would imply that ACE2 up-regulation would be associated with COVID-19 severity and adverse outcome, there is evidence that the opposite is the case.

In their May 2020 report "*The role of nicotine in COVID-19 infection*" published by The Centre for Evidence-Based Medicine, Jamie Hartmann-Boyce and Nicola Lindson state that "Commentaries regarding nicotine and COVID-19 all agree nicotine potentially has a role to play based on its role in the renin-angiotensin system. In particular, nicotine can impact the angiotensin-converting enzyme (ACE) 2, which is relevant because coronaviruses bind to ACE2." However, they then add that while "some authors interpret this as suggesting nicotine is likely to be harmful in the context of COVID-19, and others suggest the opposite." They concluded that "It is extremely difficult to synthesise evidence on nicotine and COVID-19 as much of the literature is inconsistent."

Current evidence for a protective effect of nicotine in COVID-19 remains controversial, and as such, the role of alternate nicotine delivery products such as e-cigarettes and heated tobacco products on the severity of COVID-19 hospitalizations should be included in COVID-19 surveillance - particularly in countries where nicotine vaping is prevalent.

The final word on this must come from the WHO, which stated in May 2020 that "There is currently insufficient information to confirm any link between tobacco or nicotine in the prevention or treatment of COVID-19. WHO urges researchers, scientists and the media to be cautious about amplifying unproven claims that tobacco or nicotine could reduce the risk of COVID-19." This would imply that there is also no evidence to link nicotine as a factor in catching COVID-19, and that researchers, scientists and the media should also be cautious about amplifying unproven claims that tobacco or nicotine could increase the risk of contracting COVID-19.

3 Excerpts : COVID risk / Vaping

3.1 Smoking and COVID-19

30 June 2020 | Scientific Brief, World Health Organization, Western Pacific Division

https://www.who.int/news-room/commentaries/detail/smoking-and-covid-19

Background

The harms of tobacco use are well-established. Tobacco causes 8 million deaths every year from cardiovascular diseases, lung disorders, cancers, diabetes, and hypertension.1 Smoking tobacco is also a known risk factor for severe disease and death from many respiratory infections.2-4 In the COVID-19 pandemic, questions have been asked about clinical outcomes for smokers, and whether they are equally susceptible to infection, and if nicotine has any biological effect on the SAR-CoV-2 virus (the virus that causes COVID-19). 5-7 At the time of writing, one clinical trial to test the effects of nicotine has been announced, but no trial registration record was found as of 12 May 2020. This review therefore assesses the available peer-reviewed literature on the association between smoking and COVID-19, including 1) risk of infection by SARS-CoV-2; 2) hospitalization with COVID-19; and 3) severity of COVID-19 outcomes amongst hospitalized patients such as admission into intensive care units (ICU), use of ventilators and death.

What is the risk of smokers being infected by SARS-CoV-2?

There are currently no peer-reviewed studies that have evaluated the risk of SARS-CoV-2 infection among smokers. This research question requires well-designed population-based studies that control for age and relevant underlying risk factors.

What is the risk of smokers being hospitalized for COVID-19?

There are currently no peer-reviewed studies that directly estimate the risk of hospitalization with COVID-19 among smokers. However, 27 observational studies found that smokers constituted 1.4-18.5% of hospitalized adults. 8-32 Two meta-analyses have been published which pooled the prevalence of smokers in hospitalized patients across studies based in China. The meta-analysis by Emami et al. 33 analysed data for 2986 patients and found a pooled prevalence of smoking of 7.6% (3.8% -12.4%) while Farsalinos et al. 34 analysed data for 5960 hospitalized patients and found a pooled prevalence of 6.5% (1.4% - 12.6%).

What is the risk of severe COVID-19 disease and death amongst smokers?

Meta-analyses:

Zhao et al.35 analysed data from 7 studies (1726 patients) and found a statistically significant association between smoking and severity of COVID-19 outcomes amongst patients (Odds Ratio (OR) 2.0 (95% CI 1.3 – 3.1). The statistical significance disappeared when the largest study by Guan et al.13 was removed from the analysis (a sensitivity test to see the impact of a single study on the findings of the meta-analysis). An updated version of this meta-analysis which included an additional study remained significant when this same sensitivity test was applied however.36 Zheng et al.37 analysed data from 5 studies totalling 1980 patients and found a statistically significant association between smoking and COVID-19 severity when using a fixed effects model: OR: 2.0 (95% CI 1.3 – 3.2). Lippi et al.38 analysed data from 5 studies totalling 1399 patients and found a non-significant association between smoking and severity. Guo et al., 39 however, later identified errors in the calculation and concluded that this association was indeed statistically significant (OR 2.2 (95% CI 1.3 – 3.7). Vardavas et al.40 analysed data from 5 studies totalling 1549 patients and calculated a relative risk that indicated a non-significant relationship between smoking and severity of COVID-19. However, the same authors found a statistically significant association between smoking status and primary endpoints of admission to Intensive Care Unit (ICU), ventilator use or death.

Conclusions

At the time of this review, the available evidence suggests that smoking is associated with increased severity of disease and death in hospitalized COVID-19 patients. Although likely related to severity, there is no evidence to quantify the risk to smokers of hospitalization with COVID-19 or of infection by SARS-CoV-2 was found in the peer-reviewed literature. Population-based studies are needed to address these questions.

Related WHO Recommendations

Given the well-established harms associated with tobacco use and second-hand smoke exposure;2 WHO recommends that tobacco users stop using tobacco. Proven interventions to help users quit include toll-free quit lines, mobile text-messaging cessation programmes, nicotine replacement therapies and other approved medications.

3.2 Coronavirus disease (COVID-19): Tobacco

27 May 2020 | Q&A, World Health Organization, Western Pacific Division

https://www.who.int/westernpacific/news/q-a-detail/coronavirus-disease-covid-19-tobacco#:~:text=There%20is%20currently%20insufficient%20information,and%20COVID%2D19

As a smoker, is my risk of getting the COVID-19 virus higher than that of a non-smoker?

At the time of preparing this Q&A, there are no peer-reviewed studies that have evaluated the risk of SARS-CoV-2 infection associated with smoking.

As a smoker, am I likely to get more severe symptoms if infected?

Available research suggests that smokers are at higher risk of developing severe COVID-19 outcomes and death.

As a vaper, am I more likely to be infected or to have more severe symptoms if infected?

There is no evidence about the relationship between e-cigarette use and COVID-19. However, existing evidence indicates that electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS), more commonly referred to as e-cigarettes, are harmful and increase the risk of heart disease and lung disorders. Given that the COVID-19 virus affects the respiratory tract, the hand-to-mouth action of e-cigarette use may increase the risk of infection.

Does nicotine use affect my chances in the context of COVID-19?

There is currently insufficient information to confirm any link between tobacco or nicotine in the prevention or treatment of COVID-19. WHO urges researchers, scientists and the media to be cautious about amplifying unproven claims that tobacco or nicotine could reduce the risk of COVID-19. WHO is constantly evaluating new research, including that which examines the link between tobacco use, nicotine use, and COVID-19.

3.3 COVID-19: counter-intuitive data on smoking prevalence and therapeutic implications for nicotine

US National Institutes of Health | Intern Emerg Med. 2020 May 19 : 1–4.| Riccardo Polosa and Grazia Caci

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7236870/

Report

Some conclusive predictors of the risks for severe illness have been clearly described: the presence of co-morbidities [1], older age [2], breathlessness [3] and lymphopenia [4]. Many other predictors of COVID-19 that result in clinical severity have been proposed, but their validity has been questioned. The difficulty in identifying predictors is not surprising considering that anamnestic and behavioral data might have been

collected inaccurately due to the extremely challenging situations at wards/ICUs with work overloads and operating in a persistent state of emergency.

Intuitively, one vulnerability to severe illness from COVID-19 would be assumed to be cigarette smoking [8] because it is known to increase the risk of serious respiratory infections [5–7]. But is this in fact true? In this issue of Internal and Emergency Medicine, Farsalinos et al. [9] explore the hypothesis that smokers are at higher risk and unexpectedly found data that point to the opposite and counter-intuitive conclusion that smoking may actually have a protective effect. Their systematic review observed that smoking is vastly protective for hospitalized COVID-19 based on the surprisingly low prevalence of smoking in patients hospitalized with COVID-19.

While it is possible that the prevalence of smokers in Chinese case series may be underrepresented due to inaccurate recording of their smoking status, similar findings have been now being reported in the US, Germany and in France. The Centers for Disease Control and Prevention (CDC) [10] report an unusually low prevalence of current smoking among COVID-19 cases at 1.3% compared to population smoking prevalence in US of 16.5% [11].

A cross-sectional analysis of 4103 laboratory-confirmed COVID-19 patients treated at academic hospitals in New York City, demonstrated again a low smoking prevalence of 5.2% [12]. A multivariate analysis performed by the New York researchers showed a significant protective effect against hospitalization among current and former tobacco users (OR = 0.71, 95% CI 0.57–0.87 p = 0.001). Moreover, smoking was not a risk factor for critical disease or death. In Germany, a recent case series of hospitalized COVID-19 patients found a low smoking prevalence of about 6% [13]. The protective association has been also recently observed in France where smoking prevalence reported for various age groups and levels of disease severity roughly average to about 1/5 of the population prevalence [14]. These findings are consistent with the Chinese findings of Farsalinos et al. [9].

Based on the research that shows nicotine can prevent acute lung injury which is similar to COVID-19 pneumonia, and that nicotine inhibits the production of pro-inflammatory cytokines, the review authors hypothesize that nicotine might reduce the risk for severe COVID-19. In light of these findings, they propose that pharmaceutical nicotine may be used as a potential treatment option in COVID-19.

There is concern about this potential therapy because the impact of long term use of nicotine replacement therapy on the immune system is not known. Yet nicotine is relatively safe for human consumption at low concentrations as nicotine replacement therapy as well as nicotine-containing vaping and heated tobacco products and has been used for relatively short periods of time in non-smokers [22–24]. In addition, the World Health Organization (WHO) lists nicotine replacement as an essential medicine. Therefore, health and regulatory authorities have sufficient evidence of clinical safety these medicines to fast-track clinical trials of nicotine patches.

In the same way, the impact of other popular nicotine delivery products such as e-cigarettes and heated tobacco products on the severity of COVID-19 hospitalizations should be included in COVID-19 surveillance particularly in countries such as the UK where nicotine vaping is highly prevalent. The consistent observation that smoking prevalence is surprisingly low among hospitalized COVID-19 patients, should not be dismissed out of hand but monitored. The use of nicotine patches as a treatment for COVID-19 appears to have some potential in the race to find solutions for this terrible pandemic.

3.4 Does vaping increase COVID-19 risk?

Safer Nicotine Wiki
https://safernicotine.wiki/mediawiki/index.php/Does_vaping_increase_COVID-19_risk%3F

A large Icelandic study reported that the proportion of e-cigarette users was lower among patients with COVID-19 than in the general population of Iceland and that patients using e-cigarettes did not have more severe symptoms than other patients. A non-peer reviewed UK study found that vaping was not associated with self-reported COVID-19.

There is a considerable amount of evidence that current tobacco smoking is associated with a reduced chance of testing positive. Former smokers appear to face more serious outcomes than current or never smokers. Outcome data on current smoking are mixed.

Association Between Youth Smoking, Electronic Cigarette Use, and COVID-19

Journal of Adolescent Health | August 11, 2020 | Shivani Mathur Gaiha, Ph.D., Jing Cheng, Ph.D., Bonnie Halpern-Felsher, Ph.D.

https://doi.org/10.1016/j.jadohealth.2020.07.002

Abstract

Purpose

This study aimed to assess whether youth cigarette and electronic cigarette (e-cigarette) use are associated with coronavirus disease 2019 (COVID-19) symptoms, testing, and diagnosis.

Methods

An online national survey of adolescents and young adults (n = 4,351) aged 13–24 years was conducted in May 2020. Multivariable logistic regression assessed relationships among COVID-19–related symptoms, testing, and diagnosis and cigarettes only, e-cigarettes only and dual use, sociodemographic factors, obesity, and complying with shelter-in-place.

Results

COVID-19 diagnosis was five times more likely among ever-users of e-cigarettes only (95% confidence interval [CI]: 1.82–13.96), seven 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). Testing was nine times more likely among past 30-day dual-users (95% CI: 5.43–15.47) and 2.6 times more likely among past 30-day e-cigarette only users (95% CI: 1.33–4.87). Symptoms were 4.7 times more likely among past 30-day dual-users (95% CI: 3.07–7.16).

Conclusions

COVID-19 is associated with youth use of e-cigarettes only and dual use of e-cigarettes and cigarettes, suggesting the need for screening and education.

Implications and Contribution

The findings from a national sample of adolescents and young adults show that electronic cigarette use and dual use of electronic cigarettes and cigarettes are significant underlying risk factors for coronavirus disease 2019. Health care providers, parents, schools, community-based organizations, and policymakers must help make youth aware of the connection between smoking and vaping and coronavirus disease.

As of June 2020, more than 2.1 million people have been infected, and approximately 116,000 have died from Coronavirus Disease 2019 (COVID-19) in the U.S. [1], and the numbers continue to rise. Both cigarette and electronic cigarette (e-cigarette) use damage the respiratory system [2], [3], [4], potentially increasing the risk of experiencing COVID-19–related symptoms, a positive diagnosis and exacerbated health outcomes [5]. A meta-analysis of studies mostly in China found that smokers were at elevated risk of COVID-19 progression compared with non-smokers [6]. Hospitalizations in the U.S. show that factors such as obesity, male sex, and older age are associated with COVID-19 [7]. Although youth are at relatively lower risk of contracting COVID-19 compared with older adults, given the proportion of youth using e-cigarettes [8], youth e-cigarette and cigarette use may pose an important risk factor for COVID-19.

Currently, there are no U.S. population-based studies assessing the relationship between cigarette smoking, e-cigarette use, and COVID-19–related outcomes. In the absence of information on smoking and e-cigarette use history of youth diagnosed with COVID-19, we conducted a population-level examination of whether youth cigarette and/or e-cigarette use is associated with increased likelihood of experiencing COVID-19–related symptoms, being tested, and being diagnosed with COVID-19.

Conclusion

Our findings from a national sample of adolescents and young adults show that e-cigarette use and dual use of e-cigarettes and cigarettes are significant underlying risk factors for COVID-19 that has previously not been shown. The findings have direct implications for health care providers to ask all youth and COVID-19–infected youth about cigarette and e-cigarette use history; for parents, schools, and community-based organizations to guide youth to learn more about how e-cigarettes and dual use affect the respiratory and immune systems; for the Food and Drug Administration to effectively regulate e-cigarettes during the COVID-19 pandemic; and for the development and dissemination of youth-focused COVID-19 prevention messaging to include e-cigarette and dual use.

3.5 Association of SARS-CoV-2 infection to smoking and ecigarettes

May 07, 2020 | Journal of Medical Internet Research | Josep M Ramon-Torrell MD, ; Sergio Morchon MD, ; Fernando Aguero MD, ; Cristina Masuet-Aumatell MD,

https://www.jmir.org/preprint/19949?fbclid=IwAR3gavGTaIw_URTvVOYSaalGESkuMREAt9QGFmn7ebWLYhOf0L1CtTOznzU

Methods: : A cross-sectional study was carried out using an online questionnaire-based survey between April 6,2020 to April 19, 2020. Participants were males and females enrolled via link from website. We also posted the link in Facebook, Twitter and anti-tobacco, smokers and e-cigarette users forums. For this analysis, only participants residing in Spain were included. To measure the association between infection and independent variables odds ratios (ORs) were calculated for each category by conditional logistic regression and the corresponding 95% confidence intervals (CIs) and adjusted by age and gender.

Results: A total of 3,517 participants were included in the study. Of all the participants, 170 reported a diagnosis of SARSCoV-2 infection (4.6 % 95% CI 3.9-5.1) of which 35 (0,99 %; 95% CI 0.6-1.06)), reported a confirmed diagnosis and 135 (3.8 %; 95% CI 2.9-4.01) a clinical diagnosis. Rate of daily smokers of conventional tobacco among all participants was of 12.2 % (14.3 % of males and 9.8 of females). The number of smokers (4.7%) and users of electronic cigarettes (3.9%) among the group with infection was lower than the number of non-smokers (10.2%) (p <.01). A negative association was observed between tobacco consumption (0.52 95%CI 0.27-0.98) and the use of electronic cigarettes (0.45 95%CI 0.28-0.71) and SARS-CoV-2 infection.

Conclusions: The results must be corroborated by analytical studies. In relation to the electronic cigarette, the basis would be similar to those of conventional cigarettes and based on the role of nicotine in the incidence and progression of SAR-CoV-2 infection.

3.6 The role of nicotine in COVID-19 infection

26 May 2020 | The Centre for Evidence-Based Medicine | Jamie Hartmann-Boyce and Nicola Lindson

https://www.cebm.net/covid-19/nicotine-replacement-therapy/

VERDICT

There are biologically plausible pathways through which nicotine may impact SARS-CoV-2, but the clinical significance of these is entirely unclear.

BACKGROUND

There is mixed evidence on the role of smoking in COVID-19 infection and associated outcomes. Whereas the expectation is that smoking would predispose to worse outcomes from COVID-19, as is the case in other acute respiratory infections, some (but not all) studies of COVID-19 have detected fewer people who smoke

than would be expected in hospitalised patients with COVID-19. It is unclear whether this is due to biases, confounding, misreporting, or a potential protective effect of smoking on COVID-19 outcomes. Irrespective of COVID-19, smoking is uniquely deadly. However, nicotine, the addictive component of cigarettes, can be safe when used in other forms, and there is some biological plausibility regarding a possible role of nicotine in COVID-19 infection. Below we briefly review evidence to date on the role of nicotine in COVID-19. This is important to people who smoke, but it could also be of general relevance, as some have hypothesised nicotine may be a potential treatment for COVID-19.

CURRENT EVIDENCE

We searched the literature for studies relating to COVID-19 and nicotine. Some are underway, and this piece will be updated as new findings emerge. In the meantime, the available research literature is mainly in the form of speculative commentaries, with some lab studies also reported.

Commentaries regarding nicotine and COVID-19 all agree nicotine potentially has a role to play based on its role in the renin-angiotensin system. In particular, nicotine can impact the angiotensin-converting enzyme (ACE) 2, which is relevant because coronaviruses bind to ACE2. However, some authors interpret this as suggesting nicotine is likely to be harmful in the context of COVID-19, and others suggest the opposite.

It is extremely difficult to synthesise evidence on nicotine and COVID-19 as much of the literature is inconsistent. Below we highlight pathways/hypothetical mechanisms through which at least one paper has speculated nicotine might impact SARS-Cov-2:

- Current and past tobacco smoking are associated with changes in ACE2 receptor expression
- Nicotine up-regulates the ACE/angiotensin (ANG)-II/ANG II type 1 receptor axis, and down-regulates the compensatory ACE2/ANG-(1–7)/Mas receptor axis (commentary; commentary)
- Nicotine may bind with the ACE2 receptor, particularly in people with COVID-19, and thus could interfere with further SARS-CoV-2-ACE2 binding (pre-print in silico study)
- Nicotine and cigarette smoke decrease levels of ACE2 in multiple organs
- Cytokine storms could be prevented or suppressed by nicotine through its impact on the cholinergic anti-inflammatory system; nicotine may inhibit hyperinflammation and platelet reactivity
- Poor COVID-19 outcomes in people who smoke could be driven by nicotine withdrawal when acutely ill, thus nicotine patches “should be urgently considered and discussed” (note, nicotine patch use in hospital is a common approach across conditions)

France has had to place restrictions on sales of nicotine replacement therapy because of fears it may start to be stockpiled for inappropriate use relating to COVID-19. Studies are underway testing nicotine replacement therapy in COVID-19 patients, and until results are available from those, there is no evidence to support the general public’s use of nicotine replacement therapy for COVID-19 infection. Nicotine replacement therapy is a mainstay of smoking cessation treatment and is safe and effective in this capacity.

CONCLUSIONS

- There are biologically plausible pathways through which nicotine may impact SARS-CoV-2, but the clinical significance of these is entirely unclear
- Early studies are underway regarding the role of nicotine replacement therapy as a therapeutic aid for COVID-19
- Evidence so far is too limited to inform any decisions about use of nicotine replacement therapy in COVID-19
- When used for smoking cessation, there is high certainty evidence that nicotine replacement therapy is safe and effective.

3.7 Current smoking is not associated with COVID-19

4 June 2020 | European Respiratory Journal | Marco Rossato, Lucia Russo, Sara Mazzocut, Angelo Di Vincenzo, Paola Fioretto, Roberto Vettor

https://erj.ersjournals.com/content/55/6/2001290

Article

We have read with interest the paper by Leung et al. [1] recently published in the European Respiratory Journal, reporting a higher expression of the protein angiotensin-converting enzyme II (ACE-2) in the small airway epithelia of smokers and COPD patients with putatively important implications for coronavirus disease 2019 (COVID-19) patients, since ACE-2 has been shown to be the receptor utilised by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter the host cell [2]. Furthermore, the authors reported that current smokers showed a higher expression of ACE-2 gene expression than non-smokers, concluding that the increased ACE-2 expression in smokers might predispose to increased risk of SARS-CoV-2 infection [1].

To this regard, all epidemiological data published so far reported that COVID-19 patients show a very low prevalence of smokers, with no significant association between current smoking and severe disease in COVID-19 patients [3–6].

Thus, the conclusions of Leung et al. [1] to consider cigarette smoking as a severe risk factor for COVID-19 pneumonia are in contrast with the strong and consolidated epidemiological data coming from China [3–6] that have been confirmed also in our patients.

3.8 COVID-19 and vaping: risk for increased susceptibility to SARS-CoV-2 infection?

16 July 2020 | European Respiratory Journal | Kielan Darcy McAlinden, Mathew Suji Eapen, Wenying Lu, Collin Chia, Greg Haug, Sukhwinder Singh Sohal

https://erj.ersjournals.com/content/56/1/2001645?utm_source=TrendMD&utm_medium=cpc&utm_campaign=European_Respiratory_Journal_TrendMD_0

With great interest we read and commend the study done by Russo et al. [1], highlighting their findings that nicotine induces an increase in angiotensin-converting enzyme 2 (ACE-2) expression in human bronchial epithelial cells (HBEpC) and is mediated by α7-subtype nicotinic receptors (α7-nAChR). It raises the concern that all electronic nicotine-delivery systems may put users at greater risk of succumbing to coronavirus disease 2019 (COVID-19).

We [2], along with Leung et al. [3], have shown that ACE-2 expression is upregulated in the small airway epithelia of smokers and patients with COPD. In particular, we observed increased ACE-2 expression in type-2 pneumocytes and alveolar macrophages along with the small airway epithelium of smokers compared to healthy never-smokers [2].

Similar studies are yet to be done in the context of electronic cigarettes (e-cigarettes), heat-not-burn devices (IQOS) or waterpipe exposure to human airways. ACE-2 is the binding site for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mediating entry of the virus into cells [4]. Binding affinity between the spike proteins of the virus and ACE-2 on respiratory cells has been identified to be much higher than any previously identified human coronavirus. The significance of such overexpression of ACE-2 in smokers should not be ignored. COVID-19 and progression of severe pneumonia may be more likely to occur in smokers, particularly in those that have smoking-related comorbidities [5]. We are beginning to elucidate the role of traditional cigarette smoking and nicotine-driven changes to the lungs in the context of coronavirus transmission and susceptibility. Cigarette smoke has been identified and linked to increasing expression of the binding site for the cause of the 2020 pandemic (SARS-CoV-2) via mediating nicotine receptors. With this, an avoidable and potentially gigantic risk-factor has emerged for COVID-19, as the pandemic continues to claim ultimate grasp over the year of 2020.

Here, we bring to the discussion whether the increased susceptibility and virulence of SARS-CoV-2 via α7-nAChR and the upregulation of small airway ACE-2 expression may also be relevant for those who vape using nicotine-based e-cigarettes. E-cigarette vapour studies, although in their infancy, have already shown that they can enhance the virulence and inflammatory profile of pathogens such as Streptococcus pneumoniae,

among other deleterious biological effects [6]. Vaping intensifies pneumococcal adherence through an increase in platelet-activating factor receptor expression, ultimately rendering those who vape with an increased risk of pneumonia [7, 8].

We, among others, have previously shown that e-cigarettes and IQOS are not "safer", as having a vast pro-inflammatory response [9]. We compared cigarette smoke versus e-cigarette and IQOS on airway epithelial and smooth muscle cells [9]. All tested pathological biomarkers were elevated in cells exposed to e-cigarette aerosols and IQOS, which included chemokine CXCL8, extracellular matrix proteins and markers of mitochondrial dysfunction. We found these products toxic to the cells, evident from decreased cellular viability and integrity. More devastatingly, vaping also interfered with cellular energetics. Our results further substantiate current research that e-cigarettes and IOQS are indeed detrimental with increases in oxidative stress, inflammation, infections and airway remodelling in the lungs of these device users. As the scientific evidence mounts, confirming the fears that e-cigarettes and IQOS are strongly associated with the development and progression of debilitating lung diseases [10], now may be the prime time to include all electronic nicotine delivery systems in the vocalisation of concerns concerning tobacco-related death and disease.

3.9 IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette

10 February 2019 | European Respiratory Society | Sukhwinder Singh Sohal, Mathew Suji Eapen, Vegi G.M. Naidu, Pawan Sharma

https://openres.ersjournals.com/content/5/1/00159-2018?ijkey=0c80d801b311d1d02c5e8437d9a741d82f3d9d2f&keytype2=tf_ipsecsha

Heat-not-burn (HNB) devices can alter vital physiological functions in the lung. HNB devices may not be a safer option than cigarette smoking or eCig vaping; this does not support the recommendation of their use over other nicotine delivery products.

While cigarette smoking still remains one of the most pressing global health issues of our time, newer forms of smoking device have been introduced across the globe in the last decade [1].

- Electronic nicotine/non-nicotine delivery systems commonly known as electronic cigarettes (eCig) heat a solution (e-liquid) to create vapour [2];
- the latest addition to this list is the introduction of heat-not-burn (HNBs) tobacco products branded as IQOS [3]. HNBs are hybrids between eCigs and traditional cigarettes i.e. they are equipped with a device that heats the product, without burning to generate aerosol and the product being heated is not a liquid but real tobacco [4, 5].

Long-term eCig-exposure studies in humans are currently sparse, limiting our understanding of its direct effect(s) on both disease development and progression. eCig vaping is already at its highest level globally, and many countries are imposing stringent regulations in light of the emerging evidence showing the adverse effects of vaping on human health.

IQOS use is comparatively new; it will take years before we start to know its detrimental effect on human health. We demonstrate here for the first time that IQOS exposure is as detrimental as cigarette smoking and vaping to human lung cells. Persistent allergic, smoke or environmental-triggered inflammation leads to airway remodelling/scarring through re-organisation of ECM and airway cell proliferation, and mitochondrial dysfunction plays a pivotal role in this process. These are the principal causes for airflow limitation in asthma and COPD.

3.10 Associations between vaping and COVID-19: cross-sectional findings from the HEBECO study

Dec 7 2020 | News-Medical.Net | Dr. Ramya Dwivedi, Ph.D.

https://www.news-medical.net/news/20201207/Associations-between-vaping-and-COVID-19-cross-sectional-findings-from-the-HEBECO-study.aspx

In this study, the research team from the University College London, UK, highlight: 1) there is no difference found in diagnosed/suspected COVID-19 in between never, current, and ex-vapers; 2) half of the current vapers changed their vaping consumption since COVID-19; 3) motivation to quit vaping was partly related to COVID-19.

- In conclusion, the study found that the diagnosed/suspected COVID-19 is not associated with vaping status, when assessed by self-report in a UK population sample.

3.11 Does Nicotine Prevent Cytokine Storms in COVID-19?

28 October 2020 | Cureus.com | Luiz Dratcu, Xavier Boland

https://www.cureus.com/articles/41018-does-nicotine-prevent-cytokine-storms-in-covid-19

Given the association of smoking with COPD, smokers would be expected to be particularly vulnerable to COVID-19 complications [3,12]. However, a retrospective cohort study in France reported that smokers had a SARS-CoV-2 infection attack rate four times lower than non-smokers [13]. Another retrospective French study reported that, compared to the general population, smokers had a dramatically lower risk of developing symptomatic or severe COVID-19 [14]. Further similar findings elsewhere [15,16] have raised the question as to whether nicotine may have any biological effect on the SAR-CoV-2 virus.

Nicotine can selectively reduce the inflammatory response in various infection states, including Legionella pneumophila and Chlamydia pneumoniae infection, via the cholinergic anti-inflammatory pathway [6]. Nicotine is an agonist at the α7 subunit of nicotinic acetylcholine (α7-nACh) receptors on innate immune cells such as macrophages. These receptors respond to acetylcholine from different sources, including other immune cells and the vagus nerve, and their activation causes suppression of pro-inflammatory cytokines. Nicotine is able to suppress the production of pro-inflammatory cytokines by mimicking the binding of acetylcholine.

The SARS-CoV-2 virus may itself antagonise the nACh receptor pathway and reduce its anti-inflammatory action [17]. Nicotine, again through its action at α7-nACh receptors in the lungs, could prevent the virus-induced nACh receptor dysregulation by activating the cholinergic anti-inflammatory pathway. Smoking could thus attenuate the normal defensive function of the immune system and reduce the hyperinflammatory response seen in severe COVID-19, while the immune system of non-smokers may be more prone to SARS- CoV-2 cytokine release syndrome [17]. However, as nicotine increases the expression of ACE2 in the lung and ACE2 increase is mediated by α7-nACh receptors, smoking may promote cellular uptake mechanisms of SARS2 CoV-2 through α7-nAch receptor signalling [18].

Current evidence for a protective effect of nicotine in COVID-19 remains controversial. Nonetheless, there has been a support to the notion of repurposing NRT products [19], such as nicotine patches [20], as an adjunctive treatment for COVID-19 in smokers as our case seems to suggest, the potential role of NRT in the management of COVID-19 warrants further scrutiny.

3.12 Abstract: Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette

Nov 2018 | Addiction, Volume113, Issue11, Pages 2099-2106 | Konstantinos E. Farsalinos, Nikoletta Yannovits, Theoni Sarri, Vassilis Voudris, Konstantinos Poulas, Scott J. Leischow

https://onlinelibrary.wiley.com/doi/abs/10.1111/add.14365

Aims

To measure carbonyl emissions from a heated tobacco product (IQOS) in comparison with an e‐cigarette (Nautilus Mini) and a commercial tobacco cigarette (Marlboro Red).

Findings

At the Health Canada Intense regimen, heated tobacco products emitted 5.0–6.4 μg/stick formaldehyde, 144.1–176.7 μg/stick acetaldehyde, 10.4–10.8 μg/stick acrolein, 11.0–12.8 μg/stick propionaldehyde and 1.9–2.0 μg/stick crotonaldehyde. Compared with the tobacco cigarette, levels were on average 91.6% lower for formaldehyde, 84.9% lower for acetaldehyde, 90.6% lower for acrolein, 89.0% lower for propionaldehyde and 95.3% lower for crotonaldehyde. The e‐cigarette emitted 0.5−1.0 μg/12 puffs formaldehyde, 0.8–1.5 μg/12 puffs acetaldehyde and 0.3–0.4 μg/12 puffs acrolein, but no propionaldehyde and crotonaldehyde. At more intense puffing regimens, formaldehyde was increased in heated tobacco products, but levels were three–fourfold lower compared with the tobacco cigarette. Based on the findings from Health Canada Intense puffing regimen, use of 20 heated tobacco sticks would result in approximately 85% to 95% reduced carbonyl exposure compared with smoking 20 tobacco cigarettes; the respective reduction in exposure from use of 5 g e‐cigarette liquid would be 97% to > 99%.

Conclusions

The IQOS heated tobacco product emits substantially lower levels of carbonyls than a commercial tobacco cigarette (Marlboro Red) but higher levels than a Nautilus Mini e‐cigarette.

3.13 Factors associated with hospitalization and critical illness among 4,103 patients with Covid-19 disease in New York City

| Christopher M. Petrilli,. Simon A. Jones, Jie Yang, Harish Rajagopalan, Luke O'Donnell, Yelena Chernyak, Katie A. Tobin, Robert J. Cerfolio, Fritz Francois, Leora I. Horwitz

https://www.medrxiv.org/content/10.1101/2020.04.08.20057794v1

Abstract

Background Little is known about factors associated with hospitalization and critical illness in Covid-19 positive patients.

Discussion

We find particularly strong associations of older age, obesity, heart failure and chronic kidney disease with hospitalization risk, with much less influence of race, smoking status, chronic pulmonary disease and other forms of heart disease.

Surprisingly, though some have speculated that high rates of smoking in China explained some of the morbidity in those patients, we did not find smoking status to be associated with increased risk of hospitalization or critical illness. This is consistent with a handful of other studies that have previously

shown a lack of association of smoking with pulmonary disease-associated ARDS (i.e. from pneumonia), as compared with non-pulmonary sepsis-associated ARDS.29

3.14 Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory–confirmed COVID-19 cases

30 July 2020 | European Respiratory Journal 2020 | Theodoros V. Giannouchos, Roberto A Sussman, José Mier, Konstantinos Poulas, Konstantinos Farsalinos

; **DOI:** 10.1183/13993003.02144-2020

Discussion

To the best of our knowledge, this study presents a case series with the highest number of laboratory-confirmed COVID-19 patients, and the first of this size from a LMIC. The Chinese Centers for Disease Control (CDC) recently presented data from 44 672 confirmed cases, however information about comorbidities was available for only 20 812 patients [9]. Another study in the UK examined risk factors for critical care and mortality in hospital among 20 133 hospitalised COVID-19 patients [10]. In the US, patient characteristics, comorbidities and outcomes were presented among 5700 patients hospitalised for COVID-19 in New York City area [11]. Our study adds to the current evidence by presenting information from laboratory-confirmed cases in a LMIC using a large publicly available dataset.

In agreement with previous studies [1, 10–14], age was a strong risk factor for hospitalisation, adverse outcome among COVID-19 patients. It was recognised early during the pandemic that the elderly had higher rates of hospitalisation and infection fatality ratios compared to younger people [15]. Recently, the US CDC reported that the best estimates for the COVID-19 symptomatic case fatality ratio was 0.4% for the whole population but ranged from 0.05% for those aged 0–49 years to 1.3% for those ≥65 years, a 26-fold difference [16]. Hospitalisation rates were estimated to be approximately 7-fold higher for patients aged ≥65 years compared to those aged 18 to 44 years in our study. Thus, targeted interventions tailored at the higher needs and risk of older people are clearly needed, to protect them from SARS-CoV-2 infection and to reduce the COVID-19 morbidity and mortality burden.

Our results indicate that cardiovascular and endocrine conditions were the most common comorbidities identified among confirmed COVID-19 patients. Hypertension, obesity and diabetes were not only common comorbidities but also independent correlates of hospitalisation and adverse outcomes. These findings are in-line with case series from China, the US and Europe [1, 9–13].

In contrast, while cardiovascular disease and COPD were risk factors for hospitalisation, and adverse outcomes, only a small proportion of patients suffered from these comorbidities. A case series of 1590 patients from China reported a similarly low prevalence of these comorbidities among Chine patients [12]. The Chronic Obstructive Pulmonary Disease (COPD) prevalence in Mexico City was 3.4% in a study defining airflow obstruction as $FEV1/FEV_6$ below the 5th percentile or Lower Limit of Normal [23], but it has been reported that COPD is highly underdiagnosed in Mexico and in other countries, mainly because of lack of spirometry evaluation [24]. In a 2009 study, ischemic heart disease and stroke prevalence in Mexico City ranged from 0.4% to 5.4% and from 0.4% to 3.5%, respectively, depending on age [25]. In addition, other risk factors for adverse outcomes were immunosuppression and chronic renal disease. Our findings are supported by a recent systematic review and meta-analysis which found a higher risk for adverse COVID-19 outcomes among patients with chronic renal disease [26].

Having more than one comorbidity was strongly associated with hospitalisation and adverse outcome.

Notably, smoking was not associated with a higher risk for adverse outcomes and hospitalisation. Smokers were also less likely to be diagnosed with COVID-19 compared to non-smokers. The latter is in agreement with a recent observational population study from Israel [27]. Some studies have found that smokers are under-represented

among COVID-19 patients and presented a hypothesis that nicotine may exert protective effects [28–31], while others have found that nicotine and smoking causes ACE2 up-regulation which may increase viral invasion [31, 32]. Recent meta-analyses reported that hospitalised smokers with COVID-19 had higher odds for adverse outcomes [33–35], but very few smokers relative to the population smoking rates appear to be hospitalised for COVID-19 [35]. It is possible that more smokers have been tested for COVID-19 compared to non-smokers, which could explain the lower odds for positive diagnostic test. This cannot be directly addressed in this study since all participants were by definition subjects who were tested for COVID-19. However, according to the latest data (2016), the smoking prevalence in Mexico was 14.0% in the population aged ≥15 years [36]. In our study, 9.0% of the sample were smokers. Even if we assume that none of the participants aged 0–17 were smokers (4.8% of the total sample), still smokers would represent approximately 9.6% of the adult sample, lower than the population smoking rates. Thus, it is unlikely that smokers were more likely to be tested for COVID-19 based on the proportion of smokers in the study sample and the population smoking rates. It is currently unclear whether nicotine exerts any positive effect, however, there is no doubt that smoking cannot be used as a protective measure and smoking cessation should be encouraged during the COVID-19 pandemic [29].

3.15 Low rate of daily smokers in patients with symptomatic COVID-19 (in France)

12 June 2020 | medRxiv | Makoto Miyara, Florence Tubach, Valérie Pourcher, Capucine Morélot-Panzini, Julie Pernet, Julien Haroche, Said Lebbah, Elise Morawiec, Guy Gorochov, Eric Caumes, Pierre Hausfater, Alain Combes, Thomas Similowski, Zahir Amoura

doi: https://doi.org/10.1101/2020.06.10.20127514

Abstract

Background Identification of prognostic factors in COVID-19 remains a global challenge. The role of smoking is still controversial.
Objective To evaluate the rate of daily smokers in patients with COVID-19.
Methods COVID-19 in-and outpatients from a large French university hospital were systematically interviewed for their smoking status, use of e-cigarette and nicotinic substitutes. The rates of daily smokers in in-and outpatients were compared to those in the 2019 French general population, after standardization for sex and age.
Results The inpatient group was composed of 340 patients, median age 66 years: 203 men (59.7%) and 137 women (40.3%), median age for both 66 years, with a daily smokers rate of 4.1 % CI95% [2.3–6.9] (5.4% of men, 2.2% of women). The outpatient group was composed of 139 patients, median age 44 years: 62 men (44.6%, median age 43 years), and 77 women (55.4%, median age 44 years). The daily smoker rate was 6.1 % CI 95% [2.7 - 11.6] (5.1% of men, 6.8% of women). In the 2019 French population, the daily smoker rate was 24.0% (27.5% of men, 20.7% of women). Among inpatients, daily smokers represented 2.2% and 3.4% of the 45 dead patients and of the 29 patients transferred to ICU, respectively.
The rate of daily smokers was significantly lower in COVID-19 patients, as compared to that in the French general population after standardization by age and sex, with Standardized Incidence Ratios of 0.24 [0.12-0.48] for outpatients and 0.24 [0.14-0.40] for inpatients.

Conclusion Daily smokers rate in patients with symptomatic COVID-19 is lower as compared to the general population

Introduction

As the pandemic of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still under progression, the identification of risk factors is a global challenge. Among epidemiological risk factors, the role of smoking, to date, is unclear. Smoking has been initially found associated with adverse disease prognosis of COVID-19[1], although this finding remains controversial[2]. Reported rates of current smokers among SARS-CoV-2-infected patients range from 1.4% to 12.5% in China[1, 3-10], from 1.3% to 5.1% in the USA[11, 12], mainly for hospitalized patients (see systematic review in[13]). For outpatients, data are very scarce but also suggest similar low rates[13]. At first approach, the rates of current smokers in both

COVID-19 in- and out patients seem to be low compared to the general population. These data notwithstanding, no firm conclusions can be drawn from these available COVID-19 studies because main potential confounders for smoking rate, namely age and sex, were not taken into account. Additionally, these studies included mostly hospitalized patients, and the low rate of current smokers may be related to high rate of patients with comorbidities (smokers having been advised to quit). Furthermore, these studies used data collected in the context of care in the medical files, which favors underreporting (patients being considered as non smokers when smoking status is not reported in the medical file) particularly when data collection is made by overwhelmed care healthcare teams for a disease *a priori* not related to smoking, and biased reporting (preferential smoking status collection in patients with pulmonary or cardiovascular comorbidities).
Therefore, the effect of current smoking on the risk of SARS-CoV-2 infection has yet to be determined. To accurately evaluate whether or not current smoking is associated with the risk of COVID-19, we conducted an observational study specifically designed to investigate this association, and compared the rates of daily current smokers after standardization by sex and age of two COVID-19 patients' groups, one composed of outpatients (not subsequently hospitalized) and one of hospitalized patients (inpatients), with those reported in the 2019 French general population[14]

Results

Demographic and Clinical Characteristics

A total of 340 inpatients and 139 outpatients were included. The demographic and clinical characteristics of the two groups are shown in TABLE 1. As shown in figure 1, age distribution differed between outpatients and inpatients, with outpatients being younger and inpatients older.

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TABLE 1:

Clinical characteristics and smoking habits of COVID-19 patients

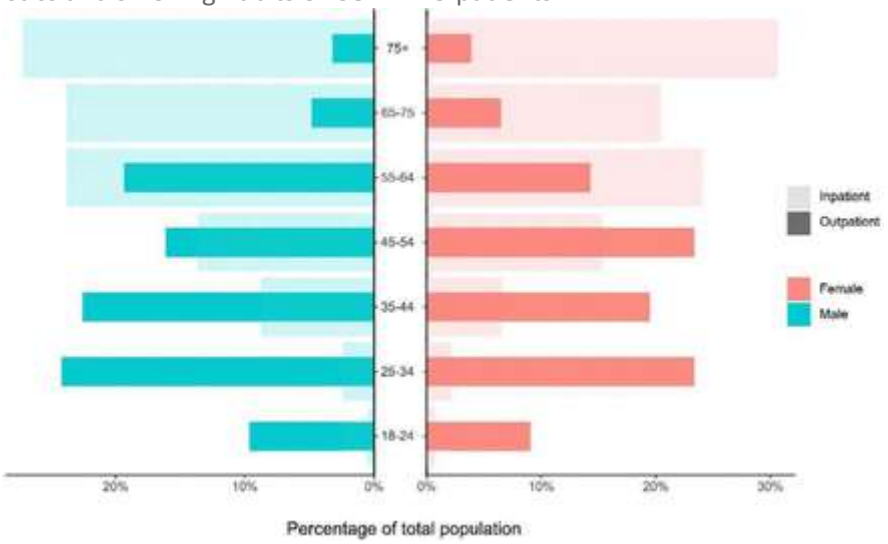

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Figure 1.

Age and sex distribution in COVID-19 inpatients and outpatients.

Dark and light shaded histograms represent outpatients and inpatients with confirmed COVID-19 status, respectively

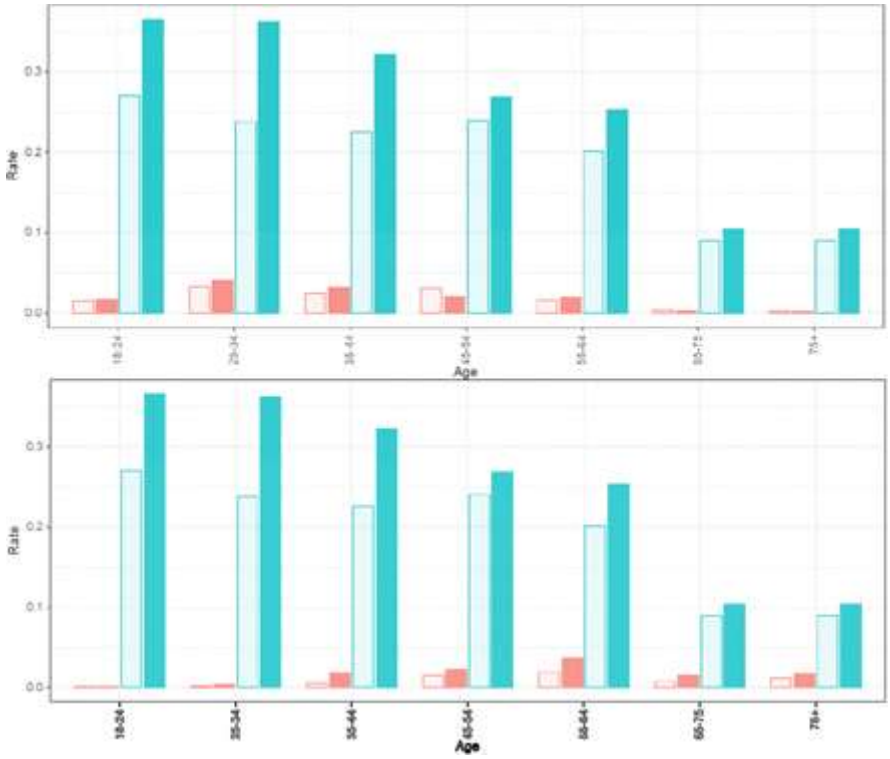

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Figure 2.

Age and sex expected rates of daily smokers in COVID-19 patients

(A) For outpatients. (B) For inpatients

Light shaded and dark histograms represent women and men daily smokers, respectively.

In blue: expected incidence rate in each age and sex class; in red: expected incidence rate in each age and sex class.

The inpatient group was composed of 340 patients, median age 66 years: 203 men (59.7%, median age 66 years) and 137 women (40.3%, median age 66 years). The rate of daily smokers was 4.1% CI95% [2.3 – 6.9] (5.4% of men and 2.2% of women) corresponding to 14 patients. Among them, 4 smoked 5 cigarettes/day or less, 3 smoked 6 to 10 cigarettes/day, 1 smoked 15 cigarettes/day and 5 smoked 20 or more cigarettes/day (and the data was missing for 1). For former smoker inpatients (n=111, 32.8 %), time duration since quitting was available for all but 6 patients. Five (4.8%) patients had quitted 2 months, and 2 (1.9%) patients 6 months before the clinical onset of the disease and 98 (93.3 %) more than one year before disease onset. Two former smokers (1.9%) were using nicotine substitutes (one by e-cigarettes and one by patches) at the time of disease onset.

The outpatient group was composed of 139 patients, median age 44 years: 62 men (44.6 %, median age 43 years), and 77 women (55.4 %, median age 44 years). In all, 68 (51.5%) were healthcare workers. Smoking status was missing for 7 patients. The daily smokers rate was 6.1% CI95% [2.7 - 11.6] (5.1% of men and 6.8 % of women) corresponding to 8 outpatients. Among them, 3 smoked less than 5 cigarettes/day, 3 smoked 6 to 10 cigarettes/day, and 2 smoked 20 or more cigarettes/day. After COVID-19 onset, 2 have stopped smoking, and none have taken nicotinic substitutes. Occasional smokers were 6 (4.5%), 2 have stopped smoking since COVID-19 onset and none have taken nicotinic substitutes. Former smokers were 41 (31,1%; 21 men and 20 women). Among these, 2 (4.9%) had quitted three months before COVID-19 symptoms onset and 39 (95.1%) more than 1 year before; 2 (4.9%) were using nicotinic substitutes (1 by use of e-cigarette). Among the 77 non-smokers, none were using nicotinic substitute (data was missing for 7).

The comorbidities were more frequently observed in inpatients than in outpatients: hypertension (age and sex-adjusted OR : OR_{adj}= 2.5; 95%CI(1.4-4.8); p=0.004), diabetes (OR_{adj}=5.4; 95%CI(2.4-13.7); p<0.001),

obesity (OR_{adj}=3.7; 95%CI(1.7-8.9), p=0.002), immune deficiencies (OR_{adj}==12.45; 95%CI(4.6-44.3); p<0.001) except for COPD (OR_{adj}==2.0; 95%CI(0.5-13.3), p=0.38).

Outcome of COVID-19 inpatients

The outcome of inpatients is described in TABLE 2 and was as follows: 211 discharges without any ICU stay (62.1%), 54 still hospitalized in medical ward without any ICU stay (15.9%) by one month after onset of clinical symptoms and 29 transfers to ICU (8.5%) and 46 deaths in ICU or medical wards (13.5%). Among the 14 daily smokers, 1 (7.1%) patient died and 1 (7.1 %) has been referred to intensive care unit by day 30 after clinical onset, while all occasional smokers were discharged. 23 former smokers (20.7 %) and 21 non smokers (10%) died while 11 former smokers (9.9%) and 17 non smokers (8.1%) have been transferred to ICU. Thus, active smokers represented 2.2% and 3.4% of the 45 dead patients and the 29 patients transferred to ICU respectively, whereas they represented 4.1% of the inpatients.

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TABLE 2:

OUTCOME OF INPATIENTS

Comparison of the daily smoker rate with the French general population

The age and sex-SIR for daily smokers are shown in TABLE 3. In the main analysis, SIRs were 0.24 [0.12 - 0.48] and 0.24 [0.14 - 0.40] for outpatients and inpatients, respectively. The SIR in outpatients did not significantly differ from that in inpatients (p = 0.99). In the outpatients, the SIR was 0.17 [0.05-0.53] in the healthcare workers, and 0.32 [0.13-0.76] in the others. Sensitivity analyses yielded similar results.

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TABLE 3:

Standardized Incidence Ratios for daily smokers

To note, the daily smoker rate in the 76-85 years inpatients and outpatients was 1.6% and 3.8%, respectively, lower than 4.8% observed in the French 76-85 years people in 2019 population.

Discussion

This cross sectional study shows that the daily smokers rate is significantly lower in symptomatic COVID-19 patients than in the French general population, either for outpatients and inpatients. The SIRs of daily smokers in COVID-19 outpatients and inpatients were 0.24 [0.12 - 0.48] and 0.24 [0.14 - 0.40], respectively, which means a decrease of 76% as compared to the French population, accounting for age and sex distribution. This result suggests that daily smokers have a lower probability of developing symptomatic SARS-CoV-2 infection as compared to the general population. The SIRs did not differ between outpatients and inpatients, suggesting that the potential effect of smoking is towards symptomatic COVID-19, irrespective of the severity. In the rare daily smokers in the COVID-19 patients of our study, we did not observed any effect of the daily cigarette consumption. Actually some were heavy smokers and others not. To note, in 2019, the mean number of daily cigarettes by current smokers in the French general population was 12.5 cigarettes, or equivalent, with 13.5 cigarettes for men and 11.4 for women [14]. We also observed a very rare use of nicotinic substitutes in the former smokers (2/111 in the inpatients and 2/41 in the outpatients, one of each group with e-cigarette), and in none of the outpatients not-smokers, which is in line with the national survey indicating that e-cigarette use is still low in France (4.4% of daily users), and is not used by non smokers (1% of e-cigarette users).

Because this is a cross-sectional study, we cannot conclude to the causality of the association. We cannot also identify which of the many compounds of tobacco exerts the protective effect of smoking on COVID-19. There are however, sufficient scientific data to suggest that smoking protection is likely to be mediated by nicotine. SARS-CoV2 is known to use the angiotensin converting enzyme 2 (ACE2) receptor for cell entry[23-25], and there is evidence that nicotine modulates ACE2 expression[26] which could in turn modulate the nicotinic acetyl choline receptor[27]. We hypothesize that SARS-CoV2 might alter the control of the nicotine receptor by acetylcholine. This hypothesis may also explain why previous studies have found an association between smoking and Covid-19 severity.

In conclusion, our results suggest that active smokers may be protected against symptomatic COVID-19. This was evidenced for outpatients (who have less serious infections) as well as for hospitalized patients. The physiopathological process underlying this effect may involve nicotine through the nicotinic receptor (and not the smoke of cigarettes per se), a hypothesis that deserves further evidence.

In light of the possible increased risk of severe form of COVID-19 among smokers once infected and of the long-term harmful consequences of smoking which is responsible for a very heavy public health burden with more than 78,000 deaths per year in France, our findings needs careful consideration and cannot be translating it into a clinical practice. Careful investigation of the potential protective effect of nicotine should be investigated both in *in vitro* and *in vivo* before any firm conclusion can be drawn.

4 Library – COVID risk / Vaping

Yellow – positive / Blue – Negative

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1 Smoking and COVID-19

30 June 2020 | Scientific Brief, World Health Organization, Western Pacific Division

https://www.who.int/news-room/commentaries/detail/smoking-and-covid-19

1.1 Conclusions

At the time of this review, the available evidence suggests that smoking is associated with increased severity of disease and death in hospitalized COVID-19 patients. Although likely related to severity, there is no evidence to quantify the risk to smokers of hospitalization with COVID-19 or of infection by SARS-CoV-2 was found in the peer-reviewed literature. Population-based studies are needed to address these questions.

1.2 Related WHO Recommendations

Given the well-established harms associated with tobacco use and second-hand smoke exposure;2 WHO recommends that tobacco users stop using tobacco. Proven interventions to help users quit include toll-free quit lines, mobile text-messaging cessation programmes, nicotine replacement therapies and other approved medications.

2 Coronavirus disease (COVID-19): Tobacco

27 May 2020 | Q&A, World Health Organization, Western Pacific Division

https://www.who.int/westernpacific/news/q-a-detail/coronavirus-disease-covid-19-tobacco#:~:text=There%20is%20currently%20insufficient%20information,and%20COVID%2D19

2.1 As a smoker, is my risk of getting the COVID-19 virus higher than that of a non-smoker?

At the time of preparing this Q&A, there are no peer-reviewed studies that have evaluated the risk of SARS-CoV-2 infection associated with smoking. However, tobacco smokers (cigarettes, waterpipes, bidis, cigars, heated tobacco products) may be more vulnerable to contracting COVID-19, as the act of smoking involves contact of fingers (and possibly contaminated cigarettes) with the lips, which increases the possibility of transmission of viruses from hand to mouth. Smoking waterpipes, also known as shisha or hookah, often involves the sharing of mouth pieces and hoses, which could facilitate the transmission of the COVID-19 virus in communal and social settings.

2.2 As a smoker, am I likely to get more severe symptoms if infected?

Smoking any kind of tobacco reduces lung capacity and increases the risk of many respiratory infections and can increase the severity of respiratory diseases. COVID-19 is an infectious disease that primarily attacks the lungs. Smoking impairs lung function making it harder for the body to fight off coronaviruses and other respiratory diseases. Available research suggests that smokers are at higher risk of developing severe COVID-19 outcomes and death.

2.3 As a vaper, am I more likely to be infected or to have more severe symptoms if infected?

There is no evidence about the relationship between e-cigarette use and COVID-19. However, existing evidence indicates that electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS), more commonly referred to as e-cigarettes, are harmful and increase the risk of heart disease and lung disorders. Given that the COVID-19 virus affects the respiratory tract, the hand-to-mouth action of e-cigarette use may increase the risk of infection.

2.4 What about using smokeless tobacco, like chewing tobacco?

Using smokeless tobacco often involves some hand to mouth contact. Another risk associated with using smokeless tobacco products, like chewing tobacco, is that the virus can be spread when the user spits out the excess saliva produced during the chewing process.

2.5 What does WHO recommend for tobacco users?

Given the risks to health that tobacco use causes, WHO recommends quitting tobacco use. Quitting will help your lungs and heart to work better from the moment you stop. Within 20 minutes of quitting, elevated heart rate and blood pressure drop. After 12 hours, the carbon monoxide level in the bloodstream drops to normal. Within 2-12 weeks, circulation improves and lung function increases. After 1-9 months, coughing and shortness of breath decrease. Quitting will help to protect your loved ones, especially children, from exposure to second-hand smoke.

WHO recommends the use of proven interventions such as toll-free quit lines, mobile text-messaging cessation programmes, and nicotine replacement therapies (NRTs), among others, for quitting tobacco use.

2.6 What can I do to protect people from the risks associated with smoking, smokeless tobacco use and vaping?

1. If you smoke, use e cigarettes or use smokeless tobacco, now is a good time to quit completely.
2. Do not share devices like waterpipes and e-cigarettes.
3. Spread the word about the risks of smoking, using e-cigarettes and using smokeless tobacco.
4. Protect others from the harms of second-hand smoke.
5. Know the importance of washing your hands, physical distancing, and not sharing any smoking or e-cigarette products.
6. Do not spit in public places

2.7 Does nicotine use affect my chances in the context of COVID-19?

There is currently insufficient information to confirm any link between tobacco or nicotine in the prevention or treatment of COVID-19. WHO urges researchers, scientists and the media to be cautious about amplifying unproven claims that tobacco or nicotine could reduce the risk of COVID-19. WHO is constantly evaluating new research, including that which examines the link between tobacco use, nicotine use, and COVID-19.

3 COVID-19: counter-intuitive data on smoking prevalence and therapeutic implications for nicotine

US National Institutes of Health | Intern Emerg Med. 2020 May 19 : 1–4.| Riccardo Polosa and Grazia Caci

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7236870/

3.1 Report

All the world is aware of the Coronavirus pandemic, and as of the 23rd of April 2020 globally 2.629.801 cases had been confirmed, and 183.454 fatalities had occurred (https://coronavirus.jhu.edu/map.html). The world is struggling and working to contain the disease and death of this active new virus. On top of the medical toll, the COVID-19 pandemic has resulted in severe economic devastation that has tragic and widespread consequences for human health and suffering.

Multiple strategies are necessary to end this pandemic. Some of these actions are supplying all health professionals with personal protective equipment, reorganizing healthcare systems with COVID-19 dedicated high-dependency hospitals/wards, testing new treatments and vaccines, and motivating people to maintain social distancing practices even when the pandemic recedes.

In the absence of long-term immunization against SARS-CoV-2 or effective therapies for COVID-19, healthcare professionals must have access to clear information that accurately predicts which patients with the virus would go on to develop clinical deterioration of COVID-19 (high-risk populations). A better clinical definition of those at high-risk for severe illness with COVID-19 is vital for effective clinical assessment, risk stratification, resource allocation repositioning, and targeted public health interventions.

Some conclusive predictors of the risks for severe illness have been clearly described: the presence of co-morbidities [1], older age [2], breathlessness [3] and lymphopenia [4]. Many other predictors of COVID-19 that result in clinical severity have been proposed, but their validity has been questioned. The difficulty in identifying predictors is not surprising considering that anamnestic and behavioral data might have been collected inaccurately due to the extremely challenging situations at wards/ICUs with work overloads and operating in a persistent state of emergency.

Intuitively, one vulnerability to severe illness from COVID-19 would be assumed to be cigarette smoking [8] because it is known to increase the risk of serious respiratory infections [5–7]. But is this in fact true? In this issue of Internal and Emergency Medicine, Farsalinos et al. [9] explore the hypothesis that smokers are at higher risk and unexpectedly found data that point to the opposite and counter-intuitive conclusion that smoking may actually have a protective effect. Their systematic review observed that smoking is vastly protective for hospitalized COVID-19 based on the surprisingly low prevalence of smoking in patients hospitalized with COVID-19.

While it is possible that the prevalence of smokers in Chinese case series may be underrepresented due to inaccurate recording of their smoking status, similar findings have been now being reported in the US, Germany and in France. The Centers for Disease Control and Prevention (CDC) [10] report an unusually low prevalence of current smoking among COVID-19 cases at 1.3% compared to population smoking prevalence in US of 16.5% [11].

A cross-sectional analysis of 4103 laboratory-confirmed COVID-19 patients treated at academic hospitals in New York City, demonstrated again a low smoking prevalence of 5.2% [12]. A multivariate analysis performed by the New York researchers showed a significant protective effect against hospitalization among current and former tobacco users (OR = 0.71, 95% CI 0.57–0.87 p = 0.001). Moreover, smoking was not a risk factor for critical disease or death. In Germany, a recent case series of hospitalized COVID-19 patients found a low smoking prevalence of about 6% [13]. The protective association has been also recently observed in France where smoking prevalence reported for various age groups and levels of disease severity roughly average to about 1/5 of the population prevalence [14]. These findings are consistent with the Chinese findings of Farsalinos et al. [9].

Given the circumstances of the pandemic, the quality of Chinese, US and German data is uncertain. The counter-intuitive implications of these findings make it difficult to accept that somehow smoking could be a protective factor. Yet those who warn of increased risks for COVID-19 incidence and severity from smoking should not present this advice as anything but a supposition based on the known link between smoking and COVID-19 datasets.

For the evidence about the effects of smoking on COVID-19, the accuracy of Chinese reporting could be questioned. Guan et al. [1] recently reported frequency of comorbidities in 1590 laboratory-confirmed hospitalized COVID-19 patients and added an additional 489 COVID-19 Chinese patients to the original sample of 1099 patients, altering the dataset that the authors had published a few weeks earlier [15]. A careful examination of both papers points to substantial discrepancies. The most inexplicable relates to the number of patients with chronic renal disease, with a phenomenal 34-fold increase of cases from 8 (0.7% of the total sample of 1099) to 269 (16.9% of the total sample of 1590). The same discrepancy occurs with the number of COVID-19 patients with cancer increasing 13-fold from 0.9 to 8.2% and patients with immunodeficiency increasing 30-fold from 0.2 to 3.7%.

Another puzzling discrepancy is that the larger study has fewer current/former smokers (n = 111) compared to numbers reported in the smaller study (n = 158). In a retrospective case–control Chinese study comparing hospitalized COVID-19 patients with ARDS to hospitalized H1N1 patients with ARDS, 11% of the 73 patients with ARDS due to SARS-CoV-2 were smokers and 47% of the 75 patients with ARDS due to H1N1 were smokers [16]. This substantial difference in the number of patients who smoke suggests that Chinese clinicians do not appear to be under-reporting patients' smoking status in their medical records. Moreover, one Chinese paper that actively gathered detailed smoking data rather than relying on medical records reported that only 2 of 140 COVID-19 patients smoked and that seven were former smokers [17]. Thus, similar low smoking prevalence among hospitalized COVID-19 patients was also found even when using better data collection methods for reporting smoking status. Of note, the Chinese paper which accurately

reports smoking status observed the lowest smoking prevalence of all those included in the analysis by Farsalinos et al. ([9]; see Fig. 1).

Assuming limited confidence in the accuracy of the reporting of the studies from China, the US, and Germany, what are the implications of the findings? Given the magnitude of the protective effect, should people consider smoking until the pandemic subsides? Of course, such a highly provocative proposition is medically indefensible. Yet in the quest for new therapies to stem the spread of the Coronavirus pandemic and limit morbidity and mortality from COVID-19 these findings deserve serious scientific consideration.

The frantic search for new therapies and vaccines to stem the spread of the Coronavirus pandemic and limit morbidity and mortality from COVID-19 drives the ultimate 21st century gold rush, to which new protagonists are continuously added on a weekly basis. As of the 23rd of April 2020, ClinicalTrials.gov listed a massive 801 ongoing clinical studies on COVID-19, including randomized trials investigating antivirals, biologics, immunomodulatory drugs, monoclonal antibodies, antibiotics, anti-inflammatory drugs, anticoagulants, and many others (https://clinicaltrials.gov/ct2/results?cond=COVID&term=&cntry=&state=&city=&dist =).

The analysis by Farsalinos et al. [9] may have therapeutic implications. Cigarette smoke is a complex mixture of thousands of harmful and potentially harmful constituents. Although the health risks of cigarette smoking are well documented, experimental evidence indicates that cigarette smoking may exert both adverse and beneficial effects of cigarette smoke to modulate the immune system [18]. Amongst the many constituents of cigarette smoke, carbon monoxide [19], several flavorings (e.g., menthol) [20], and nicotine [21] have been shown to exert anti-inflammatory and positive immune-modulatory function.

Based on the research that shows nicotine can prevent acute lung injury which is similar to COVID-19 pneumonia, and that nicotine inhibits the production of pro-inflammatory cytokines, the review authors hypothesize that nicotine might reduce the risk for severe COVID-19. In light of these findings, they propose that pharmaceutical nicotine may be used as a potential treatment option in COVID-19. There is concern about this potential therapy because the impact of long term use of nicotine replacement therapy on the immune system is not known. Yet nicotine is relatively safe for human consumption at low concentrations as nicotine replacement therapy as well as nicotine-containing vaping and heated tobacco products and has been used for relatively short periods of time in non-smokers [22–24]. In addition, the World Health Organization (WHO) lists nicotine replacement as an essential medicine. Therefore, health and regulatory authorities have sufficient evidence of clinical safety these medicines to fast-track clinical trials of nicotine patches.

Further evidence of the effect of nicotine on COVID-19 should be observed in Sweden where snus—an oral tobacco product that releases high concentrations of nicotine—consumption is highly prevalent. If the hypothesis of nicotine being protective against hospitalized COVID-19 is correct, this should be evident by analyzing the prevalence of snus usage in Swedish patients hospitalized with COVID-19. In the same way, the impact of other popular nicotine delivery products such as e-cigarettes and heated tobacco products on the severity of COVID-19 hospitalizations should be included in COVID-19 surveillance particularly in countries such as the UK where nicotine vaping is highly prevalent. The consistent observation that smoking prevalence is surprisingly low among hospitalized COVID-19 patients, should not be dismissed out of hand but monitored. The use of nicotine patches as a treatment for COVID-19 appears to have some potential in the race to find solutions for this terrible pandemic.

Given the importance of the active role that internists, general physicians and hospital staff play in assisting patients with COVID-19 and for patients with smoking-related diseases, Internal and Emergency Medicine remains committed to further advancing the scientific debate on COVID-19, including addressing the impact of smoking and vaping on COVID-19 disease.

Conflict of interest

RP is full-time employee at the University of Catania, Italy. In relation to the topic of communicable disease, RP has received research funding from Alfa-Wassermann, manufacturer of broad spectrum antibiotics. RP is also founder of the Center of Excellence for the acceleration of Harm Reduction at the University of Catania (CoEHAR), which has received a grant from Foundation for a Smoke Free World to develop and carry out 8

research projects and scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League). GC has no conflict of interest.

Statement of human and animal rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent

Informed consent was not required for this type of study.

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4 Does vaping increase COVID-19 risk?

4.1 Safer Nicotine Wiki

https://safernicotine.wiki/mediawiki/index.php/Does_vaping_increase_COVID-19_risk%3F

Since the beginning of the COVID-19 pandemic, many have speculated that vaping could increase the risk of getting COVID-19 and experiencing more severe outcomes from the disease. The claims were grounded in little to no evidence, and almost none has emerged since.

The authors of a California study (4.2) claimed that their survey showed young vapers were five to seven times more likely than never vapers to test positive. It received a massive amount of media coverage. It also received scathing criticism and calls for retraction from longtime researchers in the field who cited multiple methodological issues.

A large Icelandic study reported that the proportion of e-cigarette users was lower among patients with COVID-19 than in the general population of Iceland and that patients using e-cigarettes did not have more severe symptoms than other patients. A non-peer reviewed UK study found that vaping was not associated with self-reported COVID-19.

There is a considerable amount of evidence that current tobacco smoking is associated with a reduced chance of testing positive. Former smokers appear to face more serious outcomes than current or never smokers. Outcome data on current smoking are mixed.

The association of smoking status with SARS-CoV-2 infection, hospitalization and mortality from COVID-19: a living rapid evidence review with Bayesian meta-analyses (version 7)

Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory–confirmed COVID-19 cases

A twitter thread with links to hundreds of studies which report smoking status data of COVID-19 patients

4.2 Association Between Youth Smoking, Electronic Cigarette Use, and COVID-19

Journal of Adolescent Health | August 11, 2020 | Shivani Mathur Gaiha, Ph.D., Jing Cheng, Ph.D., Bonnie Halpern-Felsher, Ph.D.

https://doi.org/10.1016/j.jadohealth.2020.07.002

Abstract

4.2.1.1 Purpose

This study aimed to assess whether youth cigarette and electronic cigarette (e-cigarette) use are associated with coronavirus disease 2019 (COVID-19) symptoms, testing, and diagnosis.

4.2.1.2 Methods

An online national survey of adolescents and young adults (n = 4,351) aged 13–24 years was conducted in May 2020. Multivariable logistic regression assessed relationships among COVID-19–related symptoms, testing, and diagnosis and cigarettes only, e-cigarettes only and dual use, sociodemographic factors, obesity, and complying with shelter-in-place.

4.2.1.3 Results

COVID-19 diagnosis was five times more likely among ever-users of e-cigarettes only (95% confidence interval [CI]: 1.82–13.96), seven 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). Testing was nine times more likely among past 30-day dual-users (95% CI: 5.43–15.47) and 2.6 times more likely among past 30-day e-cigarette only users (95% CI: 1.33–4.87). Symptoms were 4.7 times more likely among past 30-day dual-users (95% CI: 3.07–7.16).

4.2.1.4 Conclusions

COVID-19 is associated with youth use of e-cigarettes only and dual use of e-cigarettes and cigarettes, suggesting the need for screening and education.

Implications and Contribution

The findings from a national sample of adolescents and young adults show that electronic cigarette use and dual use of electronic cigarettes and cigarettes are significant underlying risk factors for coronavirus disease 2019. Health care providers, parents, schools, community-based organizations, and policymakers must help make youth aware of the connection between smoking and vaping and coronavirus disease.

As of June 2020, more than 2.1 million people have been infected, and approximately 116,000 have died from Coronavirus Disease 2019 (COVID-19) in the U.S. [1], and the numbers continue to rise. Both cigarette and electronic cigarette (e-cigarette) use damage the respiratory system [2], [3], [4], potentially increasing the risk of experiencing COVID-19–related symptoms, a positive diagnosis and exacerbated health outcomes [5]. A meta-analysis of studies mostly in China found that smokers were at elevated risk of COVID-19 progression compared with non-smokers [6]. Hospitalizations in the U.S. show that factors such as obesity, male sex, and older age are associated with COVID-19 [7]. Although youth are at relatively lower risk of contracting COVID-19 compared with older adults, given the proportion of youth using e-cigarettes [8], youth e-cigarette and cigarette use may pose an important risk factor for COVID-19.

Currently, there are no U.S. population-based studies assessing the relationship between cigarette smoking, e-cigarette use, and COVID-19–related outcomes. In the absence of information on smoking and e-cigarette use history of youth diagnosed with COVID-19, we conducted a population-level examination of whether youth cigarette and/or e-cigarette use is associated with increased likelihood of experiencing COVID-19–related symptoms, being tested, and being diagnosed with COVID-19.

Methods

We conducted a national cross-sectional online survey of adolescents and young adults aged 13–24 years from May 6 to 14, 2020 in the U.S., using Qualtrics [9], a leading enterprise survey technology platform. Participants were recruited from Qualtrics' existing online panels using a survey Web link on gaming sites, social media, customer loyalty portals, and through website intercept recruitment. Qualtrics panels are widely used to conduct social/behavioral research [10]. The online survey took 15–20 minutes to complete. Through quota sampling, we recruited e-cigarette ever-users (50.2%) and nonusers (49.8%); and adolescents (aged 13–17; 33.7%), young adults (aged 18–20 years; 41.6%), and adults (aged 21–24 years; 24.7%), while balancing gender and race/ethnicity. This study was approved by the Institutional Review Board at Stanford University.

Multivariable logistic regression was conducted to assess associations of ever-use and past 30-day use of cigarettes only, e-cigarettes only, and dual use of e-cigarettes and cigarettes with COVID-19 (self-reported symptoms, testing, and positive diagnosis). The model used weights for age group; gender; lesbian, gay, bisexual, transgender, and questioning; race/ethnicity; and e-cigarette ever-use per U.S. population-based data; accounted for clustering by region and state; and controlled for demographics, mother's education (as an indicator of socioeconomic status), body mass index (obesity as an underlying condition) [11], [12], complying with county shelter-in-place orders and state percentage of COVID-19–positive cases [13], All measures, percentages corresponding to weighted data in logistic regressions, and marginal population proportions used to calculate weight are included in Supplementary Material. Missing values were treated as not missing completely at random for Taylor series variance estimation. Statistical significance was set at $p < .05$, and all tests were two-tailed.

Results

A total of 4,351 participants completed the online survey from 50 U.S. states, the District of Columbia, and three union territories. Table 1 provides weighted sample characteristics. Table 2 shows factors associated with COVID-19–related symptoms, getting a COVID-19 test and a positive COVID-19 diagnosis.

Table 1: Participant characteristics (unweighted %) and COVID-19–related outcomes (weighted %) by never- and ever-e-cigarette users

	Participant characteristics a (unweighted)			COVID-19–related symptoms (weighted)		COVID-19 test (weighted)		COVID-19–positive diagnosis (weighted)	
	Sample Size	Never-users (2,168)	E-cigarette users (2,183)	Never-users (2,168)	E-cigarette users (2,183)	Never-users (2,168)	E-cigarette users (2,183)	Never-users (2,168)	E-cigarette users (2,183)
Total	4,351	49.8	50.2	13.7	25.8	5.7	17.5	0.8	2.3
Age									
Adolescents (13–17)	1,442	50.3	49.7	16.1	25.5	2.8	16.3	0.1	1.2
Young adults (18–21)	1,810	49.3	50.7	13.4	23.5	7.2	16.1	1	3.1
Adults (22–24)	1,063	49.9	50.1	10.4	30.9	7.8	25.4	1.6	6.5
Sex									
Male	1,421	48.6	51.4	11.7	33.8	7.8	28.3	1.3	3.7
Female	2,832	50.4	49.6	15.5	17.4	3.8	6.1	0.3	0.9
Other b	71	51.5	48.5	18	21.7	6	21.7	0	8.7
LGBTQ									
Yes	780	43.1	56.9	17.8	32.8	9.7	10.3	1.4	1.8
No	3,566	51.3	48.7	13.1	23.9	5.1	19.3	0.7	2.5
Race/ethnicity									
White, non-Hispanic	2,611	57.5	42.5	11.4	15.8	4.4	10.3	0.5	1.2
AA/black, non-Hispanic	602	46.5	53.5	21.2	42.3	11.5	29.6	1.8	1.2
Asian/Native Hawaiian or	210	30	70	14.3	29.3	10.7	16	3.2	0.8

Pacific Islander, non-Hispanic									
Hispanic, non-AA/black	663	36.7	63.3	18.3	26.9	4.1	19.7	0.8	3.3
Other/multiracial, non-Hispanic	265	30.6	69.4	9.1	54.6	17.3	37.5	0.4	15.6
Complying with shelter-in-place									
Yes	3,463	50.7	49.3	19.1	39.5	9.2	30.8	2.3	4.3
No	709	43.5	56.5	12.6	22.9	5.4	14.7	0.6	2
U.S. Region									
Northeast	909	47.5	52.5	7.8	16.9	6.1	18.1	0.6	2.4
Midwest	918	53.4	46.6	13.6	19.7	4.3	13.1	0.3	4.1
South	1,505	48.1	51.9	14.3	27.7	5.3	16.9	0.6	1.6
West	990	51.7	48.3	17.1	25	7.2	19.7	1.6	2.4
U.S. territories	11	27.3	72.7	0	97.5	0	35.9	0	0
BMI									
Underweight	350	38.9	61.1	29.4	40.37	22.9	47.69	2	12.85
Normal/healthy	2,939	50.9	49.1	15.12	20.16	5.29	15.99	0.53	3.05
Overweight	615	53.5	46.5	7.8	20.09	8.06	11.42	1.25	1.95
Obese	381	48.1	51.9	17.45	49.56	3.74	18.88	1.06	3.47
Mother's highest level of education									
High school or below	998	49	51	19.59	25.2	8.07	16.12	0.48	2.42
Started college	609	48	52	18.67	28.4	5.63	13.1	1.16	2.99

Completed college (2 or 4 yr degree)	1,432	51.8	48.2	12.32	27.04	5.87	21.53	1.16	4.19
Graduate or professional degree (Masters, Ph.D., M.D., J.D., etc.)	885	48	52	14.86	31.15	10.87	26.57	0.36	7.23
Don't know	410	51.2	48.8	12.02	22.1	1.5	18.87	0.66	5.19

AA = African American; BMI = body mass index; COVID-19 = coronavirus disease 2019; LGBTQ = lesbian, gay, bisexual, transgender, and questioning.

a Unweighted percentages in observed sample.

b Other includes people whose sex is neither male or female, such people commonly describe themselves as non-binary or intersex.

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Table 2 : Association between COVID-19 and use of inhaled tobacco products, adjusting for sociodemographic factors, weighted

	Ever-use of inhaled tobacco and…			Past 30-day use of inhaled tobacco and…		
	COVID-19–related symptoms (4,043)	COVID-19 test (4,048)	COVID-19–positive diagnosis (4,048)	COVID-19–related symptoms (4,043)	COVID-19 test (4,048)	COVID-19–positive diagnosis (4,048)
	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Inhaled tobacco products						
Cigarettes only	1.40 (.83, 2.38)	3.94 (1.43, 10.86)	2.32 (.34, 15.86)	1.15 (.58, 2.27)	1.16 (.64, 2.12)	1.53 (.29, 8.14)
E-cigarettes only	1.18 (.80, 1.73)	3.25 (1.77, 5.94)	5.05 (1.82, 13.96)	1.43 (.84, 2.43)	2.55 (1.33, 4.87)	1.91 (.77, 4.73)
Dual use	1.36 (.90, 2.04)	3.58 (1.96, 6.54)	6.97 (1.98, 24.55)	4.69 (3.07, 7.16)	9.16 (5.43, 15.47)	6.84 (2.40, 19.55)
Never used	Ref	Ref	Ref	Ref	Ref	Ref
Age						
Adolescents (13–17)	.85 (.59, 1.23)	.43 (.24, .78)	.64 (.18, 2.30)	1.11 (.73, 1.68)	.54 (.30, .97)	.81 (.22, 2.96)
Young adults (18–21)	.79 (.50, 1.24)	.58 (.32, 1.07)	.52 (.22, 1.22)	.91 (.57, 1.44)	.66 (.36, 1.21)	.63 (.26, 1.54)
Adults (22–24)	Ref	Ref	Ref	Ref	Ref	Ref
Sex						
Male	1.34 (.95, 1.89)	2.58 (1.70, 3.93)	4.75 (2.37, 9.50)	1.15 (.82, 1.62)	2.11 (1.33, 3.35)	3.65 (1.86, 7.15)
Other	1.13 (.37, 3.42)	2.92 (.98, 8.70)	6.38 (1.45, 28.03)	1.19 (.38, 3.76)	3.10 (.90, 10.71)	7.20 (1.49, 34.87)
Female	Ref	Ref	Ref	Ref	Ref	Ref
LGBTQ						
Yes	1.81 (1.04, 3.13)	.78 (.52, 1.19)	.95 (.40, 2.23)	1.69 (.98, 2.90)	.71 (.43, 1.18)	.95 (.38, 2.39)
No	Ref	Ref	Ref	Ref	Ref	Ref
Race/ethnicity						
AA/black, non-Hispanic	2.06 (1.22, 3.50)	1.87 (1.05, 3.34)	1.18 (.45, 3.08)	2.13 (1.32, 3.46)	1.97 (1.17, 3.33)	1.18 (.51, 2.72)
Asian/Native Hawaiian or Pacific Islander, non-Hispanic	1.92 (.93, 3.98)	1.24 (.47, 3.28)	.08 (.01, .49)	1.89 (.98, 3.66)	1.26 (.47, 3.35)	.10 (.02, .51)
Hispanic, non-AA/black	2.01 (1.28, 3.18)	1.76 (.93, 3.33)	2.84 (1.18, 6.87)	1.98 (1.30, 3.02)	1.77 (.98, 3.21)	2.97 (1.15, 7.71)

Other/multiracial, non-Hispanic	1.89 (1.16, 3.08)	2.74 (1.43, 5.25)	3.88 (1.27, 11.85)	1.69 (.99, 2.88)	2.57 (1.23, 5.35)	3.71 (1.14, 12.02)
White, non-Hispanic	Ref	Ref	Ref	Ref	Ref	Ref
Complying with shelter-in-place						
No	1.54 (1.02, 2.34)	.74 (.45, 1.22)	1.00 (.47, 2.13)	1.62 (1.04, 2.51)	.83 (.54, 1.26)	1.22 (.51, 2.95)
Yes	Ref	Ref	Ref	Ref	Ref	Ref
State % of COVID-19 positive cases						
21–30	.75 (.33, 1.70)	.94 (.17, 5.05)	4.07 (.84, 19.80)	.69 (.31, 1.54)	.85 (.19, 3.70)	3.54 (.70, 18.00)
11–20	1.29 (.56, 2.99)	1.16 (.21, 6.47)	4.91 (.90, 26.77)	1.30 (.58, 2.90)	1.26 (.28, 5.65)	5.05 (1.19, 21.39)
6–10	1.05 (.46, 2.38)	1.16 (.21, 6.27)	4.27 (.67, 27.34)	.93 (.41, 2.07)	.96 (.22, 4.18)	3.96 (.98, 16.01)
0–5	Ref	Ref	Ref	Ref	Ref	Ref
Body mass index						
Underweight	2.50 (1.50, 4.20)	2.90 (1.63, 5.18)	2.56 (1.05, 6.20)	1.92 (1.05, 3.51)	2.12 (1.19, 3.77)	1.95 (.82, 4.64)
Overweight	.69 (.50, .95)	.57 (.31, 1.03)	.65 (.24, 1.72)	.77 (.56, 1.06)	.74 (.38, 1.45)	.79 (.32, 1.96)
Obese	2.19 (1.37, 3.51)	.90 (.48, 1.71)	1.40 (.53, 3.71)	1.87 (1.14, 3.01)	.53 (.28, 1.02)	.90 (.31, 2.66)
Normal/healthy	Ref	Ref	Ref	Ref	Ref	Ref
Mother's highest level of education completed						
Started college	1.13 (.71, 1.80)	.76 (.39, 1.47)	1.61 (.65, 4.04)	1.06 (.67, 1.68)	.65 (.29, 1.45)	1.37 (.52, 3.60)
Completed college (2 or 4 year degree)	.97 (.57, 1.66)	1.06 (.62, 1.81)	2.10 (1.08, 4.11)	.93 (.54, 1.60)	.97 (.59, 1.61)	1.84 (.91, 3.75)
Graduate or professional degree (Masters, Ph.D., M.D., J.D., etc.)	1.29 (.78, 2.14)	1.83 (.98, 3.42)	3.28 (1.20, 8.93)	1.11 (.66, 1.68)	1.43 (.75, 2.70)	2.33 (.87, 6.22)
Don't know	.79 (.38, 1.65)	.83 (.40, 1.73)	2.42 (.55, 10.69)	.88 (.43, 1.81)	1.03 (.49, 2.18)	2.72 (.64, 11.60)
High school or below	Ref	Ref	Ref	Ref	Ref	Ref

Bold indicates $p < .05$; adjusted for state- and region-level clustering effects.

COVID-19 = coronavirus disease 2019; CI = confidence interval; LGBTQ = lesbian, gay, bisexual, transgender, and questioning; Ref = reference.

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As shown in Table 2, past 30-day dual-users were 4.7 times more likely to experience COVID-19–related symptoms (95% confidence interval [CI]: 3.07–7.16). Experiencing such symptoms was nearly twice more likely among African American/black, Hispanic, other/multiracial, underweight, and obese participants; 1.8 times more likely among lesbian, gay, bisexual, transgender, and questioning youth; and 1.6 times more likely among those not complying with shelter-in-place.

Ever-users of e-cigarettes only were 3.3 times (95% CI: 1.77–5.94), ever-dual-users were 3.6 times (95% CI: 1.96–6.54), and ever-users of cigarettes only were 3.9 times (95% CI: 1.43–10.86) more likely to get COVID-19 tested. Past 30-day dual-users were nine times (95% CI: 5.43–15.47) and past 30-day e-cigarette only users were 2.6 times (95% CI: 1.33–4.87) more likely to get COVID-19 tested. Testing was 2–3 times more likely among male, African American/black, other/multiracial, and those who were underweight.

Ever-dual-users were seven times (95% CI: 1.98–24.55), ever-users of e-cigarettes only were five times (95% CI: 1.82–13.96), and past 30-day dual-users were 6.8 times (95% CI: 2.40–19.55) more likely to be diagnosed with COVID-19. Sociodemographic factors associated with a positive COVID-19 diagnosis included being male, other/nonbinary gender, Hispanic, other/multiracial, and mother's completion of college- or graduate-level education. As a possible underlying risk factor for low immunity to COVID-19 among youth, being underweight was associated with 2.5 times greater risk of a positive COVID-19 diagnosis (95% CI: 1.05–6.20). In addition, being in a state with 11%–20% positive COVID-19 cases made a person nearly five times more likely to be diagnosed positive (95% CI: 1.19–21.39).

4.3 Discussion

Our population-based research provides timely evidence that youth using e-cigarettes and dual-users of e-cigarettes and cigarettes are at greater risk of COVID-19. Given the predominance of e-cigarette use among U.S. youth, our investigation informs public health concerns that the ongoing youth e-cigarette epidemic contributes to the current COVID-19 pandemic. Surprisingly, exclusive ever-use of combustible cigarettes was only associated with COVID-19–related testing, whereas both past 30-day use and ever-use of e-cigarettes and dual use were associated with COVID-19 testing and positive diagnosis.

There are a number of potential reasons why both dual use and e-cigarette use were associated with getting infected with COVID-19. Heightened exposure to nicotine and other chemicals in e-cigarettes adversely affects lung function [14], with studies showing that lung damage caused by e-cigarettes is comparable to combustible cigarettes [4], [15], [16]. COVID-19 spreads through repeated touching of one’s hands to the mouth and face, which is common among cigarette and e-cigarette users [17]. Furthermore, sharing devices (although likely reduced while staying at home) is also a common practice among youth e-cigarette users [18].

Our finding that some racial/ethnic groups, especially among African American, Hispanic, and multirace youth, are at higher risk for COVID-19 is supported by evidence of densely populated living conditions that make social distancing challenging, greater economic stress, and service-industry work environments where working from home is less feasible and lower access to health care contribute to underlying health issues [19], [20], [21]. Both obesity and underweight conditions were associated with COVID-19 outcomes. Although at this point obesity is a more well-established risk factor for COVID-19 [7], being underweight also impacts lung function [22], [23], [24], [25], and therefore it is not surprising that it is also a risk factor for COVID-19. We also found that other/nonbinary gender was associated with COVID-19 testing and diagnosis, a population that has received little attention so far. The significant relationship between mother's college or graduate education and a positive COVID-19 diagnosis needs further investigation.

We adjusted our sample to be representative of the U.S. population and included confounders such as sex and race/ethnicity to provide conservative estimates of association. Based on recommendations for studies on smoking and COVID-19 [26], our study adjusted for obesity, which we found was also an underlying risk factor among 13- to 24-year-olds. However, we did not include or adjust for other comorbid conditions such as hypertension due to low prevalence among 13- to 24-year-olds [27]. Furthermore, we did not ask participants about hospitalization or severity of symptoms and cannot

ascertain asymptomatic respondents. We recommend biomarker-based studies to determine causality, as this study is based on self-report.

4.4 Conclusion

Our findings from a national sample of adolescents and young adults show that e-cigarette use and dual use of e-cigarettes and cigarettes are significant underlying risk factors for COVID-19 that has previously not been shown. The findings have direct implications for health care providers to ask all youth and COVID-19–infected youth about cigarette and e-cigarette use history; for parents, schools, and community-based organizations to guide youth to learn more about how e-cigarettes and dual use affect the respiratory and immune systems; for the Food and Drug Administration to effectively regulate e-cigarettes during the COVID-19 pandemic; and for the development and dissemination of youth-focused COVID-19 prevention messaging to include e-cigarette and dual use.

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4.6 Supplementary Data

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Footnotes

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institues of Health or the Food and Drug Administration.

Clinical trials registry site and number: Not applicable to this cross-sectional survey study.

4.9 Tables

- **Table 1**Participant characteristics (unweighted %) and COVID-19–related outcomes (weighted %) by never- and ever-e-cigarette users
- **Table 2**Association between COVID-19 and use of inhaled tobacco products, adjusting for sociodemographic factors, weighted

5 Association of SARS-CoV-2 infection to smoking and ecigarettes

May 07, 2020 | Journal of Medical Internet Research | Josep M Ramon-Torrell MD, ; Sergio Morchon MD, ; Fernando Aguero MD, ; Cristina Masuet-Aumatell MD,

https://www.jmir.org/preprint/19949?fbclid=IwAR3gavGTaIw_URTvVOYSaalGESkuMREAt9QGFmn7ebWLYhOf0L1CtTOznzU

5.1 Abstract

Background: The coronavirus disease 2019 (COVID-19) is spreading worldwide. Several factors have been studied in relation to SARS-CoV-2 infection. One of the factors that has been related and in an uncertain way has been tobacco consumption. To our knowledge, no studies measuring the association between e-cigarettes and SARS-CoV-2 had been reported.

Objective: The aim of this study was to evaluate, through a cross-sectional survey, the current prevalence estimation of SARSCoV-2 infection among smokers and e-cigarette users.

Methods: : A cross-sectional study was carried out using an online questionnaire-based survey between April 6,2020 to April 19, 2020. Participants were males and females enrolled via link from website. We also posted the link in Facebook, Twitter and anti-tobacco, smokers and e-cigarette users forums. For this analysis, only participants residing in Spain were included. To measure the association between infection and independent variables odds ratios (ORs) were calculated for each category by conditional logistic regression and the corresponding 95% confidence intervals (CIs) and adjusted by age and gender.

Results: A total of 3,517 participants were included in the study. Of all the participants, 170 reported a diagnosis of SARSCoV-2 infection (4.6 % 95% CI 3.9-5.1) of which 35 (0,99 %; 95% CI 0.6-1.06)), reported a confirmed diagnosis and 135 (3.8 %; 95% CI 2.9-4.01) a clinical diagnosis. Rate of daily smokers of conventional tobacco among all participants was of 12.2 % (14.3 % of males and 9.8 of females). The number of smokers (4.7%) and users of electronic cigarettes (3.9%) among the group with infection was lower than the number of non-smokers (10.2%) (p <.01). A negative association was observed between tobacco consumption (0.52 95%CI 0.27-0.98) and the use of electronic cigarettes (0.45 95%CI 0.28-0.71) and SARS-CoV-2 infection.

Conclusions: The results must be corroborated by analytical studies. In relation to the electronic cigarette, the basis would be similar to those of conventional cigarettes and based on the role of nicotine in the incidence and progression of SAR-CoV-2 infection.

5.2 Introduction

The coronavirus disease 2019 (COVID-19) is spreading worldwide causing more than two and half millions of cases and more than 200,000 deaths [1]. In the current pandemic SARS-CoV-2 infection several factors have been studied in relation to the disease, mainly its severity and its clinical characteristics. The emergent SARS-CoV-2 virus, transmitted most readily by droplets and aerosol, is highly contagious and manifests with severe or critical bilateral pneumonia in 20% of symptomatic infected cases. The severe coronavirus disease-2019 (COVID-19) resulting from SARS-CoV-2 infection is characterized by respiratory distress and decreased oxygen saturation. However, even in asymptomatic

patients, imaging features representing diffuse peripheral bilateral ground-glass opacities have been highlighted, and asymptomatic carrier state is suspected to be contagious.

Individuals with comorbidities are more likely to develop more serious complications. In your initial report Guan et al [2] observed that hypertension, obesity, diabetes and immune deficiencies were more frequently observed among patients with COVID-19. The association between active smoking and SARS-CoV-2 infection has been hypothesized due to decreased angiotensin converting enzyme (ACE2) levels seen in smokers. Both epidemiological and clinical evidence and the in silico findings may suggest that Covid-19 infection is a nAChR disease that could be prevented and may be controlled by nicotine.

Nicotine would then sterically or allosterically compete with the SARS-CoV-2 binding to the nAChR. [3] Two recent meta-analysis have measured the association between smoking and hospitalization and severity of COVID-19 [4-5]. Lippi et al (4) conclude that the results suggest that active smoking does not appear to be significantly associated with the decreased risk of progression of severe disease. On the other hand, Farsalinos et al [5], in a preliminary analysis, remarks that nicotine may have a certain role in the reduction of severe disease. The results in China and the USA observed, in both populations, low prevalence of smokers among patients admitted for SARS-CoV-2 infection [6].

To our knowledge, no studies measuring the association between e-cigarettes and SARSCoV-2 had been reported. The aim of this study was to evaluate, through a cross-sectional survey, the current prevalence estimation of SARS-CoV-2 infection among smokers and ecigarette users.

5.3 Methods

Study design

A cross-sectional study was carried out using an online questionnaire-based survey between April 6,2020 to April 19, 2020. Participants were males and females enrolled via link from website which offers information and support to the smoker (www.tabaquisme.cat) and, on the other hand, a second website for information and advice on international health (www.bellvitgetravel.com). We also posted the link in Facebook, Twitter and anti-tobacco, smokers and e-cigarette users forums. For this analysis, only participants residing in Spain were included.

Always participants were informed that their answers was anonymous and they not be transmitted out of study authors. Consent was implicit and not formal consent was required.

Protocol was submitted to ethics Committee of the University of Bellvitge Hospital.

Procedures

Questionnaire was posted in Spanish, English and Portuguese. Before answering the questionnaire, the participants were informed of the objectives of the study. Survey was designed for the study to obtain four blocks of data: demographic characteristics, diagnosis of SARS-CoV-2 infection in the last 40 days, smoking status (time without smoking in exsmokers and amount of daily consumption), use of cigarette electronic and, finally, perceptions about future trips in a post-pandemic context. The questionnaire was designed to avoid multiple submissions. Participants were not required to answer all questions.

Participant with current consumption, ex-smokers with less than three months of abstinence and users of electronic cigarettes with dual consumption were classified as smokers.

Electronic cigarette users were classified as those users who only use the electronic cigarette at least once a day.

Statistical analysis

The quantitative variables are described by means (and SD) and medians. Categorical variables are described using percentages and 95% CI. Chi-square test were performed to test differences between percentages. Means were compared using T-test for means.

To measure the association between infection and independent variables odds ratios (ORs) were calculated for each category by conditional logistic regression and the corresponding 95% confidence intervals (CIs) and adjusted by age and gender.

A sample size of 3,084 subjects will suffice to estimate with a 95% confidence interval and a precision +/- 0.3 percent units, a population percentage considered to be around 0.6 %. It was anticipated a replacement rate of 20 %.

5.4 Results

Between April 6, 2020 and April 19, 2020 a total of 3,754 participants were included in the study. Of those, 3,517 completed all parts of questionnaires (completion rate of of 93.7 %).

Comparison of the 237 participants who did not complete all parts of questionnaire showed no differences regarding age (p .38) and gender (p .19).

Finally, 3,517 were included for analyses, 2,121 were males (60.3 %) and 1,396 females (39,7 %) with a mean age of 38.2 years (SD ⍰0.23 years);median age for males of 44 years old and 36 years old for females, difference were statistically significant (p< .01).

Of all the participants, 170 reported a diagnosis of infection (4.6 % 95% CI 3.9-5.1) of which 35 (0,99 %; 95% CI 0.6-1.06)), reported a confirmed diagnosis of SARS-CoV-2 and 135 (3.8 %; 95% CI 2.9-4.01) a clinical diagnosis. The incidence was more frequent among men than women (p < .001) (Table 1).

Table 1. Baseline characteristics by diagnosis.

	Diagnosis SARS- Cov-2[a] N= 170	**No diagnosis SARS-CoV-2 N= 3,347**	
Age Mean (±SD)	39.5 (±0,92)	38.1 (±0,22)	p 0.182
Gender n (%)			
Males	110 (5.2 %)	2,011 (94.8%)	
Females	60 (4,3 %)	1,336 (96.2%)	p < .001
Smoking n (%)			
No	49 (10.2 %)	343 (89.8 %)	p < .01
Si	20 (4.7 %)	408 (95.3 %)	
e-cigarettes [b]	101 (3.9 %)	2,506 (96.1 %)	
Nº of cigarettes n (%)[c]			
< 10 cig/day	6 (2.9 %)	203 (97.1 %)	
10-19 cig/day	8 (6.3 %)	118 (93.7 %)	p .66
= >20 cig/day	6 (6.4 %)	87 (93.6 %)	

a. Cases confirmed plus cases with clinic diagnosis.

b. Exclusively use of e-cigarettes.

c. Participants with cigarettes consumption

When the symptoms reported by the participants were analyzed, those who reported diagnosis the 92.6% of them presented symptoms compatible with the infection compared to 34.1% of the undiagnosed. There were no significant differences between symptoms and age (p .71) and gender (p .53).

Rate of daily smokers of conventional tobacco among all participants was of 12.2 % (14.3 % of males and 9.8 of females). Current smokers rate did not differ by gender (14.3 vs 9.8 ; p .18). The e-cigarette group was composed of 2,730 users of which, 2,607 (95.5 %) were exclusively electronic cigarette users and only 123 (4.5 %) were dual consumers being analyzed as smokers. Median age for non-smokers was 48 years, 36 for smokers and 37 for electronic device users (p .01). The number of smokers (4.7%) and users of electronic cigarettes (3.9%) among the group with infection was lower than the number of nonsmokers (10.2%) (p <.01) (Table1).

Table 2 shows crude and adjusted ORs and corresponding 95% CIs according to tobacco and e-cigarette consumption. None of the e-cigarette users reported stopping use after diagnosis for more than 72 hours.

Table 2. Odds ratios and 95% confidence intervals for SARS-CoV-2 infection by smoking.

	Crude O.R[a] (95% CI)	**Adjusted [b] O.R[a] (95% CI)**
Smoking		
No	1	1
Si	0,46 (0.22-0.77)	0.52 (0.27-0.98)
Use e-cigarette [c]	0,38 (0.23-0.50)	0.45 (0.28-0.71)
Nº of cigarettes [d]		
No smoking	1	1
< 10 cig/day	0.28 (0.12-0.53)	0.27 (0.19-0.61)
10-19 cig/day	0.61 (0.52-0.97)	0.69 (0.58-0.99)
= >20 cig/day	0.63 (0.58-0.99)	0.81 (0.70-1.01)

a. Odds Ratio.

b. Adjusted by age and gender.

c Exclusively use of e-cigarettes.

d. Participants with conventional cigarettes consumption

Smoking showed an inverse association with infection with an estimated OR 0.46 (95% CI 0.22-0.77) similar to the electronic cigarette use, OR 0.38 (95% CI 0.23-0.50). The analysis based on a multivariate model which included age and gender, smoking and e-cigarette remained negatively associated with infection (OR 0.52 and OR 0.45 respectively).

When the level of consumption of conventional cigarettes was analyzed, a negative and significant relationship was observed in all the categories except among the group with consumption of 20 or more cigarettes per day, that despite the negative association, this was not statistically significant possibly due to the small number of participants in that category.

5.5 Discussion

To our knowledge, this is the first published paper reporting results on the possible association of SARS-CoV-2 infection and the use of electronic cigarettes, and also the first article to conduct an online survey on tobacco use and this infection.

The number of participants who reported infection diagnosed by PCR was very similar to that published by the Spanish health authorities for some Spanish regions but lower than global rates [7]. In our case, we estimate rates of just over 900 infected per million inhabitants (95% CI from 600 to 1,060 per million). It is remarkable that 3.8% of all participants were diagnosed exclusively for their clinical

symptoms without performing a diagnostic test. In other words, in our study, only 1 on five was diagnosed using diagnostic tests.

The current evidence on the prevalence of smokers among patients with SARS-CoV-2 infection is uncertain and has created some degree of controversy. The overall prevalence of smokers in our study was 12.2%, lower than the prevalence published for the Spanish population in 2017 (23.3%) [8]. This lower prevalence was observed for both men and women.

Our results showed that prevalence of current daily smokers was lower among the group of cases reporting infection compared to non-smokers. Prevalence of smokers among infected group was of 4.7 % in comparison of 10.2 % of non-smokers. Estimated adjusted Odds Ratio for SARS-CoV-2 infection showed a negative and significant association with current tobacco use (0.52 (0.27-0.98). The initial study published by Guan et al (2), showed lower prevalence of smokers than non-smokers among their series of patients with non-severe infection (12%) higher than that observed in our series, possibly because their series was based on hospitalized patients.

In a recent systematic review [9], five studies showed a negative association between smoking and progression and severity of COVID-19.However, Lippi in your limited metaanalysis [4] with a low number of cases, does not confirm this association. Miraya et al [10] in their recently published study observed that the smoking rates, both in patients who required hospital admission and those who did not, were lower than in the French general population.

To date, no study has been published measuring the association between electronic cigarette and SARS-CoV-2 infection. In our study, we observed, similar to conventional tobacco use, a lower prevalence of users among the group that presented infection. This correlation would be expected by the hypothesized role of nicotine against infection. The nicotinic acetylcholine receptor (nAChR) plays a key role in the pathophysiology of Covid19 infection and might represent a target for the prevention and control of Covid-19 infection [11].

Although the number of study participants is high, our findings may have some limitations. Firstly, they are based on a cross-sectional study and the observed associations do not have to be causal and, on the other hand, the diagnosis was self-reported by the study participants without the possibility of being confirmed by the authors. Second, as the method for questionnaire studies, mail survey and interview survey are frequently used. As compared with conventional methods, the advantages of the Internet approach are convenience for both investigators and respondents and the ability to quickly collect data.

However, Internet-based data collection may differ from traditional methods with respect to response rate and data quality as well as validity and reliability of the involved scales. Only a few studies have systematically evaluated Internet-based survey methods [12-14]. The main questions have addressed validity are response and completion rate. In our case, the completion rate was high.

In conclusion, and as Farsalinos et al (5) emphasizes in their review, we must consider the uncertainty of the results and the observations must be corroborated by analytical studies.

In relation to the electronic cigarette, the basis would be similar to those of conventional cigarettes and based on the role of nicotine in the incidence and progression of SAR-CoV-2 infection.

Authors contributions

All authors conceived and designed the study. The study was conducted under the supervision of IRB at the Hospital de Bellvitge. All authors were involved in drafting, revising and finalizing the manuscript, and approved the final version which was submitted for publication.

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Declaration of interest statement

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6 The role of nicotine in COVID-19 infection

26v May 2020 | The Centre for Evidence-Based Medicine | Jamie Hartmann-Boyce and Nicola Lindson

https://www.cebm.net/covid-19/nicotine-replacement-therapy/

VERDICT

There are biologically plausible pathways through which nicotine may impact SARS-CoV-2, but the clinical significance of these is entirely unclear.

BACKGROUND

There is mixed evidence on the role of smoking in COVID-19 infection and associated outcomes. Whereas the expectation is that smoking would predispose to worse outcomes from COVID-19, as is the case in other acute respiratory infections, some (but not all) studies of COVID-19 have detected fewer people who smoke than would be expected in hospitalised patients with COVID-19. It is unclear whether this is due to biases, confounding, misreporting, or a potential protective effect of smoking on COVID-19 outcomes. Irrespective of COVID-19, smoking is uniquely deadly. However, nicotine, the addictive component of cigarettes, can be safe when used in other forms, and there is some biological plausibility regarding a possible role of nicotine in COVID-19 infection. Below we briefly review evidence to date on the role of nicotine in COVID-19. This is important to people who smoke, but it could also be of general relevance, as some have hypothesised nicotine may be a potential treatment for COVID-19.

CURRENT EVIDENCE

We searched the literature for studies relating to COVID-19 and nicotine. Some are underway, and this piece will be updated as new findings emerge. In the meantime, the available research literature is mainly in the form of speculative commentaries, with some lab studies also reported.

Commentaries regarding nicotine and COVID-19 all agree nicotine potentially has a role to play based on its role in the renin-angiotensin system. In particular, nicotine can impact the angiotensin-converting enzyme (ACE) 2, which is relevant because coronaviruses bind to ACE2. However, some authors interpret this as suggesting nicotine is likely to be harmful in the context of COVID-19, and others suggest the opposite.

It is extremely difficult to synthesise evidence on nicotine and COVID-19 as much of the literature is inconsistent. Below we highlight pathways/hypothetical mechanisms through which at least one paper has speculated nicotine might impact SARS-Cov-2:

- Current and past tobacco smoking are associated with changes in ACE2 receptor expression
- Nicotine up-regulates the ACE/angiotensin (ANG)-II/ANG II type 1 receptor axis, and down-regulates the compensatory ACE2/ANG-(1–7)/Mas receptor axis (commentary; commentary)
- Nicotine may bind with the ACE2 receptor, particularly in people with COVID-19, and thus could interfere with further SARS-CoV-2-ACE2 binding (pre-print in silico study)
- Nicotine and cigarette smoke decrease levels of ACE2 in multiple organs

- Cytokine storms could be prevented or suppressed by nicotine through its impact on the cholinergic anti-inflammatory system; nicotine may inhibit hyperinflammation and platelet reactivity
- Poor COVID-19 outcomes in people who smoke could be driven by nicotine withdrawal when acutely ill, thus nicotine patches "should be urgently considered and discussed" (note, nicotine patch use in hospital is a common approach across conditions)

France has had to place restrictions on sales of nicotine replacement therapy because of fears it may start to be stockpiled for inappropriate use relating to COVID-19. Studies are underway testing nicotine replacement therapy in COVID-19 patients, and until results are available from those, there is no evidence to support the general public's use of nicotine replacement therapy for COVID-19 infection. Nicotine replacement therapy is a mainstay of smoking cessation treatment and is safe and effective in this capacity.

CONCLUSIONS

- There are biologically plausible pathways through which nicotine may impact SARS-CoV-2, but the clinical significance of these is entirely unclear
- Early studies are underway regarding the role of nicotine replacement therapy as a therapeutic aid for COVID-19
- Evidence so far is too limited to inform any decisions about use of nicotine replacement therapy in COVID-19
- When used for smoking cessation, there is high certainty evidence that nicotine replacement therapy is safe and effective.

End.

Disclaimer: the article has not been peer-reviewed; it should not replace individual clinical judgement and the sources cited should be checked. The views expressed in this commentary represent the views of the authors and not necessarily those of the host institution, the NHS, the NIHR, or the Department of Health and Social Care. The views are not a substitute for professional medical advice.

7 Current smoking is not associated with COVID-19

4 June 2020 | European Respiratory Journal | Marco Rossato, Lucia Russo, Sara Mazzocut, Angelo Di Vincenzo, Paola Fioretto, Roberto Vettor

https://erj.ersjournals.com/content/55/6/2001290

Article

We have read with interest the paper by Leung et al. [1] recently published in the European Respiratory Journal, reporting a higher expression of the protein angiotensin-converting enzyme II (ACE-2) in the small airway epithelia of smokers and COPD patients with putatively important implications for coronavirus disease 2019 (COVID-19) patients, since ACE-2 has been shown to be the receptor utilised by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter the host cell [2]. Furthermore, the authors reported that current smokers showed a higher expression of ACE-2 gene expression than non-smokers, concluding that the increased ACE-2 expression in smokers might predispose to increased risk of SARS-CoV-2 infection [1].

To this regard, all epidemiological data published so far reported that COVID-19 patients show a very low prevalence of smokers, with no significant association between current smoking and severe disease in COVID-19 patients [3–6].

At the University-Hospital of Padova, located in the Veneto Region, one of the areas in Italy most affected by COVID-19, between 15 March and 10 April, 2020, 132 patients were assessed in our clinic for SARS-CoV-2 related pneumonia. The analysis of patients' smoking history showed that no-one was a current smoker, with 112 patients (84.8%) who had never smoked and 20 (15.2%) who were former smokers. These data are in agreement with those from China [3–6]. Furthermore, there was no difference in the disease severity between patients who never smoked and former smokers. These data are even more striking if we consider that the percentage of current smokers in Italy and in the Veneto Region is 25.7% and 22.7%, respectively (www.epicentro.iss.it/passi/dati/fumo).

Thus, the conclusions of Leung et al. [1] to consider cigarette smoking as a severe risk factor for COVID-19 pneumonia are in contrast with the strong and consolidated epidemiological data coming from China [3–6] that have been confirmed also in our patients.

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8 COVID-19 and vaping: risk for increased susceptibility to SARS-CoV-2 infection?

16 July 2020 | European Respiratory Journal | Kielan Darcy McAlinden, Mathew Suji Eapen, Wenying Lu, Collin Chia, Greg Haug, Sukhwinder Singh Sohal

https://erj.ersjournals.com/content/56/1/2001645?utm_source=TrendMD&utm_medium=cpc&utm_campaign=European_Respiratory_Journal_TrendMD_0

With great interest we read and commend the study done by Russo et al. [1], highlighting their findings that nicotine induces an increase in angiotensin-converting enzyme 2 (ACE-2) expression in human bronchial epithelial cells (HBEpC) and is mediated by α7-subtype nicotinic receptors (α7-nAChR). It raises the concern that all electronic nicotine-delivery systems may put users at greater risk of succumbing to coronavirus disease 2019 (COVID-19).

We [2], along with Leung et al. [3], have shown that ACE-2 expression is upregulated in the small airway epithelia of smokers and patients with COPD. In particular, we observed increased ACE-2 expression in type-2 pneumocytes and alveolar macrophages along with the small airway epithelium of smokers compared to healthy never-smokers [2]. Similar studies are yet to be done in the context of electronic cigarettes (e-cigarettes), heat-not-burn devices (IQOS) or waterpipe exposure to human airways. ACE-2 is the binding site for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mediating entry of the virus into cells [4]. Binding affinity between the spike proteins of the virus and ACE-2 on respiratory cells has been identified to be much higher than any previously identified human coronavirus. The significance of such overexpression of ACE-2 in smokers should not be ignored. COVID-19 and progression of severe pneumonia may be more likely to occur in smokers, particularly in those that have smoking-related comorbidities [5]. We are beginning to elucidate the role of traditional cigarette smoking and nicotine-driven changes to the lungs in the context of coronavirus transmission and susceptibility. Cigarette smoke has been identified and linked to increasing expression of the binding site for the cause of the 2020 pandemic (SARS-CoV-2) via mediating nicotine receptors. With this, an avoidable and potentially gigantic risk-factor has emerged for COVID-19, as the pandemic continues to claim ultimate grasp over the year of 2020.

Here, we bring to the discussion whether the increased susceptibility and virulence of SARS-CoV-2 via α7-nAChR and the upregulation of small airway ACE-2 expression may also be relevant for those who vape using nicotine-based e-cigarettes. E-cigarette vapour studies, although in their infancy, have already shown that they can enhance the virulence and inflammatory profile of pathogens such as Streptococcus pneumoniae, among other deleterious biological effects [6]. Vaping intensifies pneumococcal adherence through an increase in platelet-activating factor receptor expression, ultimately rendering those who vape with an increased risk of pneumonia [7, 8].

We, among others, have previously shown that e-cigarettes and IQOS are not “safer”, as having a vast pro-inflammatory response [9]. We compared cigarette smoke versus e-cigarette and IQOS on airway epithelial and smooth muscle cells [9]. All tested pathological biomarkers were elevated in cells exposed to e-cigarette aerosols and IQOS, which included chemokine CXCL8, extracellular matrix proteins and markers of mitochondrial dysfunction. We found these products toxic to the cells, evident from decreased cellular viability and integrity. More devastatingly, vaping also interfered with cellular energetics. Our results further substantiate current research that e-cigarettes and IOQS are indeed detrimental with increases in oxidative stress, inflammation, infections and airway remodelling in the lungs of these device users. As the scientific evidence mounts, confirming the fears that e-cigarettes and IQOS are strongly associated with the development and progression of debilitating lung diseases [10], now may be the prime time to include all electronic nicotine delivery systems in the vocalisation of concerns concerning tobacco-related death and disease.

We recirculate the simple notion that the lungs are not designed for the chronic inhalation of anything but air and that the indication for a smoking- and nicotine-induced increase in ACE2 is more evidence to the stacking weight of toxicity that tobacco is for humanity. Given the role of the nicotine receptor, vaping may also lead to the upregulation of ACE-2. Research in this area will be invaluable in the

development of e-cigarette research and providing trusted, peer-reviewed and real evidence for the youth of the 2020s. We strongly recommend that the World Health Organization and countries act to advance their efforts to reduce smoking, vaping and waterpipe use. During a pandemic it is difficult to focus on anything other than the immediate threat. The "primacy of rescue" has overwhelmed preventive action. Additional research into the relationship of smoking, and all electronic nicotine delivery systems to the infection, transmission and progression of COVID-19 is required. Progress towards easily identifying those susceptible to severe disease or capable of asymptomatic transmission are important goals for managing the disease at a community level. COVID-19 is a dress rehearsal for the next pandemic, and the next, and the one after that: the new norm.

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9 IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette

10 February 2019 | European Respiratory Society | Sukhwinder Singh Sohal, Mathew Suji Eapen, Vegi G.M. Naidu, Pawan Sharma

https://openres.ersjournals.com/content/5/1/00159-2018?ijkey=0c80d801b311d1d02c5e8437d9a741d82f3d9d2f&keytype2=tf_ipsecsha

Heat-not-burn (HNB) devices can alter vital physiological functions in the lung. HNB devices may not be a safer option than cigarette smoking or eCig vaping; this does not support the recommendation of their use over other nicotine delivery products.

While cigarette smoking still remains one of the most pressing global health issues of our time, newer forms of smoking device have been introduced across the globe in the last decade [1]. Electronic nicotine/non-nicotine delivery systems commonly known as electronic cigarettes (eCig) heat a solution (e-liquid) to create vapour [2]; the latest addition to this list is the introduction of heat-not-burn (HNBs) tobacco products branded as IQOS [3]. HNBs are hybrids between eCigs and traditional cigarettes i.e. they are equipped with a device that heats the product, without burning to generate aerosol and the product being heated is not a liquid but real tobacco [4, 5]. eCig vaping is comparatively new but its use is increasing at an alarming rate; it is believed it will surpass the use of traditional cigarettes in next 5 years, with global sales reaching US$10 billion [6]. Since its launch in Italy and Japan in 2014, IQOS has become the leader in the HNB market [4, 7]. To date, IQOS is available in 41 countries, including 22 from the WHO-European region, and its market share has now reached the level of cigars in Italy [4]. Emerging data shows that eCig use, particularly in the young, is associated with future cigarette use [8]. Similarly, over half of the people interested in IQOS are never-smokers [4]. Therefore, both eCigs and IQOS may represent a gateway for nicotine addiction among never-smokers rather than a substitute used for harm-reduction purposes in current smokers [4]. It is now clear that eCig vapour contains high levels of toxic compounds [9], which adversely affect respiratory, gastrointestinal and cardiovascular systems both in vitro and in vivo [10–12]. It is also important to recognise that IQOS products are comparatively new but emerging research suggests that IQOS emits substantially high levels of carbonyls [13]. There is as yet no published comparison between the effect of eCigs, IQOS and tobacco smoke on human lungs. Here, we examine whether exposure to IQOS has the same damaging effect on human airway epithelial and smooth muscle cells as traditional tobacco cigarette and eCigs in vitro.

We used human bronchial epithelial cells (Beas-2B, ATCC CRL-9609) and primary human airway smooth muscle (ASM) cells (ATCC PCS-130-010). eCig vapour was generated using an eCig device (KangerTech 3rd Generation; KangerTech, Shenzhen, China) and e-liquid (Blu, Charlotte, NC, USA) (1.2% nicotine); IQOS aerosol was generated using HNB heat-sticks (Philip Morris, Tokyo, Japan) (1.4 mg nicotine); and cigarette-smoke-extract (CSE) was generated using Marlboro Red cigarettes (Philip Morris, Washington, DC, USA) (1.2 mg nicotine). eCig vapour/IQOS aerosol/cigarette smoke was “bubbled” through a T-75 flask containing 25-mL media at a constant rate with modification [14–18]. This freshly generated (100%) eCig vapour, IQOS aerosol and CSE were diluted to the final working concentration and used immediately. Beas-2B or primary human ASM cells were treated with increasing concentrations of CSE, eCig vapour or IQOS aerosol for 72 h, and cell cytotoxicity (Thaizolyl blue tetrazolium bromide (MTT) and lactate dehydrogenase (LDH)), chemokine release (CXCL8), extracellular matrix (ECM) (collagen 1 and fibronectin) release and mitochondrial respiration (glycolysis and proton leak) were measured.

GraphPad (La Jolla, CA, USA) was used for statistical analysis using one-way ANOVA followed by Bonferroni's multiple comparison test.

Using two different cytotoxicity assays (MTT and LDH), CSE, eCig or IQOS exposure showed cellular toxicity with increasing concentration (figure 1a–h). A CSE concentration of >10% is highly toxic; therefore, we only used concentrations <10% in our experiments, which is also used widely in many studies [14–18]. In both Beas-2B and ASM cells, we found that CSE exposure significantly reduced cell viability and increased LDH release at 1, 5 and 10% (figure 1i–n). eCig exposure showed similar toxicity at 5 and 10% exposure. Interestingly, IQOS exposure was as toxic as CSE at 1, 5 and 10%. It is evident that both CSE and eCig vapour can induce inflammation in the lung [18, 19], and as shown in figure 1a–h), CSE exposure in a concentration-dependent manner induced the release of CXCL8 in Beas-2B (figure 1a) and ASM cells (figure 1e). eCig exposure induced CXCL8 release at the highest concentration, whereas IQOS exposure showed a similar induction to CSE, suggesting that IQOS is as effective as CSE in inducing chemokine release from both types of airway cells. Next, we measured the induction of ECM proteins with airway cells; CSE, eCig and IQOS exposure in a concentration-dependent manner increased collagen 1 (figure 1b and f) and fibronectin (figure 1c and g) release with both Beas-2B (figure 1b and c) and ASM (figure 1c and g) cells. Finally, we measured mitochondrial respiration using a seahorse analyser, and found that CSE, eCig and IQOS exposure increased the extracellular acidification rate (a measure of glycolysis) (figure 1a–h) and proton leak (a measure of mitochondrial uncoupling) (figure 1i–n) in both Beas-2B (figure 1d) and ASM (figure 1h) cells, respectively.

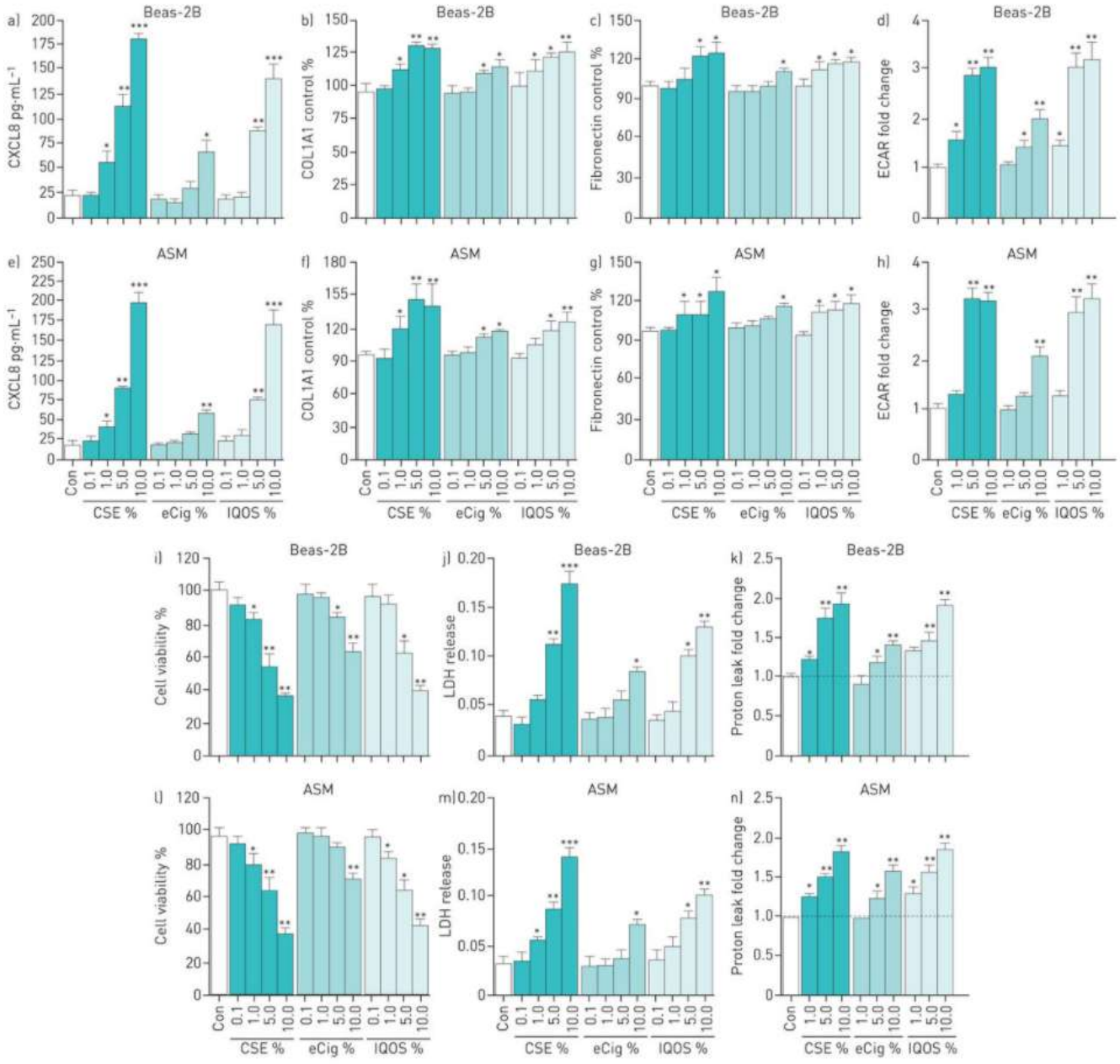

Figure 1

- a–h) Comparison of the effects of cigarette smoke extract (CSE), electronic cigarette (eCig) vapour and IQOS aerosol exposure on a–d) human airway epithelial (Beas-2B) and e–h) human airway smooth muscle (ASM) cells. a and e) show the release of CXCL8 from Beas-2B and ASM cells.
- The concentration of CXCL8 in supernatant from Beas-2B and ASM cells after 72 h of stimulation with CSE, eCig vapour or IQOS aerosol exposure was measured using ELISA.
- Deposition of b and f) collagen I alpha 1 (COL1A1) and c and g) fibronectin from Beas-2B and human ASM cells after 72 h of stimulation with CSE, eCig vapour or IQOS aerosol exposure was measured using extracellular matrix (ECM) ELISA at an absorbance of 450 nm and 570 nm, respectively. d and h)
- The level of glycolysis was determined in Beas-2B and ASM cells using a seahorse analyser, and extracellular acidification rate (ECAR); an index of glycolysis was measured after 72 h of stimulation with CSE, eCig vapour or IQOS aerosol exposure.
- Data are presented as mean±sem (n=5–7). i–n) The effect of CSE, eCig and IQOS exposure on cellular toxicity and respiration. The cell viability (i and l), the lactate dehydrogenase (LDH) release (j and m) and the mitochondrial respiration (k and n) from Beas-2B and human ASM cells was measured using Thaizolyl blue tetrazolium bromide (MTT) and LDH assays at an absorbance of 570 nm and 490 nm, respectively. k and n)
- Mitochondrial respiration was measured in Beas-2B and ASM cells using a mito-stress kit on a seahorse analyser (Agilent Technologies Inc., Santa Clara, CA, USA), and proton leak was measured as oxygen consumption rate shown as fold change to control. Cells were stimulated with serial dilution of CSE, eCig vapour or IQOS aerosol for 72 h (n=5).
- Data are presented as mean±sem. A one-way ANOVA plus Bonferroni post-test was used to determine statistical significance. *: $p<0.05$ compared with control; **: $p<0.01$ compared with control; ***: $p<0.001$ compared with control.

Cigarette smoking has been linked to chronic lung diseases such as chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis, cancer and related comorbidities [1]. It took us nearly five decades to understand the detrimental effects of cigarette smoke on humans.

Long-term eCig-exposure studies in humans are currently sparse, limiting our understanding of its direct effect(s) on both disease development and progression. eCig vaping is already at its highest level globally, and many countries are imposing stringent regulations in light of the emerging evidence showing the adverse effects of vaping on human health.

IQOS use is comparatively new; it will take years before we start to know its detrimental effect on human health. We demonstrate here for the first time that IQOS exposure is as detrimental as cigarette smoking and vaping to human lung cells. Persistent allergic, smoke or environmental-triggered inflammation leads to airway remodelling/scarring through re-organisation of ECM and airway cell proliferation, and mitochondrial dysfunction plays a pivotal role in this process. These are the principal causes for airflow limitation in asthma and COPD.

Here, we have analysed all of these mechanisms: inflammation (CXCL8), ECM release (collagen 1 and fibronectin) and mitochondrial respiration (glycolysis and proton leak). We observed collagen-1 and fibronectin induction by both Beas-2B and ASM cells to CSE, eCig and IQOS exposure. ECM proteins facilitate the conversion of mesenchymal cells to ECM secreting active myofibroblasts and epithelial mesenchymal transition (EMT) in chronic lung disease [20, 21]. Our data suggests that like eCigs and traditional cigarettes, IQOS exposure contributes to altered mitochondrial function which can further exaggerate airway inflammation, airway remodelling and lung cancer through active EMT, as seen in smokers [22]. It is widely understood that mitochondria of airway epithelium and mesenchymal cells play differential roles, consistent with their contributions to disease and essential for cell existence. Mitochondrial dysfunction also underpins many normal physiological processes and in certain pathological conditions, such as obesity or with an oxidant trigger such as smoke, eCigs and IQOS, it may impact lung diseases. Cigarette smoking and eCigs can exaggerate respiratory infections by increasing microbial adherence to the airways [23, 24]; IQOS may increase respiratory infections through similar mechanisms.

Given our current findings and those of previous studies, in a manner very similar to cigarette smoke and eCigs, IQOS has the potential to increase oxidative stress and inflammation, infections, airway remodelling and initiate EMT-related changes in the airways of users of these devices. However, prospective clinical studies must be conducted to verify our in vitro, cell-based but highly important and novel findings on IQOS.

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10 Associations between vaping and COVID-19: cross-sectional findings from the HEBECO study

Dec 7 2020 | News-Medical.Net | Dr. Ramya Dwivedi, Ph.D.

https://www.news-medical.net/news/20201207/Associations-between-vaping-and-COVID-19-cross-sectional-findings-from-the-HEBECO-study.aspx

Even though tobacco smoking is harmful to the lungs, some research suggests that smokers may be at reduced risk of the coronavirus disease 2019 (COVID-19) infection. COVID-19 primarily attacks the human respiratory system, causing mild to severe illness and death.

While using e-cigarettes, or vaping, is not harmless to lung function, based on various studies it appears that the COVID-19 pandemic may have affected rates of vaping. So far there are contradictory observations; changes in vaping due to COVID-19 are inconclusive.

E-cigarettes deliver nicotine without many of the harmful toxicants and carcinogens found in cigarette smoke. The association between vaping and COVID-19 infection may help delineate some of the proposed mechanisms for any potential protective or harmful effects of nicotine on COVID-19 outcomes. Also, understanding the impact of COVID-19 on vaping rates can help identify targets for intervention during future periods of social distancing and lockdown measures.

In this context, in a recent medRxiv* preprint publication, Dimitra Kale et al. explore the associations between vaping and self-reported diagnosed/suspected COVID-19.

In this study, the research team from the University College London, UK, highlight: 1) there is no difference found in diagnosed/suspected COVID-19 in between never, current, and ex-vapers; 2) half of the current vapers changed their vaping consumption since COVID-19; 3) motivation to quit vaping was partly related to COVID-19.

The researchers found that 17.4% of recent ex-vapers had quit vaping because of COVID-19, while 40.7% of recent ex-vapers were considering taking up vaping again since COVID-19, mostly out of boredom.

The study design involved analysis of cross-sectional data (from the baseline wave) of an ongoing longitudinal online study of UK adults: the HEalth BEhaviour during the COVID-19 pandemic (HEBECO) study. HEBECO study data were collected and managed using REDCap electronic data capture tools that are hosted at University College London. The analysis plan is available here.

The study involved 2791 UK-based adults, aged 18 and over, who completed the baseline survey of the HEBECO study between 30th April 2020 and 14th June 2020. This period covers the first national lockdown in the UK to mitigate the COVID-19 infection spread. Of the whole analytic sample (2792 participants), three quarters were never smokers and the rest were current or ex-vapers.

The participants were recruited online and through several channels including paid and unpaid advertisements on social media (including vaping forums) and relevant mailing lists.

Related Stories

- A common compound in mouthwashes found to inhibit SARS-CoV-2 in vitro
- Loss of taste and smell may be most reliable COVID-19 symptoms for digital surveillance
- A paper-based sensor for detecting COVID-19
- The participants self-reported their data on sociodemographic characteristics, diagnosed/suspected COVID-19, vaping status, changes in vaping, and motivation to quit vaping since COVID-19. The paper discusses in detail the questions given to the participants for assessment.
- Among current vapers, while 50% of them did not change their vaping consumption since COVID-19, 40% reported an increase in vaping and 10% reported a decrease in vaping.

- It is also observed that vaping is less when associated with being female, not living with children, and concurrent smoking. And vaping is more when associated with being younger, living alone, and diagnosed/suspected COVID-19.
- Due to COVID-19, vapers were motivated to quit. However, the researchers also found that nearly half of recent ex-vapers were considering taking up vaping again. Most of the common reasons for taking up vaping were 'struggling with cravings' and 'feeling stressed' - they were non-COVID-19 related reasons.
- In addition, this study supports that COVID-19 may have contributed to reinforcing different behavioral patterns - a proportion of people stopping completely since COVID-19, and others vaping more. The researchers also discuss the limitations of the study in detail.
- The findings in this study suggest that vapers who believe they have/had COVID-19 started vaping more because of stress or believing that nicotine is protective against COVID-19.
- The participants may also have misinterpreted their symptoms as many other respiratory infections share symptoms with COVID-19. This study does not address whether nicotine may be a protection against COVID-19 infection.
- This is an important study in real-time investigating the differences in diagnosed/suspected COVID-19 between vapers, ex-vapers, and never vapers, after adjustment for sociodemographic characteristics, smoking status, and health conditions. It also reports changes in vaping during the COVID-19 pandemic and factors associated with these changes.
- In conclusion, the study found that the diagnosed/suspected COVID-19 is not associated with vaping status, when assessed by self-report in a UK population sample.

11 Does Nicotine Prevent Cytokine Storms in COVID-19?

28 October 2020 | Cureus.com | Luiz Dratcu, Xavier Boland

https://www.cureus.com/articles/41018-does-nicotine-prevent-cytokine-storms-in-covid-19

11.1 Abstract

COVID-19 has a benign outcome in most cases, yet it can also be fatal and no specific treatment is available as of yet. Older age and several medical comorbidities are risk factors for COVID-19 complications. We report on an elderly man with a longstanding history of bipolar affective disorder associated with heavy smoking, alcohol abuse and multiple comorbidities, including severe chronic obstructive pulmonary disease and recurrent pulmonary sepsis, who contracted COVID-19 during his inpatient treatment of a manic episode, and who fully recovered from COVID-19 without any need for respiratory support. We discuss how his excessive use of nicotine replacement therapy may have contributed to his emerging unscathed from COVID-19. Nicotine, an α7-nACh receptor agonist, may boost the cholinergic anti-inflammatory pathway and hinder the uncontrolled overproduction of pro-inflammatory cytokines triggered by the SARS-CoV-2 virus, which is understood to be the main pathway to poor outcomes and death in severe COVID-19.

11.2 Introduction

The elderly, the immunosuppressed, and patients with cardiopulmonary disease and diabetes are all at greater risk of COVID-19 complications [1,2]. Chronic obstructive pulmonary disease (COPD) increases 5-fold the risk of severe COVID-19 [3]. Mental illness may also increase the risk of COVID-19 complications [4]. We report on a 63-year-old frail man with the bipolar affective disorder (BAD), severe medical comorbidities, and a history of heavy smoking and alcohol abuse, who contracted COVID-19 during inpatient treatment for a manic episode, and who fully recovered from COVID-19 without any need for respiratory support. We discuss how nicotine replacement therapy (NRT) may have contributed to the favourable outcome of his COVID-19.

11.3 Case Presentation

A 63-year-old cachectic white British man, who looked much older than his age, was admitted to our acute psychiatric unit for treatment of a manic relapse of his bipolar affective disorder. He had been previously prescribed oral olanzapine and sodium valproate, but complied erratically with treatment and was admitted following a relapse of his manic symptoms. He was a lifelong smoker (over 100 pack-years), with a history of alcohol misuse (100-120 units/week for years), who suffered from severe chronic obstructive pulmonary disease (COPD) (forced expiratory volume in 1 second 42% of predicted value, forced expiratory volume in 1 second/full vital capacity ratio of 55%, Modified Medical Research Council Dyspnea Score +2) and alcoholic liver disease. In the year leading to the current admission, he had four infective exacerbations of COPD requiring hospitalisation and on one of these admissions required non-invasive ventilation for type 2 respiratory failure. Between exacerbations, his COPD was treated with a regular salbutamol inhaler (a short-acting beta agonist), a regular combination inhaler with umeclidinium (a muscarinic antagonist) and vilanterol (a long-acting beta-agonist), oral hyoscine hydrobromide 300mcg daily (a muscarinic antagonist) and oral carbocysteine 750mg daily (a mucolytic agent). He also had Crohn's disease which required multiple bowel resections, including a right hemicolectomy and a splenectomy. He was on no regular medication for the treatment of his Crohn's disease. In the previous year, a computed tomography colonoscopy revealed a sigmoid lesion

suspicious of bowel cancer, but he declined further investigations. He was severely frail (score of 7 on Rockwood Frailty scale) and was completely dependent on others for all aspects of his care. In the first two months, he suffered two episodes of bacterial pneumonia requiring administration of intravenous antibiotics and oxygen, each followed by extended periods of delirium. In between episodes of pneumonia, his presentation fluctuated from periods of confusion to briefer periods of lucidity. His olanzapine was changed for paliperidone long-acting injections. He was offered nicotine replacement therapy (NRT) in nicotine patches (21 mg/day) and inhalators (15mg cartridges, six cartridges/day). He also used e-cigarettes continually (one 3 ml cartridge/day, 18mg/ml) instead of his normal cigarettes. In addition to parenteral nicotine, he inhaled 120-150 mg of nicotine daily after also borrowing e-cigarettes and inhalators from other patients.

Three months into his admission, he became acutely unwell with hypothermia (34.6 Celsius), drowsiness, hypotension (90/70 mmHg), tachypnoea (34 breaths/minute) and hypoxia (oxygen saturation of 79% on air). A nasopharyngeal swab for SARS-COV 2 RNA was positive, and he was transferred to accident and emergency and later a general medical ward. While both C-reactive protein (160 mg/L) and neutrophil count (11.2x109/L) were raised, lymphocyte count was suppressed (1.04x109/L) and other markers of inflammation, including platelet count and alkaline phosphatase levels, were normal. A chest radiograph showed lung hyperinflation consistent with COPD, with bilateral peripheral, infiltrates (figure *1*). He received a 7-day course of empirical oral antibiotics, and the hypoxemia was managed with controlled oxygen therapy via a 24% venturi mask only (oxygen flow rate of 1-2 litres/minute). NRT was continued throughout his hospital stay. Three days into this illness, he suffered a self-limiting tonic-clonic seizure. A head computer tomography scan showed no abnormality. Over the following 10 days, he made an impressive recovery, having never required any mechanical ventilator support or anti-inflammatory treatment. He was transferred back to our unit medically well, in good spirits, and with no COVID-19 symptoms.

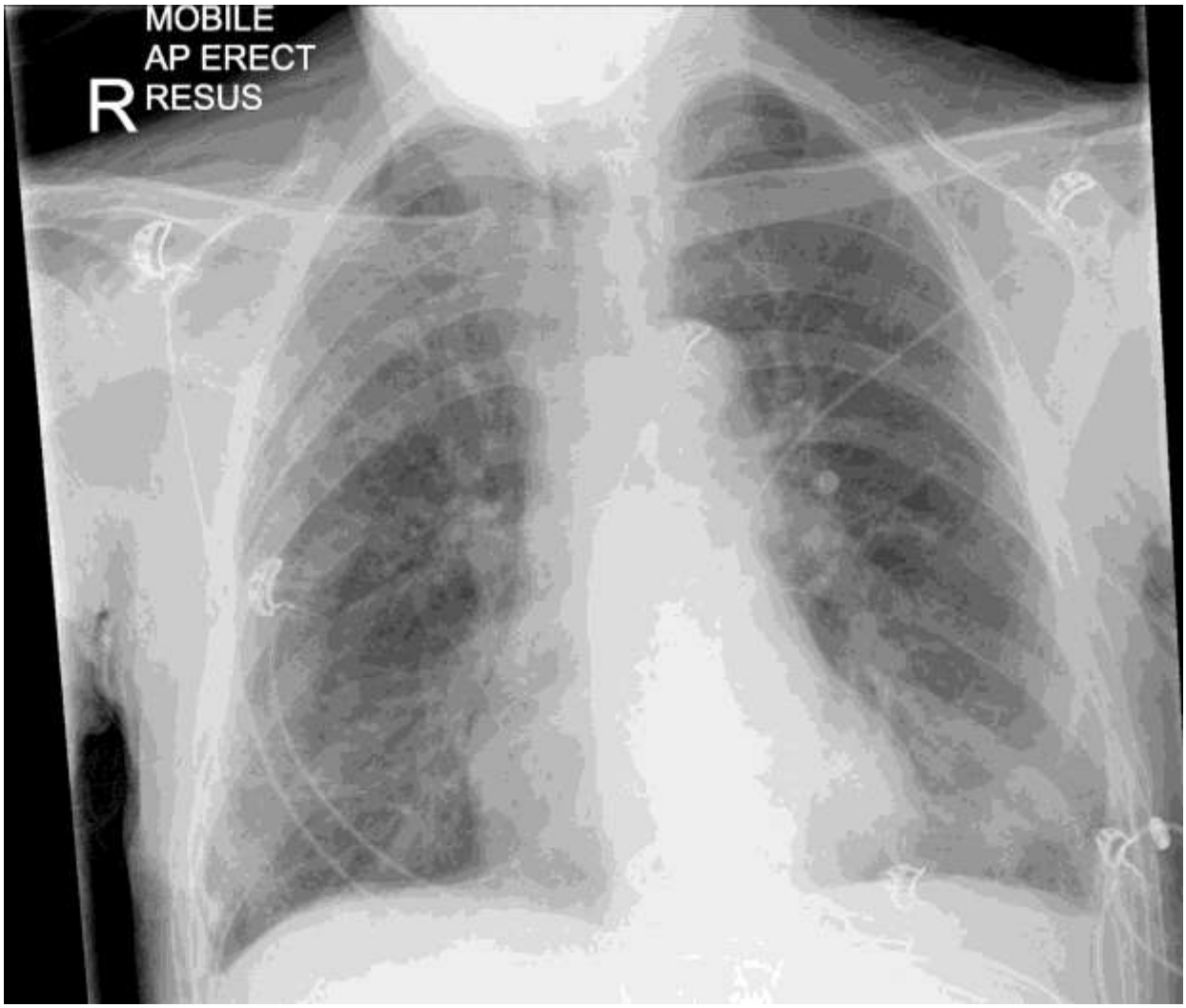

Figure 1: Chest radiograph taken on arrival to accident and emergency

Radiograph shows lung hyperinflation, consistent with chronic obstructive airways disease, and diffuse peripheral infiltrates suggestive of viral pneumonia.

11.4 Discussion

The course of COVID-19 varies, with up to 80% of patients having no or only mild symptoms, 15% developing pneumonia with or without hypoxaemia, and 5% progressing to acute respiratory distress syndrome (ARDS) and multiorgan involvement [1]. Some patients progress suddenly from mild dyspnoea to ARDS requiring urgent ventilatory support. The median time from first symptoms to hospitalisation and ARDS is eight days [2]. However, ten days after exhibiting COVID-19 symptoms, our patient never experienced any complication other than a seizure unrelated to COVID-19 [5].

His unscathed recovery defied our worst predictions. He might just have been lucky. COVID-19 is a novel disease that is not yet fully understood, and most of those who fall ill suffer flu-like symptoms lasting a week or so. He was, however, an older man with a bipolar affective disorder associated with alcohol abuse. He was a heavy smoker and suffered from COPD, inflammatory bowel disease, recurrent chest sepsis and probable bowel cancer. He also was asplenic. As a patient with significant risk factors for COVID-19 complications, another plausible explanation is that he may have been spared from the "cytokine storms" that can be triggered by SARS-CoV-2 virus infection.

Inflammation is the body's first line of defence against infection, and microbes have evolved strategies to avoid precipitating inflammatory responses. However, some pathogens, like the influenza virus and the Gram-negative bacterium Francisella tularensis, do trigger life-threatening "cytokine storms" in the host [6]. "Cytokine storms" also seem to contribute to severe COVID-19 [7]. In the lungs, the angiotensin-converting enzyme two receptors (ACE2), the principal receptor for the SARS-CoV-2 virus, is highly expressed on epithelial cells, through which the virus enters the organism [8]. In the absence of neutralising antibodies, the ensuing cellular and cytokine inflammatory response in the infected lungs is capable of clearing the virus but can cause severe impairment of lung function [7]. Damage to alveolar pneumocytes and release of inflammatory mediators, along with activation of neighbouring dendritic cells, attract macrophages, then T-lymphocytes, and cause the release of pro-inflammatory interleukins and TNF-α. The overproduction of pro-inflammatory cytokines, together with the activation of the coagulation cascade and microthrombi formation in the lung vasculature, may lead to ARDS and later to multiorgan failure and death [7].

The multiple severe diseases from which our patient suffered might have compromised his immune system, thereby paradoxically protecting him by reducing the likelihood of an uncontrolled inflammatory response to the virus. Crohn's disease, which, in his case necessitated several surgical interventions, has been associated with immunodeficiency of macrophages [9]. Bowel cancer may likewise hinder an excessive inflammatory response. The spleen is involved in cytokine production following infections, but patients who have had a splenectomy, as this man has, are at increased risk of bacterial sepsis; in the UK, people with splenectomy are included in the shielding list for COVID-19. Moreover, he received antipsychotics, and there is evidence that antipsychotics may reduce inflammatory activity [10]. However, he also had alcoholic liver disease, which in turn may activate innate liver immunity and the expression of pro-inflammatory cytokines [11].

Whether the combined effect of his medical comorbidities prevented a "cytokine storm" is, however, a matter for speculation. What is clear is that his immune system was healthy enough to enable him to fully recover from COVID-19 unaided by any treatment, except for empirical antibiotics and, perhaps, nicotine. His heavy smoking, the likeliest cause of his severe COPD and an exacerbator of his Crohn's disease, was also a source of large amounts of nicotine to which he was addicted. Throughout his admission, he used NRT in copious amounts. His craving for hefty doses was obvious when his cigarettes were replaced by NRT, which he supplemented with nicotine from e-cigarettes, reaching an estimated consumption equivalent to over 5-6 packs of cigarettes a day. In the light of emerging evidence of a possible role of nicotine on the clinical course of COVID-19, and also of our patient's pre-existing poor medical state, his continuous use of such excessive amounts of nicotine would be hard to

ignore, as it may not only account for his low body temperature at the onset of his COVID-19 symptoms but may also have played a decisive role in the outcome of his illness.

Given the association of smoking with COPD, smokers would be expected to be particularly vulnerable to COVID-19 complications [3,12]. However, a retrospective cohort study in France reported that smokers had a SARS-CoV-2 infection attack rate four times lower than non-smokers [13]. Another retrospective French study reported that, compared to the general population, smokers had a dramatically lower risk of developing symptomatic or severe COVID-19 [14]. Further similar findings elsewhere [15,16] have raised the question as to whether nicotine may have any biological effect on the SAR-CoV-2 virus.

Nicotine can selectively reduce the inflammatory response in various infection states, including Legionella pneumophila and Chlamydia pneumoniae infection, via the cholinergic anti-inflammatory pathway [6]. Nicotine is an agonist at the α7 subunit of nicotinic acetylcholine (α7-nACh) receptors on innate immune cells such as macrophages. These receptors respond to acetylcholine from different sources, including other immune cells and the vagus nerve, and their activation causes suppression of pro-inflammatory cytokines. Nicotine is able to suppress the production of pro-inflammatory cytokines by mimicking the binding of acetylcholine.

The SARS-CoV-2 virus may itself antagonise the nACh receptor pathway and reduce its anti-inflammatory action [17]. Nicotine, again through its action at α7-nACh receptors in the lungs, could prevent the virus-induced nACh receptor dysregulation by activating the cholinergic anti-inflammatory pathway. Smoking could thus attenuate the normal defensive function of the immune system and reduce the hyperinflammatory response seen in severe COVID-19, while the immune system of non-smokers may be more prone to SARS- CoV-2 cytokine release syndrome [17]. However, as nicotine increases the expression of ACE2 in the lung and ACE2 increase is mediated by α7-nACh receptors, smoking may promote cellular uptake mechanisms of SARS2 CoV-2 through α7-nAch receptor signalling [18].

Current evidence for a protective effect of nicotine in COVID-19 remains controversial. Nonetheless, there has been a support to the notion of repurposing NRT products [19], such as nicotine patches [20], as an adjunctive treatment for COVID-19 in smokers as our case seems to suggest, the potential role of NRT in the management of COVID-19 warrants further scrutiny.

11.5 Conclusions

In the absence of any effective treatment for COVID-19, further research as to whether nicotine replacement offers protection against severe SAR-CoV-2 infection in smokers is clearly essential. If the mechanisms through which nicotine may interact with the virus remain speculative, the effects of route of administration, duration, dosing and frequency of use of nicotine on any such interaction are unknown. Should NRT be found to be of help in the management of COVID-19, it would be yet another strong reason to persuade smokers to switch to NRT and ultimately quit smoking.

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12 Abstract: Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette

Nov 2018 | Addiction, Volume113, Issue11, Pages 2099-2106 | Konstantinos E. Farsalinos, Nikoletta Yannovits, Theoni Sarri, Vassilis Voudris, Konstantinos Poulas, Scott J. Leischow

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Aims

To measure carbonyl emissions from a heated tobacco product (IQOS) in comparison with an e‐cigarette (Nautilus Mini) and a commercial tobacco cigarette (Marlboro Red).

Design

Regular and menthol variants of the heated tobacco product were tested. A tank‐type atomizer was tested with a tobacco‐flavoured liquid at 10 and 14 W. Aerosol and smoke were collected in impingers containing 2,4‐dinitrophenylhydrazine. Health Canada Intense and two more intense puffing regimens were used.

Setting

Analytical laboratory in Greece.

Measurements

Carbonyl levels in the aerosol and smoke.

Findings

At the Health Canada Intense regimen, heated tobacco products emitted 5.0–6.4 μg/stick formaldehyde, 144.1–176.7 μg/stick acetaldehyde, 10.4–10.8 μg/stick acrolein, 11.0–12.8 μg/stick propionaldehyde and 1.9–2.0 μg/stick crotonaldehyde. Compared with the tobacco cigarette, levels were on average 91.6% lower for formaldehyde, 84.9% lower for acetaldehyde, 90.6% lower for acrolein, 89.0% lower for propionaldehyde and 95.3% lower for crotonaldehyde. The e‐cigarette emitted 0.5−1.0 μg/12 puffs formaldehyde, 0.8–1.5 μg/12 puffs acetaldehyde and 0.3–0.4 μg/12 puffs acrolein, but no propionaldehyde and crotonaldehyde. At more intense puffing regimens, formaldehyde was increased in heated tobacco products, but levels were three–fourfold lower compared with the tobacco cigarette. Based on the findings from Health Canada Intense puffing regimen, use of 20 heated tobacco sticks would result in approximately 85% to 95% reduced carbonyl exposure compared with smoking 20 tobacco cigarettes; the respective reduction in exposure from use of 5 g e‐cigarette liquid would be 97% to > 99%.

Conclusions

The IQOS heated tobacco product emits substantially lower levels of carbonyls than a commercial tobacco cigarette (Marlboro Red) but higher levels than a Nautilus Mini e‐cigarette.

13 Factors associated with hospitalization and critical illness among 4,103 patients with Covid-19 disease in New York City

| Christopher M. Petrilli,. Simon A. Jones, Jie Yang, Harish Rajagopalan, Luke O'Donnell, Yelena Chernyak, Katie A. Tobin, Robert J. Cerfolio, Fritz Francois, Leora I. Horwitz

https://www.medrxiv.org/content/10.1101/2020.04.08.20057794v1

13.1 Abstract

Background Little is known about factors associated with hospitalization and critical illness in Covid-19 positive patients.

Methods We conducted a cross-sectional analysis of all patients with laboratory-confirmed Covid-19 treated at an academic health system in New York City between March 1, 2020 and April 2, 2020, with follow up through April 7, 2020. Primary outcomes were hospitalization and critical illness (intensive care, mechanical ventilation, hospice and/or death). We conducted multivariable logistic regression to identify risk factors for adverse outcomes, and maximum information gain decision tree classifications to identify key splitters.

Results

- Among 4,103 Covid-19 patients, 1,999 (48.7%) were hospitalized, of whom 981/1,999 (49.1%) have been discharged, and 292/1,999 (14.6%) have died or been discharged to hospice.
- Of 445 patients requiring mechanical ventilation, 162/445 (36.4%) have died.
- Strongest hospitalization risks were age ≥75 years (OR 66.8, 95% CI, 44.7-102.6), age 65-74 (OR 10.9, 95% CI, 8.35-14.34), BMI>40 (OR 6.2, 95% CI, 4.2-9.3), and heart failure (OR 4.3 95% CI, 1.9-11.2).
- Strongest critical illness risks were admission oxygen saturation <88% (OR 6.99, 95% CI 4.5-11.0), d-dimer>2500 (OR 6.9, 95% CI, 3.2-15.2), ferritin >2500 (OR 6.9, 95% CI, 3.2-15.2), and C-reactive protein (CRP) >200 (OR 5.78, 95% CI, 2.6-13.8).
- In the decision tree for admission, the most important features were age >65 and obesity; for critical illness, the most important was SpO2<88, followed by procalcitonin >0.5, troponin <0.1 (protective), age >64 and CRP>200.

Conclusions Age and comorbidities are powerful predictors of hospitalization; however, admission oxygen impairment and markers of inflammation are most strongly associated with critical illness.

13.2 Background

The first announcement of a cluster of novel pneumonia-like illness was made on December 31, 2019 by China. Since then, the causative organism, SARS-Cov-2, has spread to cause a global pandemic that to date has infected over a million people and directly resulted in over 75,000 deaths.

While several reports from China,[1] Italy,[2,3] and most recently the United States Centers for Disease Control and Prevention[4,5] have described characteristics of patients with Covid-19, the disease caused by SARS-Cov-2, little is understood about factors associated with hospital admission and with severe disease. Studies to date have included few patients with severe outcomes,[1,6-10] or have not compared those to patients with less virulent disease,[11-13] making it difficult to assess characteristics associated with poor outcomes. No studies to date have conducted multivariable regression to help identify the strongest risk factors. Moreover, very few studies to date are from the United States. Differences in population demographics and behaviors may limit generalizability of those characteristics to patients in the United States, which currently has the most Covid-19 cases in the world.

Understanding which patients are most at risk for hospitalization is crucial for many reasons. It can assist emergency providers in making triage decisions and ambulatory clinicians in identifying patients who would most benefit from early treatment once available. It can help inform policymakers about highest risk populations, who may need particular protection in policy determinations. Finally, it can help epidemiologists to improve the accuracy of projections about likely need for hospital beds and staffing needs in a region given its demographic characteristics.[14]

For similar reasons, is also important to understand the risk of critical illness among those hospitalized. Clinicians need this information both to identify patients at greatest risk of deterioration, and to inform decision-making about hospital discharge. Policymakers and epidemiologists need this information to project likely need for intensive care unit capacity, ventilators and associated staffing. It would also help improve the reliability of future mortality rate estimation.

New York City is now the epicenter of the Covid-19 outbreak in the United States, with over 68,000 known cases in the city and over 2,700 deaths as of April 6: more than anywhere else in the country.[15] In this report, the largest case series from the United States to date, we describe characteristics of Covid-19 patients treated at a large quaternary academic health system in New York City and Long Island, and the association of these characteristics with adverse outcomes.

13.3 Methods

Study setting

The study was conducted at NYU Langone Health, which includes over 260 outpatient office sites and four acute care hospitals (two in Manhattan, one in Brooklyn, one in Long Island) ranging from a quaternary care hospital to a safety net institution. As the epidemic evolved, the health system added intensive care unit beds and inpatient capacity, resulting in approximately 394 ICU beds and 1,297 non-ICU beds at time of writing.

Data sources

We obtained data from the electronic health record (Epic Systems, Verona, WI), which is an integrated EHR including all inpatient and outpatient visits in the health system, beginning on March 1, 2020 and ending on April 2, 2020. Follow up was complete through April 7, 2020.

A confirmed case of Covid-19 was defined as a positive result on real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of nasopharyngeal or oropharyngeal swab specimens. Initial tests were conducted by the New York City Department of Health and Mental Hygiene; as of March 16, tests were conducted in our clinical laboratory using the Roche SARS-CoV2 assay in the Cobas 6800 instruments through emergency use authorization (EUA) granted by the FDA. On March 31 we added testing using the SARS-CoV2 Xpert Xpress assay in the Cepheid GeneXpert instruments also under EUA by FDA. The targets amplified by these assays are the ORF1/a and E in the Roche Cobas assay and N2 and E genes in the Cepheid XpertXpress. Since March 16, only pharyngeal samples were collected and tested.

Testing was performed for patients presenting to the emergency department with any complaint consistent with Covid-19, including fever, cough, shortness of breath, fatigue, gastrointestinal complaints, syncope, known exposure to a Covid-19 positive patient, or clinician concern. In addition, ambulatory testing was available by appointment with clinician's referral until March 26, 2020, when New York State recommended restricting testing of patients with mild or moderate illness. Outpatient testing of symptomatic or concerned employees has remained available throughout the study period. Repeat testing of negative specimens was conducted at clinician discretion. If testing was repeated and discordant (i.e. negative test followed by a positive test), we used the positive result.

Main outcomes

We assessed two primary outcomes: inpatient hospitalization and critical illness, defined as a composite of care in the intensive care unit, use of mechanical ventilation, discharge to hospice, or death. For patients with multiple visits, the most severe outcome was assigned. For instance, patients who did not need hospitalization at time of initial testing but were later hospitalized were assigned to the hospitalization group. Similarly, patients who were initially admitted and discharged and then readmitted requiring invasive ventilation were assigned to the critical illness group.

Predictors

We obtained from the electronic health record the following variables: age at time of testing, sex, race as reported by the patient (aggregated into white, African American, Asian, other and unknown), ethnicity as reported by the patient (Hispanic or non-Hispanic), any past cardiac history (as defined by a history of hypertension, hyperlipidemia, coronary artery disease or heart failure), any past pulmonary disease (as defined by chronic obstructive pulmonary disease or asthma), malignancy (excluding non-melanoma skin malignancy), diabetes, and obesity (defined by body mass index).

We also obtained vital signs and first set of laboratory results where available. For multivariable modeling, we bucketed vital sign and laboratory results into categories by degree of abnormality based on clinical judgment because of non-linear associations with outcome.

In the hospitalization analysis, we included only patient demographics and past history, since 1,642/2,104 (78%) patients who were not admitted were evaluated in ambulatory testing centers and did not have vitals or laboratory studies collected. For the critical illness analysis, we included the above predictors and added temperature and oxygen saturation on presentation, as well as the first result of c-reactive protein, d-dimer, ferritin, procalcitonin, and troponin when obtained. We selected these predictors based on prior published literature and our clinical experience with Covid-19 patients.

Statistical analysis

We used descriptive statistics to characterize each cohort of patients: those not hospitalized, all those hospitalized, those discharged to home, and those with critical illness (care in intensive care unit, mechanical ventilation, discharge to hospice, or death). We then fitted multivariable logistic regression models with admission and with critical illness as the outcomes to identify factors associated with those outcomes. We included all selected predictors based on *a priori* clinical significance after testing for collinearity using the variance inflation factor (VIF) and ensuring none had VIF>2.[16] For the admission model, we included all patients testing positive. For the critical illness model, we included only patients who had been discharged alive or had suffered severe complications, omitting patients still hospitalized, for whom final outcome was not yet determined. We excluded from this model four patients who expired in the emergency department before any information including vital signs could be collected. We obtained odds ratios from the models and bootstrapped confidence intervals for the odds ratios using the approach of Venables & Ripley,[17] since assuming normality of the maximum likelihood estimate to estimate confidence intervals can lead to biased estimates.[18]

Finally, we constructed maximum information gain decision tree classifications for both hospital admission and severe complication to identify the variables that best classified patients into different outcome cohorts. For a given population, the decision tree classification method splits the population into two groups using one feature at a time, starting with the feature that maximizes the split between groups relative to the outcome in question.[19,20] Subsequent splits reevaluate each split subgroup for

the next best feature. The final population in each end node has similar characteristics and outcomes. We used the decision tree classifier from Python 3.7.4 scikit-learn library. We chose to maximize information gain (which minimizes entropy) for each branch split in the classification tasks. We also pruned the trees to prevent overfitting by limiting the maximum depth, minimum samples in a leaf, and minimum sample splits. For both models, we split the data into a training set (80%) and hold-out set (20%). For the admission model, we ran 48 iterations to achieve optimal parameters. For the complications model, we ran 64 iterations.
The logistic regression models were conducted with R, version 3.6.3, and the decision trees with Python, version 3.7.4. All analyses used 2-sided statistical tests and we considered a p value < 0.05 to be statistically significant without adjustment for multiple testing.

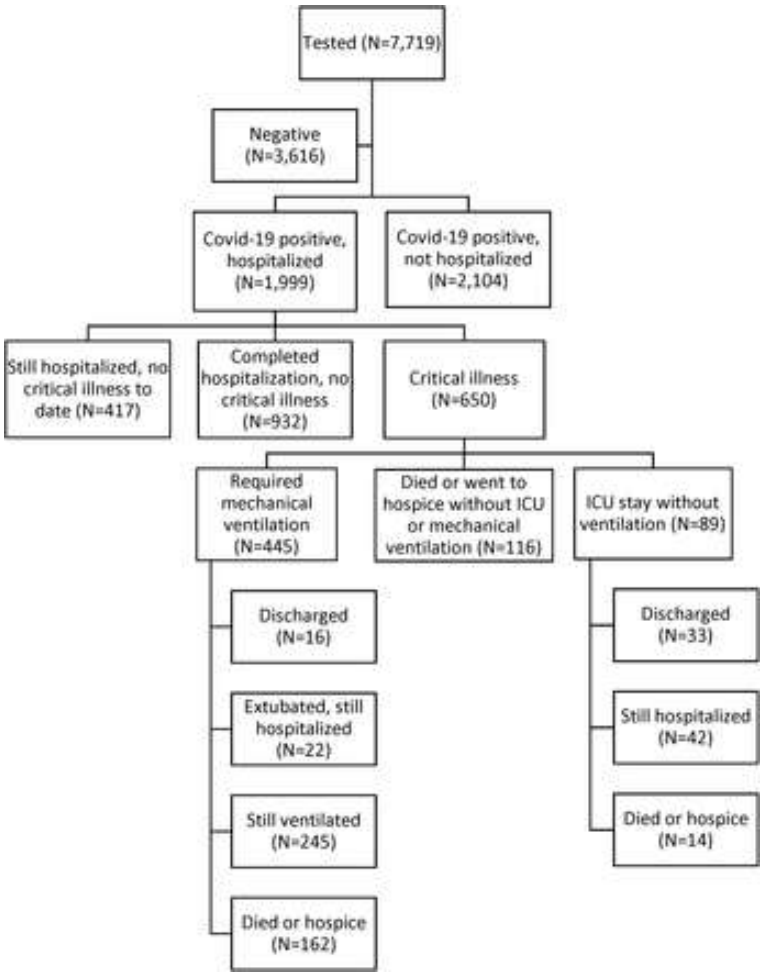
This study was approved by the NYU Grossman School of Medicine Institutional Review Board, which granted both a waiver of informed consent, and a waiver of the Health Information Portability and Privacy Act.

13.4 Results

During the study period, the health system tested 7,719 patients for Covid-19, of whom 4,103 (48.7%) were positive. Of patients testing positive, 2,104 (51.3%) were treated as outpatients, and 1,999 (48.7%) were admitted to the hospital. Among those admitted to the hospital, 1,582 (79.1%) have experienced a study outcome, among which 932/1,582 (58.9%) were discharged without complication and 650/1,582 (41.1%) experienced critical illness, including 292/1,582 (18.5%) who have been discharged to hospice or died.

Among the 650 patients with critical illness, 445/650 (68.5%) required mechanical ventilation, 89/650 (13.7%) required intensive care without mechanical ventilation, and 116/650 (17.8%) were discharged to hospice or died without either intensive care or mechanical ventilation. Final outcomes to date for each subgroup are shown in **Figure 1**.

Figure 1:Flow diagram of included patients



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Characteristics of study population

The median age of the Covid-19 positive study population was 52 years (interquartile range, 36 to 65), and 2,072 (50.5%) were male. A total of 614 (15.0%) had diabetes, 1,100 (26.8%) obesity, and 1,235 (30.1%) cardiovascular disease. Among hospitalized patients, the median length of stay among those with final discharge disposition (discharged alive or died) was 4.8 days (interquartile range, 3.3 to 7.6). Median days of follow up for those still hospitalized with critical illness was 11.4 (IQR 8.4 to 15.4).

Hospitalized patients were more likely to be male (62.6% vs 39.0%) and had substantially more comorbidities than non-hospitalized patients, particularly with regard to cardiovascular disease (44.6% vs. 16.4%), diabetes (31.8% vs 5.4%) and obesity (39.8% vs. 14.5%) (Table 1). Differences in sex and comorbidities between patients experiencing severe deterioration and those who did not were much smaller. Among these patients, differences in clinical presentation and laboratory results were more prominent. Patients experiencing severe deterioration were more likely to present with hypoxia (initial O2 saturation 25th percentile 86% versus 93%), and had higher initial levels of c-reactive protein (median 139 vs 80.8), d-dimer (median 513 vs 306), ferritin (median 980.5 vs 574.5). (Table 2).

Table 1: Characteristics of tested patients, by hospitalization status View inline View popup

Table 2: Characteristics of admitted patients, by complication status View inline View popup

Predictors of hospitalization

In multivariable analysis, the factors most associated with hospitalization were age 75 years or older (OR 66.8, 95% CI, 44.7 to 102.6), age 65-74 (OR 10.9, 95% CI, 8.35 to 14.34), BMI>40 (OR 6.2, 95% CI, 4.2-9.3), and history of heart failure (OR 4.3 95% CI, 1.9-11.2). Full model results are shown in Table 3.

Table 3:Multivariable regression results, hospitalization View inline View popup

The factors most associated with critical illness were admission oxygen saturation <88% (OR 6.99, 95% CI 4.5 to 11.0), first d-dimer>2500 (OR 6.9, 95% CI, 3.2 to 15.2), first ferritin >2500 (OR 6.9, 95% CI, 3.2-

15.2), and first C-reactive protein (CRP) >200 (OR 5.78, 95% CI, 2.6 to 13.8). Age 0-18 had a high OR of 6.3 (95% CI, 2.4 to 16.1), but this group included only 28 patients, of whom 19 were newborns; most of the critically ill were > 16 years. There were no deaths in this age group. See Table 4 for full model results.

Table 4:Multivariable regression results, critical illness View inline View popup

In a maximum information gain decision tree for admission, the most important feature at the top-level branch point was age >65, followed by obesity; for critical illness, the top branch point was SpO2<88, followed by procalcitonin >0.5, troponin <0.1 (protective), age >64 and CRP>200. (See Figure 2A **and** Figure 2B)

Figure 2A:Maximum likelihood classification tree for hospitalization Download figure Open in new tab

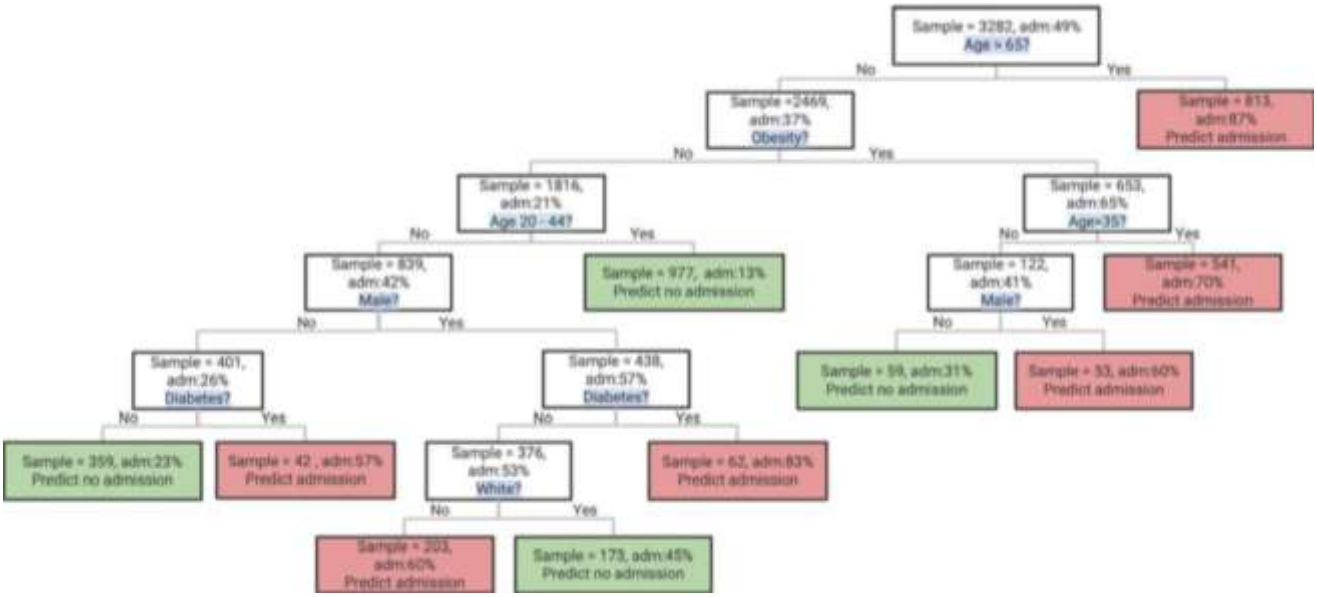
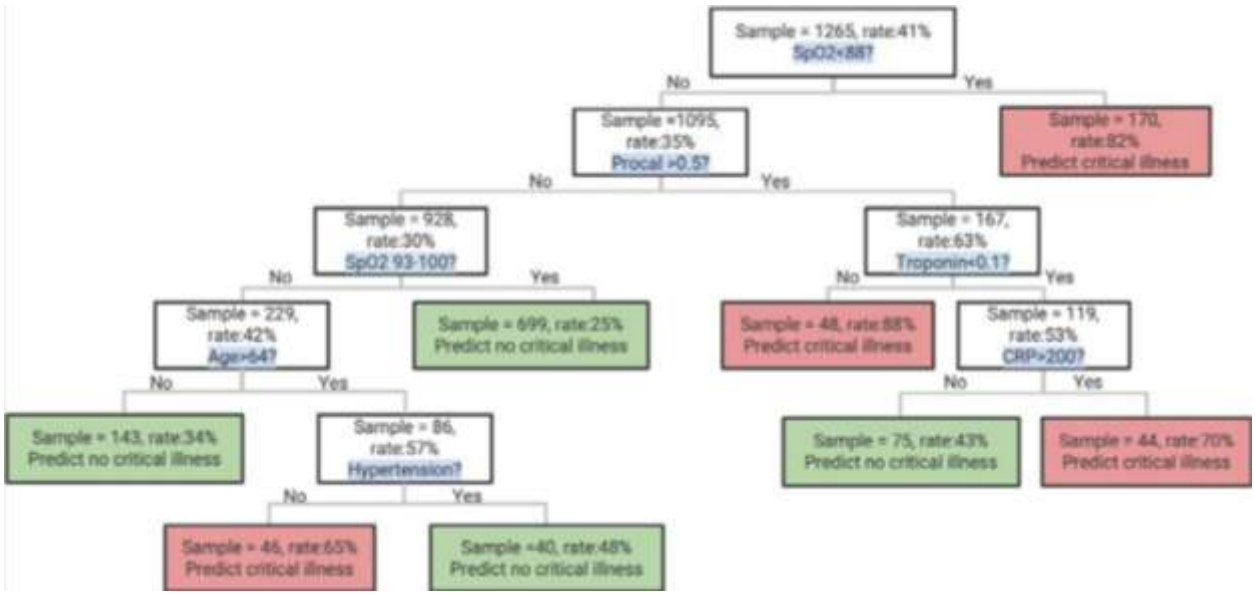


Figure 2B: Maximum likelihood classification tree for critical illness Download figure Open in new tab



13.5 Discussion

In this report, we describe characteristics of 4,103 patients with laboratory-confirmed Covid-19 disease in New York City, of whom 1,999 required hospital admission and 650 required intensive care, mechanical ventilation, were discharged to hospice and/or died. We find particularly strong associations of older age, obesity, heart failure and chronic kidney disease with hospitalization risk, with much less influence of race, smoking status, chronic pulmonary disease and other forms of heart disease. Moreover, we also noted the importance of hypoxia despite supplemental oxygen and early elevations in inflammatory markers (especially d-dimer and c-reactive protein) in distinguishing among patients who go on to develop critical illness and those who do not. In the hospitalized population, measures of inflammation were much more important than demographic characteristics and comorbidities.

The largest detailed case series published to date included 1,099 hospitalized patients with laboratory-confirmed Covid-19 infection in China, of whom only 25 (2.3%) underwent invasive ventilation and 15 (1.4%) died.[1] By contrast, 28.1% of hospitalized patients with definitive outcomes in this case series have so far required invasive ventilation and 18.5% have died. Given the very high prevalence of disease in New York City and the relative paucity of baseline hospital beds per capita (1.5-2.7 beds per 1,000 in all boroughs except Manhattan), admission thresholds may be higher in New York City than in China (4.2 beds per 1,000).[21,22] Moreover, in the series by Guan et al, only a quarter of the hospitalized patients had any chronic comorbidity, whereas in our series 71.9% of hospitalized patients had at least one chronic disease.

In fact, outcomes in the majority of reports are similar to ours. A commentary by the Chinese Center for Disease Control and Prevention described outcomes for 72,314 cases, of which 14% were severe (similar to hospitalized patients in our series) and 5% critical with respiratory or multiorgan failure (similar to those with critical illness in our series).[23] Among critical cases, mortality was 49%; ours is 45% to date. This is also similar to the typical mortality rate from acute respiratory distress syndrome (ARDS) of about 35-45%.[24,25] Finally, our results are also consistent with a recent national case series reported by the US CDC that found that 457 of 1,037 (44%) hospitalized patients required ICU admission, and that three quarters had at least one chronic condition.[5]

The risk factors we identified for hospitalization in Covid-19 are largely similar to those associated with any type of severe disease requiring hospitalization or ICU level care, though we were surprised that cancer and chronic pulmonary disease did not feature more prominently in the risk models.[26]

Moreover, the demographic distribution of hospitalized patients is also similar to other acute respiratory infections. For instance, while advanced age was by far the most important predictor of hospitalization and an important predictor of severe outcomes (as it is for most illnesses), 54% of hospitalized patients were younger than 65 years. This is typical of the hospitalization pattern in viral respiratory disease. Studies of influenza hospitalizations in the United States have found that people younger than 65 years account for 53-57% of influenza-related hospitalizations.[27,28] While men made up a grossly disproportionate number of both hospitalizations and critical illness, this difference was attenuated by multivariable adjustment for comorbidities such that gender was no longer one of the most prominent risk variables.

Surprisingly, though some have speculated that high rates of smoking in China explained some of the morbidity in those patients, we did not find smoking status to be associated with increased risk of hospitalization or critical illness. This is consistent with a handful of other studies that have previously shown a lack of association of smoking with pulmonary disease-associated ARDS (i.e. from pneumonia), as compared with non-pulmonary sepsis-associated ARDS.[29]

More striking were our findings about the importance of inflammatory markers in distinguishing future critical from non-critical illness. Among these, early elevations in c-reactive protein and d-dimer had the strongest association with mechanical ventilation or mortality. Hyperinflammatory states are well described in severe sepsis;[30] however, the degree to which Covid-19 related inflammation is similar to

or different than that typically found in sepsis is unknown. Some emerging case reports suggest that patients with critical Covid-19 disease are developing complications from hypercoagulability,[8] including both pulmonary emboli[31] and microscopic thrombi.[32] In this regard it is notable that the chronic condition with the strongest association with critical illness was obesity, with a substantially higher odds ratio than any cardiovascular or pulmonary disease. Obesity is well-recognized to be a pro-inflammatory condition.[33,34] Finally, we noted that early (relatively mild) elevation in procalcitonin was a powerful splitter in the classification tree, although Covid-19 appears to be characterized by low procalcitonin levels in general. While many patients with elevated procalcitonin and critical illness were treated with antibiotics, it remains unclear whether these patients actually had bacterial disease or whether the elevation in procalcitonin was another manifestation of a general hyperinflammatory state.

This study includes several limitations. We did not have access to symptom duration which is an important predictor of hospitalization: patients rarely require hospitalization with less than a week of symptoms. However, this limitation should not affect the demographic and clinical characteristics of those requiring admission and having severe deterioration. Importantly, as we are still early in our epidemic, many patients do not yet have final outcomes established, though the sample size of those who do is still more substantial than any prior study of associations with outcomes. Our patients were all from a single geographic region, treated within a single health system; factors associated with poor outcomes may differ elsewhere, though our patient population is very diverse. We did not have inflammatory markers available for non-hospitalized patients; it is possible that these would have been strong predictors for hospitalization risk as well if available. Finally, a standardized admission laboratory protocol was only established about two weeks into the epidemic, resulting in missing laboratory data for earlier patients, especially those who were less acutely ill.

Overall, we find that age and comorbidities are powerful predictors of requiring hospitalization rather than outpatient care; however, degree of oxygen impairment and markers of inflammation are strongest predictors of poor outcomes during hospitalization. Clinicians should consider routinely obtaining inflammatory markers during hospitalizations for Covid-19.

13.6 Other

Data Availability Individual level data are not available for this study. For aggregate data please contact the corresponding author.

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14 Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an

analysis of 89,756 laboratory–confirmed COVID-19 cases

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14.1 Abstract

Background There is insufficient information about risk factors for COVID-19 diagnosis and adverse outcomes from low and middle-income countries (LMICs).

Objectives We estimated the association between patients' characteristics and COVID-19 diagnosis, hospitalisation and adverse outcome in Mexico.

Methods This retrospective case series used a publicly available nation-level dataset released on May 31, 2020 by the Mexican Ministry of Health, with patients classified as suspected cases of viral respiratory disease. Patients with COVID-19 were laboratory-confirmed. Their profile was stratified by COVID-19 diagnosis or not. Differences among COVID-19 patients based on two separate clinical endpoints, hospitalisation and adverse outcome, were examined. Multivariate logistic regressions examined the associations between patient characteristics and hospitalisation and adverse outcome.

Results Overall, 236439 patients were included, with 89756 (38.0%) being diagnosed with COVID-19. COVID-19 patients were disproportionately older, males and with increased prevalence of one or more comorbidities, particularly diabetes, obesity, and hypertension. Age, male gender, diabetes, obesity and having one or more comorbidities were independently associated with laboratory-confirmed COVID-19. Current smokers were 23% less likely to be diagnosed with COVID-19 compared to non-smokers. Of all COVID-19 patients, 34.8% were hospitalised and 13.0% experienced an adverse outcome. Male gender, older age, having one or more comorbidities, and chronic renal disease, diabetes, obesity, COPD, immunosuppression and hypertension were associated with hospitalisation and adverse outcome. Current smoking was not associated with adverse outcome.

Conclusion This largest ever case series of COVID-19 patients identified risk factors for COVID-19 diagnosis, hospitalisation and adverse outcome. The findings could provide insight for the priorities the need to be set, especially by LMICs, to tackle the pandemic.

14.2 Tweetable abstract @ERSpublications

This large retrospective case series of COVID-19 patients in Mexico provides insight on risk factors for COVID-19 diagnosis, hospitalisation and adverse outcome and may guide low and middle income countries in tackling the pandemic.

14.3 Introduction

As the global pandemic of the Corona Virus Disease 2019 (COVID-19), a disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is evolving, it is important to understand the pathophysiology and the mechanisms of disease progression. The rapid transmission of the disease and the increased pressure across healthcare systems has led to emergency measures resulting in substantial social and economic disruption. As of May 30, almost 5.9 million people globally have been diagnosed with COVID-19 and approximately 367255 deaths have been reported. The disease has a wide range of clinical presentations, from mild symptoms resembling the common flu to severe, life threatening manifestations such as Adult Respiratory Distress Syndrome (ARDS), thrombotic complications and neurological symptoms [1–3]. Risk factors for adverse outcomes include age, hypertension, diabetes, cardiovascular disease and respiratory disease [4].

The pandemic represents a big challenge particularly for low- and middle-income countries (LMIC). The cost of epidemiologic surveillance and of infection prevention and control, the sudden flow and the need to enhance the constrained critical care capacity to treat COVID-19 patients and the implementation of non-medical interventions such as social distancing measures are expected to significantly stress the limited financial resources of these countries [5]. Therefore, understanding the factors associated with COVID-19 susceptibility and adverse prognosis is crucial to guide local authorities towards more efficient allocation of their scarce resources to avoid exceeding the limited capacity of the healthcare system.

In this study we present evidence and information about patients who were screened for COVID-19 due to suspected viral respiratory infection through the respective surveillance system implemented in Mexico. The objective of this study was to examine the association between individuals' sociodemographic and clinical characteristics and COVID-19 diagnosis. Additionally, we explored similar associations with two clinical outcomes, hospitalisation and adverse outcome, within the COVID-19 diagnosed cohort. This study extends the current literature by presenting novel information and evidence about COVID-19 patients in Mexico using a large and recent cohort of such patients, with potentially important implications at the clinical and policy level.

14.4 Methods

Study design, setting and participants

We performed a cross-sectional secondary data analysis using a publicly available individual level dataset which included patients classified as 'suspected cases of viral respiratory disease' during point of service at medical facilities in Mexico. The dataset was released by the Mexican Health Ministry and was compiled by the General Bureau of Epidemiology (Dirección General de Epidemiología, DGE) through the System of Epidemiological Surveillance of Viral Respiratory Diseases [6, 7]. The latter comprises of 475 Monitoring Units of Viral Respiratory Disease (Unidades Monitoras de Enfermedad Respiratoria Viral, USMER) spread across the country and covering all institutions affiliated to the Health Ministry collectively denoted as the Health Sector. Additional data were provided by healthcare units that did not belong to USMER but had been adapted to screen suspected COVID-19 cases. As specified by the official guidelines issued by the DGE, the entries in the dataset only correspond to data obtained from the epidemiological study of "suspected case of viral respiratory disease" at the time it was identified at medical units of the Health Sector.
This dataset is continuously updated, and we used the version released on May 31, 2020, which included 274997 patients.

No ethics approval was sought for this study since it involves analysis of an anonymized dataset of patients that is publicly available and accessible to anyone through the Mexican Health Ministry.

Data sources

Upon admission, patients were screened by healthcare professionals who were expected to verify that the subjects show specific symptoms documented as inclusion criteria for the dataset. Additionally, they recorded data about the medical history on a specific DGE form. After the case was evaluated and confirmed at the district, state and national level surveillance system, it was added to the dataset. Both USMER and Non-USMER units had to fill the same forms which were sent to an online platform (SISVER platform). According to the DGE guidance, USMER and non-USMER units should perform diagnostic testing for COVID-19 (RT-PCR) in all cases with serious symptoms. For cases with mild symptoms (classified as ambulatory cases), USMER units were expected to perform COVID-19 diagnostic testing on 10% of these cases whereas non-USMER units would test cases depending on their resource capacity.

Laboratory testing to confirm SARS-CoV-2 infection was performed according to WHO interim guidance [8]. Combined nasopharyngeal and oropharyngeal swabs were obtained and placed in a container. For intubated patients, bronchoalveolar lavage was obtained. In case of death, lung biopsies were obtained during autopsy, from an area visibly affected by disease. The samples were sent to the nearest Laboratory of Respiratory Virus (InDRE) for testing with RT-PCR.

Variables

The dataset included information on COVID-19 testing results, categorised as positive, negative and pending, as well as individual level data on sociodemographic and clinical characteristics and facility

specific information. Sociodemographic information included patients' age, gender and nationality (Mexican or not). Clinical characteristics included existing comorbidities, namely diabetes, chronic obstructive lung disease (COPD), asthma, immunosuppression, hypertension, cardiovascular disease, obesity, chronic renal disease and other comorbidities (not defined). No data on the duration or time of diagnosis of comorbidities, pharmacotherapy or clinical condition of patients relative to the comorbidities were available. Additionally, comorbidity classifications were not further defined according to specific diagnoses. For example, no information on specific cardiovascular diseases (coronary artery disease, heart failure, arrhythmias etc.) were reported. Finally, comorbidities were recorded based on past medical history; thus, there was no record of the diagnostic criteria used for each comorbidity, similarly to other studies [9–12]. Smoking was also recorded, with participants classified as smokers or non-smokers. No data on former smokers was available. All information was recorded on a specific "Respiratory Triage form by the attending physicians [7]. For patients with laboratory-confirmed COVID-19 diagnosis, the dataset included additional information related to clinical endpoints, namely whether the patient was admitted into an intensive care unit, intubated, or died. Facility level information included a dichotomous indicator on whether the healthcare unit was part of the USMER network or not, and the type of facility where the patient was diagnosed.

Outcomes and analysis

The first outcome variable of interest in the study was whether a patient was diagnosed with COVID-19 or not, defined as a dichotomous indicator. We thus excluded 36803 patients (13.4%) with pending results, resulting in a final sample of 238194 patients. We also explored two outcomes within the subgroup of patients with COVID-19 diagnosis, hospitalisation and severity. Both outcomes were dichotomous; the first was hospitalisation and the second was adverse outcome defined as intubation, intensive care unit admission or death.

We included individual level sociodemographic and clinical characteristics, and facility information based on data availability. Sociodemographic patient-level information included age, gender, and Mexican nationality (or not). Clinical information included number of comorbidities, whether the patient had a particular clinical condition or not, namely asthma, chronic obstructive pulmonary disease (COPD), diabetes, obesity, hypertension, immunosuppression, cardiovascular condition, and chronic renal disease. We also included information on whether the patient was a current smoker and whether there was previous contact with someone who was diagnosed with COVID-19. Facility specific information included the type of facility by ownership and whether the medical unit is a monitoring unit for respiratory diseases (USMER). USMER consists of medical facilities which monitor the incidence of infectious respiratory diseases as part of the government's Epidemiological Surveillance system.

We initially conducted descriptive analyses of all patients to characterise the overall study population. We then performed stratified bivariate analyses to compare patients based on whether they were diagnosed with COVID-19 or not. Subsequently, laboratory-confirmed COVID-19 cases were stratified by the two outcomes of interest (hospitalisation and adverse outcome) using similar bivariate analyses. We tested for statistical differences in the stratified analyses using Pearson's chi-square for categorical variables and the non-parametric Mann Whitney U test on the age variable (as numeric).

To estimate the association of all the independent variables with the three outcomes of interest (COVID-19 positive diagnosis for all patients, hospitalisation and adverse outcome only for COVID-19 positive patients), we then conducted two multivariate logistic regressions for each of the three outcomes (six regressions in total). For each outcome, both models included the same sociodemographic and facility specific variables. The first model also included clinical comorbidities as dichotomous indicators, while the second included the number of clinical diagnoses (comorbidities) only, due to multicollinearity, as the later was derived from the clinical diagnoses. We also included area-of-residence fixed-effects to control for unobserved regional variations. Finally, standard errors were clustered at the residence level. All analyses were conducted using Stata (version 16.1; StataCorp, College Station, TX).

14.5 Results

Our final analytic sample included 236439 patients who were suspects of a viral respiratory disease, after excluding 1755 patients (0.7%) due to missing variables. The majority were 18 to 44 years of age,

Mexicans, and around 40% of those had one or more comorbidities, while 9.0% were current smokers (**table 1**). The most prevalent clinical conditions included hypertension, diabetes, and obesity. The age distribution of comorbidities is presented in Supplementary Table 1. About 37% of the patients used a USMER facility and more than half used hospitals of the Ministry of Health (Secretaria de Salubridad y Asistencia – SSA).

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TABLE 1

Descriptive analysis on all patients with suspected viral respiratory disease and bivariate analysis stratified by positive or negative COVID-19 diagnosis

Around one-third (38.0%) of patients were diagnosed with COVID-19 (**table 1**). These patients had higher shares of males (56.4% *versus* 47.5% for non-COVID-19 patients, p<0.001), and were 6 years older on average (p<0.001). COVID-19 patients had also disproportionately higher shares of one or more comorbidities (p<0.001), and chronic conditions particularly related to diabetes, hypertension, and obesity (p<0.001 for all). We also observed greater shares for USMER related COVID-19 cases at the facility level (p<0.001 for both).

Table 2 indicates the results of the two regressions on COVID-19 diagnosis for all patients in the data. Across both models, females and younger patients (0 to 17) were significantly less likely to be diagnosed with COVID-19 compared to males and to their 18 to 44 counterparts (p<0.001 for all). In addition, current smokers were approximately 23% less likely to be diagnosed with COVID-19 compared to non-smokers (p<0.001 in both models). In contrast, older patients (45 years of age or older) and those with one or more comorbidities were more likely to be diagnosed with COVID-19 compared to those aged 18 to 44 and those without comorbidities respectively. Diabetes and obesity were particularly associated with COVID-19 diagnosis compared to patients without such conditions (p<0.001 for all).

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TABLE 2

Multivariate logistic regression analyses on the factors associated with COVID-19 diagnosis across all patients. Two regression models were examined, one with each comorbidity introduced separately as independent variable (Model 1) and one with number of comorbidities used as independent variable (Model 2)

Among the 89756 patients who were diagnosed with COVID-19, about 35% were hospitalised and 13% had high clinical severity (**table 3**). Across both subgroups, hospitalisation and adverse outcome were more frequent in males and older patients, with a mean age difference of more than 12 years. Patients with one or more comorbidities, particularly those with hypertension, obesity, diabetes, and COPD were also more prevalent in both the hospitalised and the adverse outcome groups.

- **View inline**
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TABLE 3

Descriptive bivariate analysis among patients with COVID-19 diagnosis stratified by hospitalisation and adverse outcome

Table 4 indicates the results of the two regressions for hospitalisation and adverse outcome, respectively (**table 4**). Across both models, males and older patients were significantly more likely to be hospitalised and to experience adverse outcome compared to females and to their 18 to 44 old counterparts (p<0.001 for all). Those 0 to 17 years of age were also less likely to experience adverse outcome compared to the 18 to 44 years age group. In addition, patients with chronic renal disease, diabetes, immunosuppression, COPD, obesity, and hypertension were up to 121% (adjusted OR: 2.21, 95% CI: 1.91–2.55, for those with chronic renal disease) more likely to experience hospitalisation and more severe composite endpoints compared to those without such conditions (p<0.001 for all). Similarly, having one or more comorbidities increased the likelihood of these outcomes, as expected (**table 5**). Finally, we did not observe any significant differences among current smokers compared to non-smokers across both outcomes.

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TABLE 4

Multivariate logistic regression analyses of factors associated with hospitalisation and adverse outcome among patients with COVID-19 diagnosis

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TABLE 5

Multivariate logistic regression analyses of factors associated with hospitalisation and adverse outcome among patients with COVID-19 diagnosis, in which number of comorbidities (instead of each comorbidity) was used as independent variable

14.6 Discussion

To the best of our knowledge, this study presents a case series with the highest number of laboratory-confirmed COVID-19 patients, and the first of this size from a LMIC. The Chinese Centers for Disease Control (CDC) recently presented data from 44672 confirmed cases, however information about comorbidities was available for only 20812 patients [9]. Another study in the UK examined risk factors for critical care and mortality in hospital among 20133 hospitalised COVID-19 patients [10]. In the US, patient characteristics, comorbidities and outcomes were presented among 5700 patients hospitalised for COVID-19 in New York City area [11]. Our study adds to the current evidence by presenting information from laboratory-confirmed cases in a LMIC using a large publicly available dataset.

In agreement with previous studies [1, 10–14], age was a strong risk factor for hospitalisation, adverse outcome among COVID-19 patients. It was recognised early during the pandemic that the elderly had higher rates of hospitalisation and infection fatality ratios compared to younger people [15]. Recently, the US CDC reported that the best estimates for the COVID-19 symptomatic case fatality ratio was 0.4% for the whole population but ranged from 0.05% for those aged 0–49 years to 1.3% for those ≥65 years, a 26-fold difference [16]. Hospitalisation rates were estimated to be approximately 7-fold higher for patients aged ≥65 years compared to those aged 18 to 44 years in our study. Thus, targeted interventions tailored at the higher needs and risk of older people are clearly needed, to protect them from SARS-CoV-2 infection and to reduce the COVID-19 morbidity and mortality burden.

Our results indicate that cardiovascular and endocrine conditions were the most common comorbidities identified among confirmed COVID-19 patients. Hypertension, obesity and diabetes were not only common comorbidities but also independent correlates of hospitalisation and adverse outcomes. These findings are in-line with case series from China, the US and Europe [1, 9–13]. These conditions are very common worldwide and in Mexico. Approximately 1.4 billion adults are estimated to suffer from hypertension globally, with the prevalence being higher in LMICs [17]. In Mexico the prevalence of hypertension was 25.5% in 2016 [18]. Obesity is also a major healthcare issue in Mexico. In a random sample of 2511 adults, 38.3% of Mexicans were overweight and almost 25% were obese [19]. The Organisation for Economic Cooperation and Development (OECD) reports that Mexico is the one of the countries with the highest rates of obesity in the population [20]. Obesity is a risk factor for diabetes, and Mexico had an estimated 10.4% prevalence of diabetes in 2016 with a continuously increasing trend [21, 22]. The latter, in combination with the increased prevalence of these conditions among COVID-19 patients suggests that such patients represent another population subgroup where targeted interventions and guidance are needed to prevent SARS-CoV-2 transmission.

In contrast, while cardiovascular disease and COPD were risk factors for hospitalisation, and adverse outcomes, only a small proportion of patients suffered from these comorbidities. A case series of 1590 patients from China reported a similarly low prevalence of these comorbidities among Chine patients [12]. The COPD prevalence in Mexico City was 3.4% in a study defining airflow obstruction as $FEV1/FEV_6$ below the 5th percentile or Lower Limit of Normal [23], but it has been reported that COPD is highly underdiagnosed in Mexico and in other countries, mainly because of lack of spirometry evaluation [24]. In a 2009 study, ischemic heart disease and stroke prevalence in Mexico City ranged from 0.4% to 5.4% and from 0.4% to 3.5%, respectively, depending on age [25]. In addition, other risk factors for adverse outcomes were immunosuppression and chronic renal disease. Our findings are

supported by a recent systematic review and meta-analysis which found a higher risk for adverse COVID-19 outcomes among patients with chronic renal disease [26].

Having more than one comorbidity was strongly associated with hospitalisation and adverse outcome. This is not unexpected considering that multiple comorbidities contribute to disease complexity and such patients are more susceptible and vulnerable to adverse events. Approximately 1 in 5 patients with laboratory-diagnosed COVID-19 had more than 1 comorbidity, and they had approximately 3-fold higher odds for hospitalisation and adverse outcome. Therefore, it is necessary to prioritise the assessment of these patients, offering early diagnosis and proper hospital care, while primary preventive measures to reduce disease transmission to these patients are warranted.

Notably, smoking was not associated with a higher risk for adverse outcomes and hospitalisation. Smokers were also less likely to be diagnosed with COVID-19 compared to non-smokers. The latter is in agreement with a recent observational population study from Israel [27]. Some studies have found that smokers are under-represented among COVID-19 patients and presented a hypothesis that nicotine may exert protective effects [28–31], while others have found that nicotine and smoking causes ACE2 up-regulation which may increase viral invasion [31, 32]. Recent meta-analyses reported that hospitalised smokers with COVID-19 had higher odds for adverse outcomes [33–35], but very few smokers relative to the population smoking rates appear to be hospitalised for COVID-19 [35]. It is possible that more smokers have been tested for COVID-19 compared to non-smokers, which could explain the lower odds for positive diagnostic test. This cannot be directly addressed in this study since all participants were by definition subjects who were tested for COVID-19. However, according to the latest data (2016), the smoking prevalence in Mexico was 14.0% in the population aged ≥15 years [36]. In our study, 9.0% of the sample were smokers. Even if we assume that none of the participants aged 0–17 were smokers (4.8% of the total sample), still smokers would represent approximately 9.6% of the adult sample, lower than the population smoking rates. Thus, it is unlikely that smokers were more likely to be tested for COVID-19 based on the proportion of smokers in the study sample and the population smoking rates. It is currently unclear whether nicotine exerts any positive effect, however, there is no doubt that smoking cannot be used as a protective measure and smoking cessation should be encouraged during the COVID-19 pandemic [29].

It has been established that SARS-CoV-2 uses angiotensin converting enzyme 2 (ACE2) as a receptor for cell entry and viral replication [37]. While this would imply that ACE2 up-regulation would be associated with COVID-19 severity and adverse outcome, there is evidence that the opposite is the case. Risk factors for adverse outcomes identified in this and other studies, such as age, male gender, endocrine and cardiovascular diseases, are associated with lower levels of ACE2 [38–42]. Therefore, it has been hypothesised that ACE2 deficiency may in fact be detrimental for COVID-19 [43]. Additionally, severe COVID-19 represents a hyper-inflammatory response with patients developing cytokine storm and exhibiting ineffective regulation of the immune response [44]. Risk factors identified in this study also represent inflammatory conditions [45–48]. Thus, there is a relevant pathophysiological basis explaining the association between hospitalised and adverse COVID-19 outcomes and the comorbidities identified in our analysis.

This study is not without limitations. First, given the nature and the availability of the data, we were not able to use more detailed clinical and laboratory information for the patients. For example, immunodeficiency may include a vast array of different disease conditions, however no specific information was provided in the dataset. No information was available on pharmacotherapy for comorbidities or the clinical condition of patients in relation to these comorbidities (controlled or decompensated at the time of COVID-19 diagnosis), which could have affected the outcome.

Additionally, we could not examine whether specific disease conditions (*e.g.* coronary heart disease *versus* congestive heart failure, emphysema *versus* chronic bronchitis) would differently affect the outcome. We were not able to include facility and regional specific information, due to the lack of such information in the dataset. However, we believe that we sufficiently addressed the heterogeneity between hospitals and regions using the appropriate variables in our analyses, given the research question of interest. The study sample of laboratory-confirmed COVID-19 cases was not derived from a random sample of the general population but from cases with suspected respiratory disease. This type of selection bias is almost universally applicable to case series of COVID-19 patients considering that laboratory testing capacities are limited worldwide and are usually prioritised for those with more severe symptoms or in patients with comorbidities and at risk for severe disease.

Still, caution is advised in generalising the conclusions to the general population or to population-representative samples. Finally, some of the patients may have not recovered by the time the dataset was released and, thus, the outcome is unknown, while it is also possible that some outpatients or patients with mild disease may experience disease progression and will thus require hospitalisation in the future. This limitation would have been particularly problematic had the epidemic wave been at an early stage, with many new disease cases but limited outcomes due to the time lag from disease diagnosis to final outcome. However, Mexico confirmed its first COVID-19 cases on February 28 while the first death was recorded on March 18 [**49**]. Therefore, the epidemic wave in Mexico was sufficiently advanced at the time we obtained the dataset, and substantial discrepancies in the patient characteristics between new disease cases and outcomes are probably excluded. Still, this should be considered as a limitation, and further analysis as the epidemic progresses is warranted.

In conclusion, this large retrospective case series from Mexico, the largest ever presented for COVID-19, identified risk factors for laboratory-confirmed COVID-19 diagnosis as well as for hospitalisation and adverse outcome among COVID-19 patients. These findings could provide valuable insight for Mexico and other LMICs in setting priorities, allocating healthcare resources and establish disease transmission preventive strategies in order to protect vulnerable groups, particularly the elderly and people with comorbidities.

14.7 Footnotes

- **Support statement:** No funding was provided for this study.
- This article has supplementary material available from erj.ersjournals.com
- **Data availability:** The dataset is publicly available from the Mexican Ministry of Health.
- Conflict of interest: Dr. Giannouchos has nothing to disclose.
- Conflict of interest: Dr. Sussman has nothing to disclose.
- Conflict of interest: Dr. Mier has nothing to disclose.
- Conflict of interest: Dr. Poulas has nothing to disclose.
- Conflict of interest: Dr. Farsalinos has nothing to disclose.
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15 Low rate of daily smokers in patients with symptomatic COVID-19 (in France)

12 June 2020 | medRxiv | Makoto Miyara, Florence Tubach, Valérie Pourcher, Capucine Morélot-Panzini, Julie Pernet, Julien Haroche, Said Lebbah, Elise Morawiec, Guy Gorochov, Eric Caumes, Pierre Hausfater, Alain Combes, Thomas Similowski, Zahir Amoura

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15.1 Abstract

Background Identification of prognostic factors in COVID-19 remains a global challenge. The role of smoking is still controversial.
Objective To evaluate the rate of daily smokers in patients with COVID-19.
Methods COVID-19 in-and outpatients from a large French university hospital were systematically interviewed for their smoking status, use of e-cigarette and nicotinic substitutes. The rates of daily smokers in in-and outpatients were compared to those in the 2019 French general population, after standardization for sex and age.
Results The inpatient group was composed of 340 patients, median age 66 years: 203 men (59.7%) and 137 women (40.3%), median age for both 66 years, with a daily smokers rate of 4.1 % CI95% [2.3–6.9] (5.4% of men, 2.2% of women). The outpatient group was composed of 139 patients, median age 44 years: 62 men (44.6%, median age 43 years), and 77 women (55.4%, median age 44 years). The daily smoker rate was 6.1 % CI 95% [2.7 - 11.6] (5.1% of men, 6.8% of women). In the 2019 French population, the daily smoker rate was 24.0% (27.5% of men, 20.7% of women). Among inpatients, daily smokers represented 2.2% and 3.4% of the 45 dead patients and of the 29 patients transferred to ICU, respectively.
The rate of daily smokers was significantly lower in COVID-19 patients, as compared to that in the French general population after standardization by age and sex, with Standardized Incidence Ratios of 0.24 [0.12-0.48] for outpatients and 0.24 [0.14-0.40] for inpatients.

Conclusion Daily smokers rate in patients with symptomatic COVID-19 is lower as compared to the general population

15.2 Introduction

As the pandemic of COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still under progression, the identification of risk factors is a global challenge. Among epidemiological risk factors, the role of smoking, to date, is unclear. Smoking has been initially found associated with adverse disease prognosis of COVID-19[1], although this finding remains controversial[2]. Reported rates of current smokers among SARS-CoV-2-infected patients range from 1.4% to 12.5% in China[1, 3-10], from 1.3% to 5.1% in the USA[11, 12], mainly for hospitalized patients (see systematic review in[13]). For outpatients, data are very scarce but also suggest similar low rates[13]. At first approach, the rates of current smokers in both COVID-19 in- and out patients seem to be low compared to the general population. These data notwithstanding, no firm conclusions can be drawn from these available COVID-19 studies because main potential confounders for smoking rate, namely age and sex, were not taken into account. Additionally, these studies included mostly hospitalized patients, and the low rate of current smokers may be related to high rate of patients with comorbidities (smokers having been advised to quit). Furthermore, these studies used data collected in the context of care in the medical files, which favors underreporting (patients being considered as non smokers when smoking status is not reported in the medical file) particularly when data collection is made by overwhelmed care healthcare teams for a disease *a priori* not related to smoking, and biased reporting (preferential smoking status collection in patients with pulmonary or cardiovascular comorbidities).
Therefore, the effect of current smoking on the risk of SARS-CoV-2 infection has yet to be determined. To accurately evaluate whether or not current smoking is associated with the risk of COVID-19, we conducted an observational study specifically designed to investigate this association, and compared the rates of daily current smokers after standardization by sex and age of two COVID-19 patients'

groups, one composed of outpatients (not subsequently hospitalized) and one of hospitalized patients (inpatients), with those reported in the 2019 French general population[14]

15.3 Material and methods

Patients and design

This is a cross-sectional survey specifically designed to investigate the smoking status of patients with COVID-19, both in hospitalized patients (representing the severe symptomatic cases of COVID-19) and in outpatients (i.e. patients who represent the non-severe symptomatic cases of this infection). Daily current smoker rates were compared to those of the 2019 French population as a reference, after standardization by age and sex.

Eligible patients were those with a confirmed diagnosis of COVID-19 at the APHP Pitié-Salpêtrière Hospital, France, with two groups: the inpatients: those hospitalized in medical wards of medicine (not including ICUs, as most patients cannot be adequately interviewed), and the outpatients: those having consulted for this infection in the infectious disease department and who did not require hospital care until the end of the acute infectious episode. Data of interest were collected from inpatients hospitalized from March 23 to April 9, 2020 and from outpatients who consulted from February 28 to March 30, 2020.

This study is observational. The study has been approved by the ethics committee of Sorbonne University (2020 - CER-2020-13).

Definitions and data collected

Confirmed COVID-19 was defined as a positive result on real-time reverse-transcriptase– polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens.

Smoking status was collected in all patients by specifically asking whether they were current smokers (and if so, to provide details on their smoking habits: daily or occasional smoking, number of daily cigarettes), former smokers, or not smokers ever. We used the same definition as in the French national annual survey of smoking habits (Santé Publique France Health Barometer)[14] Daily smokers were defined as individuals reporting daily smoking of cigarettes (manufactured or rolled) or other tobacco products (cigars, cigarillos, pipe, shisha). Occasional smokers were defined as individuals reporting infrequent, but not daily smoking. The group of former smokers included anyone having smoked in the past, occasionally or daily, and had abstained from smoking prior to COVID-19 onset. The term “never smoker” designated people who had never smoked.
In addition, for all outpatients and for all inpatients, we systematically asked former smokers since when they had quitted smoking, current smokers whether they quitted since the onset of COVID-19 symptoms, and if so, if they took nicotinic substitutes (including with e-cigarette), and former smokers whether they used nicotinic substitutes (including with e-cigarettes) at the time of COVID-19 onset of symptoms. We also asked non smoker oupatients whether they used nicotinic substitutes (including with e-cigarettes) at the time of COVID-19 onset of symptoms.

Finally, the following data were extracted from the medical charts: age, sex, healthcare workers or not, comorbidities, known to have potentially an impact on the prognosis of COVID-19, including diabetes, hypertension, obesity, immunodepression and COPD, and out- or inpatient status.

For inpatients, the following outcomes within one month following first day of clinical manifestation were also extracted:, still hospitalized in medical ward without any ICU stay, discharged without any ICU stay or if they occurred earlier: transfer to ICU and still alive at day 30, death (both in ICU or in medical wards).

Smoking rates in the population of reference

The French general population was used as a reference to compute the Standardized Incidence Ratio (SIR). Rates of daily smokers in France have been reported for the year 2019 by sex and age class (of 10 years) from the French national Survey “Santé Publique France Health Barometer” [14], a cross

sectional phone survey made yearly on a representative sample of 18-85 year-old people living in mainland France, with a on 2-level random sampling[14]. The 2019 survey involved a sample of 10,352 individuals. The completion of the survey took place from January 9 to June 29, 2019 and used the same definitions of daily smokers, occasional smokers, former smokers and never smokers as described above. Age and sex rates are reported only for current daily smokers (not for occasional current smokers, former smokers nor non-smokers) aged from 18 to 75 years, and the rate of current daily smokers in the 76-85 year-old people was reported globally and not by gender.

Statistical analysis

A descriptive analysis has been made by group (inpatients - outpatients). Qualitative variables were described by numbers and percentages, and quantitative variables by median and interquartile range. Inpatients and outpatients were compared for age and sex with Wilcoxon test and Pearson Chi2 tests, and for comorbidities and smoking status by logistic regression adjusted on age and sex. The SIRs were used to compare daily smoker rates in the COVID-19 inpatients and outpatients, respectively, with those of daily smokers in a reference population, here the French general population in 2019. The estimated SIR and its 95% confidence interval is the ratio between the observed number of daily smokers among the COVID-19 patients and the number of daily smokers that would be expected in the study population, on the basis of age- and gender-specific current daily smokers rates in the general population. The main analysis involved all included patients, and those older than 75 years were considered in the 65-75 years age class for standardization (reference rates of daily smokers of 10.4% in men and 9.0 in women), which for our hypothesis is a conservative approach, because daily smoker rates decreases with age (4.8% of daily smokers within the 76-85 year-old people in France in 2019, but the rates are not available by sex). For 7 outpatients and 2 inpatients, we were unable to interview the patient on his smoking status. We did not include the latter patients in the main analysis because the missing smoking status was very likely to be at random (7 outpatients that could not be reached, and among the 2 inpatients, one due to the language barrier and the other due to severe cognitive impairment). We performed two sensitivity analyses, one excluding patients older than 75 years, the other considering the patients with missing smoking status as daily smokers.

We also estimated the SIR in healthcare workers and non healthcare workers in the outpatients (as healthcare workers were overrepresented, because they were tested at their workplace in case of symptoms).

15.4 Results

Demographic and Clinical Characteristics

A total of 340 inpatients and 139 outpatients were included. The demographic and clinical characteristics of the two groups are shown in **TABLE 1**. As shown in **figure 1**, age distribution differed between outpatients and inpatients, with outpatients being younger and inpatients older.

- **View inline**
- **View popup**

TABLE 1:

Clinical characteristics and smoking habits of COVID-19 patients

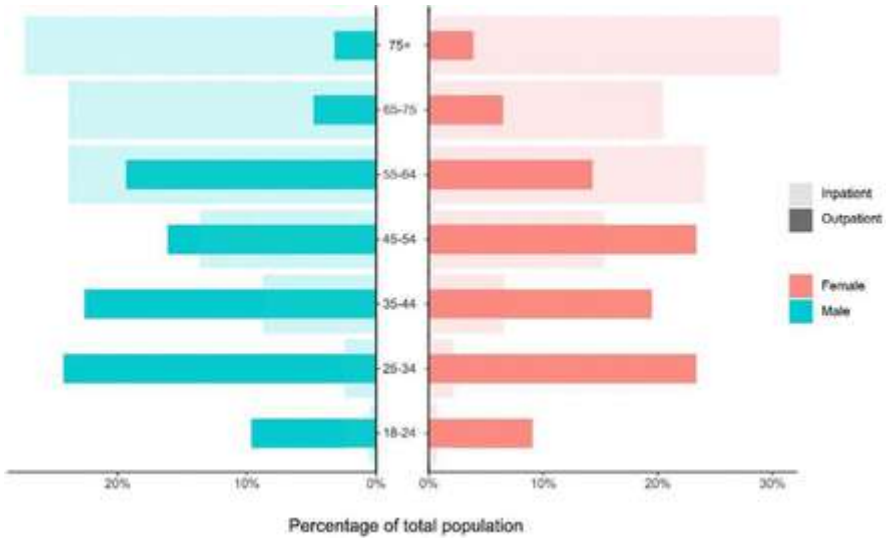

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Figure 1.

Age and sex distribution in COVID-19 inpatients and outpatients.

Dark and light shaded histograms represent outpatients and inpatients with confirmed COVID-19 status, respectively

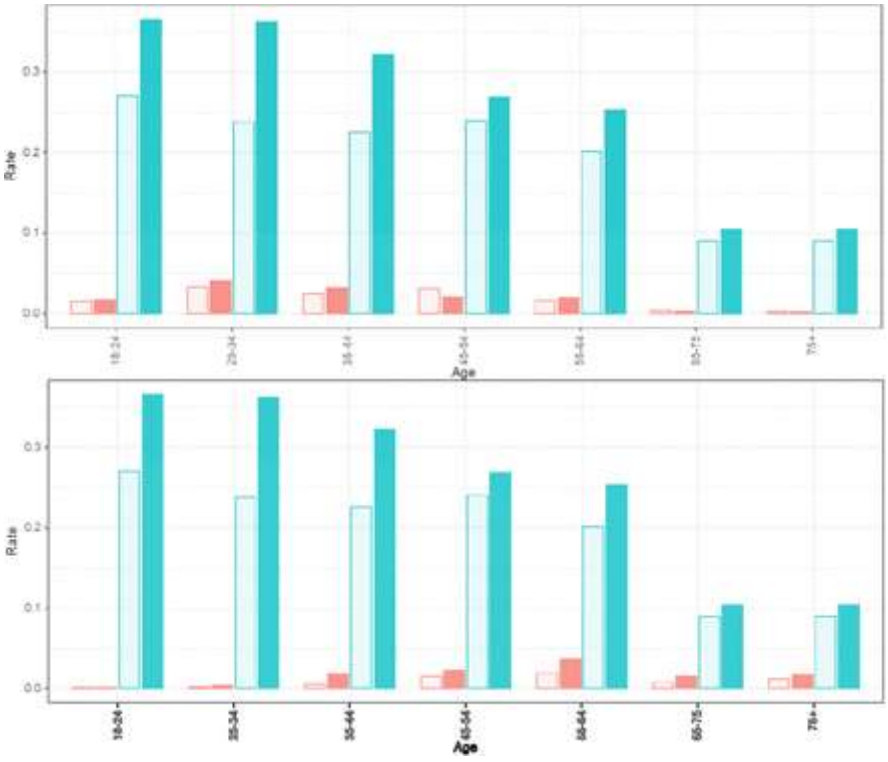

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Figure 2.

Age and sex expected rates of daily smokers in COVID-19 patients

(A) For outpatients. (B) For inpatients

Light shaded and dark histograms represent women and men daily smokers, respectively.

In blue: expected incidence rate in each age and sex class; in red: expected incidence rate in each age and sex class.

The inpatient group was composed of 340 patients, median age 66 years: 203 men (59.7%, median age 66 years) and 137 women (40.3%, median age 66 years). The rate of daily smokers was 4.1% CI95% [2.3 – 6.9] (5.4% of men and 2.2% of women) corresponding to 14 patients. Among them, 4 smoked 5 cigarettes/day or less, 3 smoked 6 to 10 cigarettes/day, 1 smoked 15 cigarettes/day and 5 smoked 20 or more cigarettes/day (and the data was missing for 1). For former smoker inpatients (n=111, 32.8 %), time duration since quitting was available for all but 6 patients. Five (4.8%) patients had quitted 2 months, and 2 (1.9%) patients 6 months before the clinical onset of the disease and 98 (93.3 %) more than one year before disease onset. Two former smokers (1.9%) were using nicotine substitutes (one by e-cigarettes and one by patches) at the time of disease onset.

The outpatient group was composed of 139 patients, median age 44 years: 62 men (44.6 %, median age 43 years), and 77 women (55.4 %, median age 44 years). In all, 68 (51.5%) were healthcare workers. Smoking status was missing for 7 patients. The daily smokers rate was 6.1% CI95% [2.7 - 11.6] (5.1% of men and 6.8 % of women) corresponding to 8 outpatients. Among them, 3 smoked less than 5 cigarettes/day, 3 smoked 6 to 10 cigarettes/day, and 2 smoked 20 or more cigarettes/day. After COVID-19 onset, 2 have stopped smoking, and none have taken nicotinic substitutes. Occasional smokers were 6 (4.5%), 2 have stopped smoking since COVID-19 onset and none have taken nicotinic substitutes. Former smokers were 41 (31,1%; 21 men and 20 women). Among these, 2 (4.9%) had quitted three months before COVID-19 symptoms onset and 39 (95.1%) more than 1 year before; 2 (4.9%) were using nicotinic substitutes (1 by use of e-cigarette). Among the 77 non-smokers, none were using nicotinic substitute (data was missing for 7).

The comorbidities were more frequently observed in inpatients than in outpatients: hypertension (age and sex-adjusted OR : OR_{adj}= 2.5; 95%CI(1.4-4.8); p=0.004), diabetes (OR_{adj}=5.4; 95%CI(2.4-13.7); p<0.001), obesity (OR_{adj}=3.7; 95%CI(1.7-8.9), p=0.002), immune deficiencies (OR_{adj}==12.45; 95%CI(4.6-44.3); p<0.001) except for COPD (OR_{adj}==2.0; 95%CI(0.5-13.3), p=0.38).

Outcome of COVID-19 inpatients

The outcome of inpatients is described in **TABLE 2** and was as follows: 211 discharges without any ICU stay (62.1%), 54 still hospitalized in medical ward without any ICU stay (15.9%) by one month after onset of clinical symptoms and 29 transfers to ICU (8.5%) and 46 deaths in ICU or medical wards (13.5%). Among the 14 daily smokers, 1 (7.1%) patient died and 1 (7.1 %) has been referred to intensive care unit by day 30 after clinical onset, while all occasional smokers were discharged. 23 former smokers (20.7 %) and 21 non smokers (10%) died while 11 former smokers (9.9%) and 17 non smokers (8.1%) have been transferred to ICU. Thus, active smokers represented 2.2% and 3.4% of the 45 dead patients and the 29 patients transferred to ICU respectively, whereas they represented 4.1% of the inpatients.

- **View inline**
- **View popup**

TABLE 2:

OUTCOME OF INPATIENTS

Comparison of the daily smoker rate with the French general population

The age and sex-SIR for daily smokers are shown in **TABLE 3**. In the main analysis, SIRs were 0.24 [0.12 - 0.48] and 0.24 [0.14 - 0.40] for outpatients and inpatients, respectively. The SIR in outpatients did not significantly differ from that in inpatients (p = 0.99). In the outpatients, the SIR was 0.17 [0.05-0.53] in the healthcare workers, and 0.32 [0.13-0.76] in the others. Sensitivity analyses yielded similar results.

- **View inline**
- **View popup**

TABLE 3:

Standardized Incidence Ratios for daily smokers

To note, the daily smoker rate in the 76-85 years inpatients and outpatients was 1.6% and 3.8%, respectively, lower than 4.8% observed in the French 76-85 years people in 2019 population.

15.5 Discussion

This cross sectional study shows that the daily smokers rate is significantly lower in symptomatic COVID-19 patients than in the French general population, either for outpatients and inpatients. The SIRs of daily smokers in COVID-19 outpatients and inpatients were 0.24 [0.12 - 0.48] and 0.24 [0.14 - 0.40], respectively, which means a decrease of 76% as compared to the French population, accounting for age and sex distribution. This result suggests that daily smokers have a lower probability of developing symptomatic SARS-CoV-2 infection as compared to the general population. The SIRs did not differ between outpatients and inpatients, suggesting that the potential effect of smoking is towards symptomatic COVID-19, irrespective of the severity. In the rare daily smokers in the COVID-19 patients of our study, we did not observed any effect of the daily cigarette consumption. Actually some were heavy smokers and others not. To note, in 2019, the mean number of daily cigarettes by current smokers in the French general population was 12.5 cigarettes, or equivalent, with 13.5 cigarettes for men and 11.4 for women [14]. We also observed a very rare use of nicotinic substitutes in the former smokers (2/111 in the inpatients and 2/41 in the outpatients, one of each group with e-cigarette), and in none of the outpatients not-smokers, which is in line with the national survey indicating that e-cigarette use is still low in France (4.4% of daily users), and is not used by non smokers (1% of e-cigarette users).

Previous studies have reported low current smokers rate (or low smokers rate, with no distinction between current and former smokers) in COVID-19 patients, ranging from 1.4% to 12.6% in China (National Chinese current smokers rate was 52% in men, 2.5 % in women in 2015, and 27.3% of adults in 2018)[15], of 1.3% in the USA in the US Center of Disease Control report[11] and 5.1% in a report from New York city (US current smokers rate of 15.6% in men and 12% in women in 2018).[12, 16]
Our study investigates the smoking status of COVID-19 outpatients (non-severe cases) and inpatients (severe cases), separately. All previous studies but two reported smokers rates only in hospitalized patients[13], thus gave no information on whether low current smoker rates was related to severe (i.e. hospitalized) patients only, who have more frequently comorbidities and may have been strongly advised to quit smoking, or to any form of COVID-19. Smoking data from inpatients and outpatients were mixed in the Guan study[1]. The CDC, reported current smokers rates of 1.3% for the whole population of COVID-19 patients, 1% for outpatients, 2% for patients, not hospitalized in an ICU, and 1% in intensive care unit (ICU)-admitted patients[11], however, the level of missing smoking status was very high. In all previous studies, data were extracted from medical files.

Furthermore, in these previous studies, only crude smokers rates are reported, not compared to a control group or the general population except in two, where the current smokers rate in the general population is reported, with no statistical comparison and thus not accounting for the age and sex distribution of the COVID-19 patients.

Our findings are in line with those from Fontanet et al. 2020[17], who reported smoking habits in a cohort of pupils, their parents and siblings, as well as teachers and non-teaching staff of a high-school located in Oise (n = 661). Smokers had a lower risk of confirmed COVID-19 (as defined by antibodies detection) compared to non-smokers (7.2% vs 28.0; age-adjusted OR = 0.23; 95% CI = 0.09 – 0.59), and the association was also significant after adjustment on occupation.
Our study has many strengths. By contrast with previously reported studies, our study was specifically designed to assess smoking habits in the COVID-19 patients. Previous studies used smoking status as recorded in the medical files, which are subject to underreporting (usually not accounted as missing data) and biased reporting. In our study, patients were systematically interviewed about their smoking habits, and use of nicotinic substitutes.

The rate of missing data - one of the more frequent caveat of studies reported so far - was very low (1.9%). Additionally, to completely rule out the impact of missing data on the conclusion of our study, we did a sensitivity analysis, considering that patients with missing smoking status as daily smokers, which is conservative regarding the hypothesis of a protective effect of smoking. In this sensitivity analysis, the SIR remained significantly below 1 showing the robustness of our results. Furthermore, we used the same definitions as the French national annual survey of smoking categories (Santé Publique

France Health Barometer)[14] that we used for reference to calculate the SIR. Finally, we investigated apart the association of daily smoking with COVID-19 separately in outpatients and inpatients, which provides relevant information in addition to previous studies.

Our study has also several limitations.

First, the study was performed in early 2020 and the reference smoking rate in France were estimated from January to June 2019, as French smoking rates in 2020 are not available yet. However, it is very unlikely that a dramatic decrease in tobacco use may have occurred in France since mid 2019, which could explain our results. Actually, from 2017 to 2019, the daily smokers rate has decreased in France from 26.9% to 24.0%. The SIRs were estimated with the assumption that the studied population who lives in a limited area around a Parisian hospital has the same smoking habits as the general French population. Smoking rates are known to be lower in the Paris region (22.1% in 2017) than in other regions (26.9 % in France in 2017)[18], and this may have contributed to slightly overestimate the protective effect. Actually, smoking rates differ across socio-professional categories, and therefore may differ across geographic areas. It should also be noted that in the present study, healthcare workers were over-represented in the outpatient group, due to systematic testing at their work place when they become symptomatic, but not in the inpatient group. Health care worker represent an heterogeneous population with heterogeneous rates of smoking habits in France[19] and in other countries. In a systematic review and meta-analysis found an overall pooled prevalence of tobacco use in HCW of 21%, 31% in males and 17% in females[20] Additionally, even when estimating the SIR separately in healthcare and non healthcare oupatients, we still observed significantly lower daily smokers rates in the outpatients than in the general population. It is very unlikely that the very low SIRs that were estimated both for the out- and inpatient groups are the result of the study setting (we observed a 76% decrease in the COVID-19 population as compared to the French population, which is very substantial). Finally, because rates of occasional smokers, former smokers and of never smoker were not available by age and sex in the general population[14], we could not calculate SIR for these two smoker categories. However, on the hypothesis of the role of nicotine, only current smokers are concerned, and among them occasional smokers are scarce.

Second, because patients primarily hospitalized in ICU were not included in the present study, we could not conclude whether daily current smoking was associated or not with very severe forms of COVID-19. However, active smokers represented 2.2% and 3.4% of the 45 dead patients and the 29 patients transferred to ICU respectively, whereas they represented 4.1% of the inpatients, which is not in favor of a less favorable outcome in smokers. Furthermore as the rate of daily smokers was very low in both out- and inpatients, the study was not powered enough to assess whether smoking was associated with severity as defined by being hospitalized. However, it provides the information of a low smoking rate of daily smokers even in COVID-19 outpatients, which is of great interest in the understanding of the phenomenon. The association between daily smoking and COVID-19 severity still remains controversial[2]. A larger well-designed study including also ICU patients will certainly help to conclusively address this question. However, collecting accurately smoking status is difficult in ICU patients.

Third, smoking status was self-reported by the patients, which tend to underestimate daily smokers rate due to social desirability bias[21]. However, we used the same methodology as the Baromètre Santé survey that we used as reference. Furthermore, in the French healthcare system, access to care is not rationed based on any potential for positive outcome, or compliance with Public Health recommendations, thus there may be no particular incentive to underreport being a current smoker. Another issue is that the low rate of smokers could be related to the association of COVID-19 with comorbidities leading to quit smoking. This limitation that could be discussed for inpatients does not however hold for outpatients who were mainly free of comorbidities.

Finally, in our study, smoking status was assessed only in symptomatic COVID-19 patients while a part of infected individuals are asymptomatic.[22] Thus we cannot conclude whether daily smoking is associated with SARS-CoV2 infection, or to symptomatic forms of this infection. The recent study by Fontanet[17], which highlights a decrease in the risk of COVID-19 of the same order of magnitude as us,

provides an answer to this question because this study, based on serological results, takes into account both symptomatic and asymptomatic forms.

Because this is a cross-sectional study, we cannot conclude to the causality of the association. We cannot also identify which of the many compounds of tobacco exerts the protective effect of smoking on COVID-19. There are however, sufficient scientific data to suggest that smoking protection is likely to be mediated by nicotine. SARS-CoV2 is known to use the angiotensin converting enzyme 2 (ACE2) receptor for cell entry[23-25], and there is evidence that nicotine modulates ACE2 expression[26] which could in turn modulate the nicotinic acetyl choline receptor[27]. We hypothesize that SARS-CoV2 might alter the control of the nicotine receptor by acetylcholine. This hypothesis may also explain why previous studies have found an association between smoking and Covid-19 severity.[1, 3, 6] As hospitals generally impose smoking cessation and nicotine withdrawal at the time of hospitalization, tobacco (nicotine) cessation could lead to the release of nicotine receptors, that are increased in smokers, and to a "rebound effect" responsible for the worsening of disease observed in hospitalized smokers. However, this hypothesis needs further investigation, and the deleterious role of smoking in hospitalized patients with COVID19 cannot be ruled out to date.
In conclusion, our results suggest that active smokers may be protected against symptomatic COVID-19. This was evidenced for outpatients (who have less serious infections) as well as for hospitalized patients. The physiopathological process underlying this effect may involve nicotine through the nicotinic receptor (and not the smoke of cigarettes per se), a hypothesis that deserves further evidence. In light of the possible increased risk of severe form of COVID-19 among smokers once infected and of the long-term harmful consequences of smoking which is responsible for a very heavy public health burden with more than 78,000 deaths per year in France, our findings needs careful consideration and cannot be translating it into a clinical practice. Careful investigation of the potential protective effect of nicotine should be investigated both in *in vitro* and *in vivo* before any firm conclusion can be drawn.

15.6 Data Availability

The data are available upon request to the corresponding author

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