

Low rate of daily active tobacco smoking in patients with symptomatic COVID-19

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Abstract

Abstract

Importance: As the pandemic of COVID-19 is still under progression, identification of prognostic factors remains a global challenge. The role of smoking has been suggested among the disease risk factors, although it is highly controversial.

Objective: To evaluate whether the rate of daily smokers in patients with COVID-19 was different to that in the French population.

Participants: COVID-19-infected in- and outpatients in a large French university hospital between February 28, 2020 and March 30, 2020 for outpatients and from March 23, till April 9, 2020 for inpatients.

Design: We systematically interviewed the patients on their smoking status, use of e-cigarette and nicotinic substitutes. The rate of daily smokers in inpatients and outpatients were compared to those in the 2018 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%, median age 66 years) and 137 women (40.3%, median age 66 years), with a rate of daily smokers of 4.1% CI95% [2.3 – 6.9] (5.4% of men and 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 smokers' rate was 6.1 % CI95% [2.7 - 11.6] (5.1% of men and 6.8 % of women). In the French population, the daily smokers' rate was 25.4% (28.2% of men and 22.9% of women).

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 0.23 [0.11 - 0.45] for outpatients and 0.23 [0.14 - 0.39] for inpatients. These ratios did not significantly differ between the two groups ($P=0.94$).

Conclusions and relevance: This cross sectional study in both COVID-19 out- and inpatients shows that 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]). Very recently, results of an observational database from 169 hospitals in Asia, Europe, and North America involving 8,910 COVID-19 hospitalized patients reported rates of current smokers of 5.6% in North America, 5.4% in Europe and 5.9% in Asia[14]. 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 outpatients 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 2018 French general population[15].

Material and methods

Patients and design

This is a cross-sectional survey investigating the smoking status of patients with a diagnosis of 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 French population as reference, after standardization by age and sex. Eligible patients were those with a confirmed diagnosis of COVID-19 at the APHP Pitié-Salpêtrière Hospital, Paris, France, with two groups, the inpatients: those hospitalized in medical wards of medicine (not including Intensive Care Units (ICU)), 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 from 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 and has been approved by the ethics committee of Sorbonne University (N° 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)[15]. 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 quit smoking, current smokers whether they quit 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 outpatients 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.

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 2018 by sex and age class (of 10 years) from the French national Survey "Santé Publique France Health Barometer", a cross sectional phone survey made yearly on a representative sample of 18-75 year-old people living in mainland France, with a on 2-level random sampling[15]. The 2018 survey involved a sample of 9,074 individuals. The completion of the survey took place from January 10 to July 25, 2018 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). Estimates of smoker rates were not available for 2019 at the time of submission of this work.

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 2018. 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, which for our hypothesis is a conservative approach, because

daily smoker rates decreases with age. 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).

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.

	Outpatients (N=139)			Inpatients (N= 343)			Outpatient/inpatient comparison p value*
	Male (N=62)	Female (N = 77)	All	Male (N=203)	Female N=137)	All	
Median (IQR) age (yr)	43 [32-55]	44 [32-54]	44 [32-55]	66 [55-76]	66 [56-79]	66 [55-77]	<0.0001
Coexisting disorder							
High blood pressure	9 (15.3%)	7 (9.6%)	16 (12.1%)	84 (41.4%)	58 (42.3%)	142 (41.8%)	0.004
Diabetes	4 (6.8%)	3 (4.1%)	7 (5.3%)	54 (26.6%)	41 (29.9%)	95 (27.9%)	<0.001
Obesity	4 (6.78%)	6 (8.2%)	10 (7.6%)	28 (14.3%)	19 (14.1%)	47 (14.2%)	0.002
Immune deficiency	4 (6.8%)	1 (1.4%)	4 (3%)	34 (16.7%)	26 (19%)	60 (17.6%)	<0.001
COPD	2 (3.4%)	0 (0%)	2 (1.5%)	17 (8.4%)	10 (7.3%)	27 (7.9%)	0.381
Smoking status							
Current active	3 (5.1%)	5 (6.8%)	8 (6.1%)	11 (5.4%)	3 (2.2%)	14 (4.1%)	0.96
Current occasional	3 (5.1%)	3 (4.1%)	6 (4.5%)	4 (2%)	0 (0%)	4 (1.2%)	0.14
Former	21 (35.6%)	20 (27.4%)	41 (31.1%)	76 (37.6%)	35 (25.7%)	111 (32.8%)	0.08
Never smoker	32 (54.2%)	45 (61.6%)	77 (58.3%)	111 (55%)	98 (72.1%)	209 (61.8%)	0.03
Missing data	4 (6.5%)	3 (3.9%)	7 (5.0%)	1 (0.5%)	1 (0.7%)	2 (0.6%)	

* Except for age, p value correspond to logistic regression models adjusted on age and sex

TABLE 1 Clinical characteristics and smoking habits of COVID-19 patients

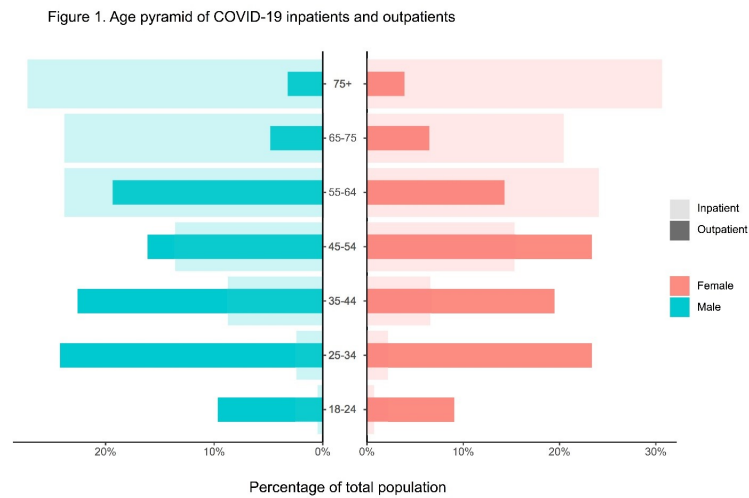


Figure 1 Age and sex distribution in COVID-19 inpatients and outpatients.

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

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). In all, 8 (2.4%) were healthcare workers. 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). Five (56%) among the 9 inpatients for whom the data was available stopped smoking after the onset of COVID-19, and none replaced smoking by nicotine substitutes. This data was not available for 5 patients who could not be asked (1 death, 1 severe cognitive impairment, 2 homeless and 1 transferred to another hospital). For former smoker inpatients (n=111, 32.8%), time duration since quitting was available for all but 6 patients. 100 (95.2%) had quit for more than 6 months before disease onset and 5 (4.8%) 5 patients (6.7%) had quit for months before the clinical onset of the disease. 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 (25%) have stopped smoking, and none has taken nicotinic substitutes. Occasional smokers were 6 (4.5%), 2 have stopped smoking since COVID-19 onset and none has taken nicotinic substitutes. Former smokers were 41 (31,1%; 21 men and 20 women). Among these, 2 (4.9%) had quit 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 : ORadj= 2.5; 95%CI(1.4-4.8); p=0.004), diabetes (ORadj=5.4; 95%CI(2.4-13.7); p<0.001), obesity (ORadj=3.7; 95%CI(1.7-8.9), p=0.002), immune deficiencies (ORadj==12.45; 95%CI(4.6-44.3); p<0.001) except for COPD (ORadj==2.0; 95%CI(0.5-13.3), p=0.38).

Comparison of the daily smoker rate with the French general population
Observed and expected daily smoker rates according to age and sex are shown in Figure2. The age and sex-SIR for daily smokers are shown in TABLE 2. In the main analysis, SIRs were 0.23 [0.11 - 0.45] and 0.23 [0.14 - 0.39] for outpatients and inpatients, respectively. The SIR in outpatients did not significantly differ from that in inpatients (p = 0.94). In the outpatients, the SIR was 0.16 [0.05-0.49] in the healthcare workers, and 0.30 [0.13-0.72] in the others. Sensitivity analyses yielded similar results.

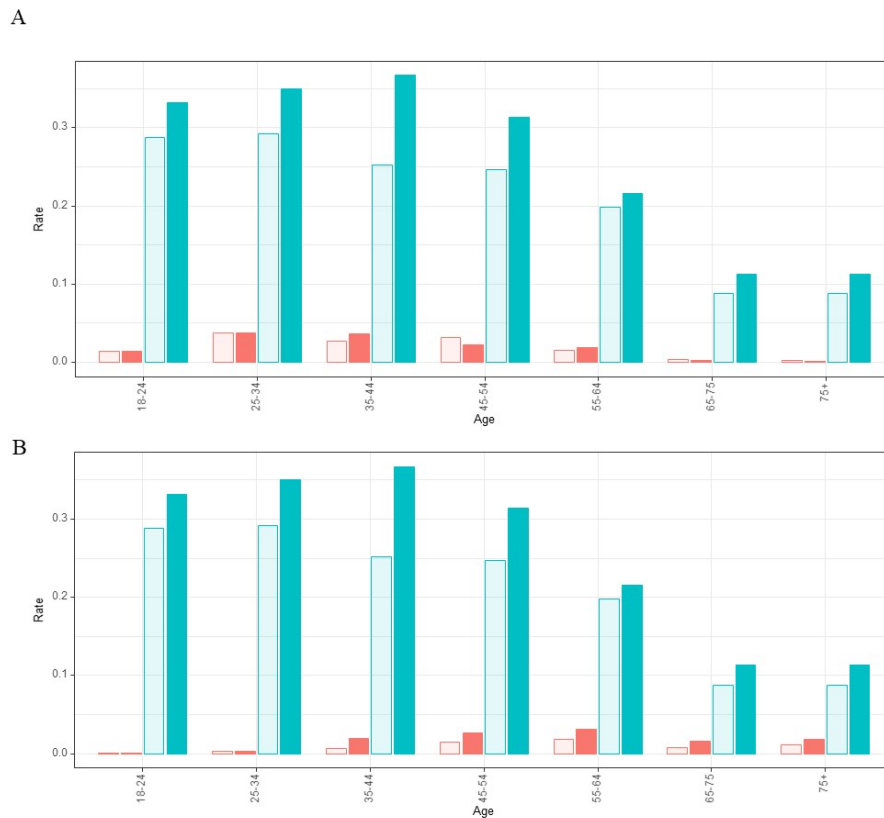


Figure 2. Observed and expected rates of daily smokers in COVID-19 patients

(A) For outpatients. (B) For inpatients. Light shaded and dark histograms represent daily smokers rates in women and men, respectively. In blue: expected rate in each age and sex class; in red: observed rate in each age and sex class

	SIR CI95%	p value
<u>Main analysis - Inpatients</u>	0.23 [0.14 - 0.39]	<0.001
<u>Main analysis - Outpatients</u>	0.23 [0.11 - 0.45]	<0.001
<u>Sensitivity analysis excluding patients older than 75 years - Inpatients</u>	0.26 [0.15 - 0.45]	<0.001
<u>Sensitivity analysis excluding patients older than 75 years - Outpatients</u>	0.17 [0.08 - 0.38]	<0.001
<u>Sensitivity analysis considering the patients with missing smoking status as daily smokers - Inpatients</u>	0.27 [0.16 - 0.43]	<0.001
<u>Sensitivity analysis considering the patients with missing smoking status as daily smokers - Outpatients</u>	0.40 [0.24 - 0.67]	<0.001
<u>Outpatients healthcare workers</u>	0.16 [0.05 - 0.49]	<0.001
<u>Outpatients without healthcare workers</u>	0.30 [0.13 - 0.72]	<0.001

Main analysis involved all included patients, and those older than 75 years were considered in the 65-75 years age class for standardization

TABLE 2: Standardized Incidence Ratios for daily smokers

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, for both outpatients and inpatients. The SIRs of daily smokers in COVID-19 outpatients and inpatients were 0.23 [0.11 - 0.45] and 0.23 [0.14 - 0.39], respectively, which means a decrease of 77% 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 observe any effect of the daily cigarette consumption. Actually some were heavy smokers and others not. To note, in 2018, the mean number of daily cigarettes by current smokers in the French general population was 13.0 cigarettes, or equivalent, with 14.0 cigarettes for men and 11.9 for women[15]. 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 non smokers, which is in line with the national survey indicating that e-cigarette use is still low in France (3.8% of daily users), and does not concern non smokers (1% of e-cigarette users)[15].

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)[16], 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, 17] Moreover, a recent observational study involving 8,910 COVID-19 hospitalized patients reported current smokers rates of 5.6% in North America, 5.4% in Europe and 5.9% in Asia[11]

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 hospitalized but not in an ICU, and 1% in 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[18], 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)[15] 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 rates in France were estimated from January to June 2018, as French smoking rates in 2019 are not available yet. However, it is very unlikely that a dramatic decrease in tobacco use may have occurred in France since mid 2018, which could explain our results. Actually, from 2017 to 2018, the daily smokers' rate has decreased in France from 26.9% to 25.9%. 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 than in other regions, 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. Health care worker represent an heterogeneous population with heterogeneous rates of smoking habits in France[19] and in other countries. However, even when estimating the SIR separately in healthcare and non healthcare outpatients, we still observe 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 77% 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[15], 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 hospitalized in ICU were not included in the present study, we could not conclude whether daily current smoking was associated with very severe forms of COVID-19. 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, because it shows that smoking appears to have an effect at least on the risk of infection. Previous studies did not make it possible to decide between two hypotheses: a protective effect on the decrease of the risk of infection or on the decrease of the risk of severe form of infection (as defined by hospitalization for COVID-19). The association between daily smoking and COVID-19 severity still remains controversial[14]. A larger well-designed study including also ICU patients will certainly help to conclusively address this question. However, collecting accurate 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[20]. 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.

Finally, in our study, smoking status was assessed only in symptomatic COVID-19 patients while a part of infected individuals are asymptomatic[21]. 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[18], which highlights a decrease in the risk of COVID-19 of the same order of magnitude as us, gives a key to 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 confirm 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[22-24], and there is evidence that nicotine modulates ACE2 expression[25] which could in turn modulate the nicotinic acetyl choline receptor[26]. 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 COVID-19 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), an hypothesis which 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 into a clinical practice as it. 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.

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