

SHORT COMMUNICATION

Tobacco smoking and severity of COVID-19: Experience from a hospital-based prospective cohort study in Lyon, France

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Abstract

Information gathered so far from published studies attest the existence of a complex relationship between tobacco smoking and the severity of COVID-19. We investigated the association between smoking habits and the severity of COVID-19 in patients hospitalized in university-affiliated hospitals in Lyon, France. Baseline sociodemographic, clinical and biological characteristics of adult COVID-19 hospitalized patients presenting from the community were prospectively collected and analyzed. Tobacco exposure was documented at admission. Characteristics of patients hospitalized in medical wards to those admitted or transferred to intensive care units (ICUs) were compared using Mann-Whitney and χ^2 or Fisher's exact test. A composite endpoint including admission or transfer to ICU or death was created as a proxy for severe outcome. Adjusted odds ratio (aOR) and 95% confidence interval (95% CI) were calculated to identify variables independently associated with a severe outcome. Of the 645 patients with documented information on smoking habits, 62.6% were never-smokers, 32.1% ex-smokers, and 5.3% active smokers. Past tobacco use was independently associated with an increased risk of severe outcome (aOR: 1.71; 95% CI: 1.12–2.63), whereas a nonsignificant protective trend was found for active smoking. The results suggest that past smoking is associated with enhanced risk of progressing toward severe COVID-19 disease in hospitalized patients.

KEYWORDS

COVID-19, France, hospital-based prospective study, SARS-CoV-2, smoking

1 | INTRODUCTION

Tobacco smoking, an established risk factor for a number of diseases including cardiovascular and chronic lung diseases, is also known to increase the susceptibility to viral respiratory infections.¹ It would be, therefore, expected for smokers to be at increased risk of more severe clinical presentation by the ongoing pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The literature showed that the odds of being diagnosed with or hospitalized for COVID-19, the SARS-CoV-2 disease, are lower in smokers as

compared to never-smokers.^{2–4} Nevertheless, the evidence of the effect of tobacco consumption on the severity of COVID-19 remains equivocal.^{5,6}

The concept of smoker's paradox was first originated from observational studies that reported lower prevalence of smokers among hospitalized COVID-19 patients as compared to the national prevalence.^{7,8} Studies published so far reported paradoxical results; some studies have suggested that smoking would worsen the COVID-19 prognosis,⁹ whereas others reported absence of association¹⁰ or even a protective effect.³

Except few studies that differentiated between active and former smokers,¹¹ others combined these two groups. Such group stratification analysis remains, however, pertinent to enable to distinguish the long-term impact of tobacco after cessation.^{1,11} The objective of this study was to investigate the impact of smoking habits on the severity of clinical presentation at admission and prognosis of laboratory-confirmed COVID-19 during hospitalization.

2 | MATERIALS AND METHODS

Patients included in the present study were symptomatic hospitalized COVID-19 patients enrolled in one of the four university-affiliated hospitals in Lyon, France, for whom information on tobacco consumption was documented. These patients are part of the NOSO-COR project (ClinicalTrials: NCT04290780), a prospective, observational, hospital-based international study.¹² The study was approved by the clinical research and ethics committee of Ile de France V on March 8, 2020 (No. 20.02.27.69817 Cat 3). Baseline demographic characteristics, underlying comorbidities, clinical and biological features, and patient outcome data were collected prospectively using electronic medical records. Information on tobacco smoking was based on self-reporting data. At hospital admission, patients were asked about their smoking status by the medical staff. Of the 1150 patients included in the NOSO-COR project by the end of Mai 2020, only 645 had documented information on tobacco smoking and were therefore included in the analysis. Clinical outcomes were monitored up to hospital discharge or death.

2.1 | Statistical analysis

We compared characteristics of patients at hospital admission according to the smoking status. Categorical variables were described as number (%) and compared by X^2 test. Continuous variables were described as median (interquartile range [IQR]) and compared by Mann-Whitney U test. Statistical tests were two-tailed with a level of statistical significance of less than 0.05. A composite endpoint including admission or transfer to intensive care unit (ICU) or death as a proxy for disease severity was generated (Yes/No) and the risk to reach this outcome was estimated according to tobacco consumption status. Univariate logistic regression allowed the identification of variables at admission that were associated with the composite endpoint. Variables that were significant at 0.15 levels in univariate analysis were first introduced one by one in turn in the multivariate regression model. The most significant variables ($p < 0.05$) were retained in the final model. Adjusted odds ratio (aOR) and 95% confidence interval (95% CI) were calculated by taking the non-smokers as the reference group. Statistical analysis was performed using STATA 13[®] (College Station).

3 | RESULTS

The clinical features at admission of the enrolled patients are reported in Table 1. Of the 645 patients with documented information on smoking habits, 62.6% were never-smokers, 32.1% ex-smokers, and 5.3% active smokers. Date of smoking cessation was available for 30.4% of past smokers, with a length of abstinence ranging from 2 to 40 years. Ex-smokers were older than active or never-smokers. Cardiovascular disease and diabetes were the most common comorbidities in all three groups. Duration of symptoms and the delay between symptom onset and hospital admission were not different between the groups. The most commonly reported signs and symptoms were abnormal lung auscultation followed by dyspnea/tachypnea and general weakness. Active smokers had significantly higher rate of chronic lung diseases as compared to never-smokers. Cardiovascular, renal and chronic lung diseases, shortness of breath, and dyspnea/tachypnoea have been found more frequently in ex-smokers compared to never-smokers. The most significant differences between active and ex-smokers were higher rates of cardiovascular disease and shortness of breath in ex-smokers. Hospitalization in ICUs and lethality were significantly higher in ex-smokers as compared to current or nonsmokers. A slight lymphocytopenia was observed among ex-smokers. The level of C-reactive protein (CRP) was higher than the reference range in all patients but was not different between the three groups. The median value of creatinine was significantly lower in ex-smokers compared to never smokers although it remained within the reference range of 45–104 $\mu\text{mol/L}$.

The variables independently associated with a severe outcome are reported in Table 2. Ex-smokers were at significantly higher risk of severity (aOR: 1.71; 95% CI: 1.12–2.63) compared to nonsmokers, whereas nonsignificant trend toward decreased disease severity among current smokers as compared to never-smokers was observed (aOR: 0.54; 95% CI: 0.20–1.47). Patients with dyspnoea, longer duration of symptoms, temperature at admission, presence of underlying renal diseases, CRP > 100 mg/L, and monocytes < 0.3 g/L had higher odds of severe outcome.

4 | DISCUSSION

The observed differences of outcomes between active and ex-smokers confirm the relevance of distinguishing these two populations when investigating the impact of smoking on the severity of COVID-19, considering the nonsmokers as the nonexposed population. Our results suggest that ex-smokers are at higher risk of ICU admission and death compared to active smokers. A meta-analysis of 18 published studies also reported that compared with ex-smokers, current smokers were less likely to experience an adverse outcome.⁶ In another meta-analysis, both current (relative risk [RR]: 1.25; 95% CI: 0.85–1.93) and former smokers (RR: 1.52; 95% CI: 1.13–2.07) were at higher risk of severe disease compared to never-smokers.¹¹ However, this

TABLE 1 Demographic and clinical characteristics at admission of confirmed COVID-19 hospitalized patients according to the smoking status (Lyon, France)

	All patients (N = 645)	Current smoker (N = 34) (5.3%), G1	Ex-smoker (N = 207) (32.1%), G2	Never smoker (N = 404) (62.6%), G3	p value (G1 vs. G3)	p value (G1 vs. G2)	p value (G2 vs. G3)
Age, median (IQR)	71 (24)	67.5 (26)	72 (15)	69 (28)	0.272	0.014	0.008
Age ≥ 75 years, n (%)	253 (39.2)	9 (26.5)	87 (42.0)	157 (38.9)	0.153	0.086	0.449
Age categories, n (%)							
<61 years	175 (27.1)	12 (35.3)	33 (15.9)	130 (32.2)	0.054	0.010	<0.001
61–80 years	283 (43.9)	18 (52.9)	114 (55.1)	151 (37.4)			
≥81 years	187 (29.0)	4 (11.8)	60 (29.0)	123 (30.4)			
Gender, n (%)							
Female	257 (40.1)	10 (29.4)	38 (18.4)	209 (51.7)	0.012	0.135	<0.001
Male	388 (60.2)	24 (70.6)	169 (81.6)	195 (48.3)			
Type of ward, n (%)							
Hospitalization in medical ward	431 (66.8)	27 (79.4)	125 (60.4)	279 (69.1)	0.206	0.033	0.032
Admission or transfer to ICU during hospitalization	214 (33.2)	7 (20.6)	82 (39.6)	125 (30.9)			
Comorbidities							
Cardiovascular disease	336 (52.1)	15 (44.1)	130 (62.8)	191 (47.3)	0.723	0.039	<0.001
Diabetes	160 (24.8)	10 (29.4)	62 (30.0)	88 (21.8)	0.305	0.949	0.026
Chronic neurological diseases	117 (18.1)	9 (26.5)	36 (17.4)	72 (17.8)	0.212	0.208	0.895
Malignancy	108 (16.7)	3 (8.8)	35 (16.9)	70 (17.3)	0.201	0.231	0.897
Renal diseases	100 (15.5)	5 (14.7)	45 (21.7)	50 (12.4)	0.694	0.349	0.003
Chronic lung disease	82 (12.7)	9 (26.5)	46 (22.2)	27 (6.7)	0.000	0.584	<0.001
Signs and symptoms at admission, n (%)							
Duration of symptoms (days), [n/N] ^a	[545/645] ^a	[26/34]	[171/207]	[348/404]			
Median (IQR)	19 (14)	18 (20)	21 (15)	18 (13)	0.810	0.772	0.123
Delays between onset of symptoms and hospital admission (days), [n/N] ^a	[626/645]	[30/34]	[199/207]	[397/404]			
Median (IQR)	6 (6)	5 (5)	6 (7)	6 (6)	0.514	0.523	0.881
Temperature (°C), [n/N] ^b	[595/645]	[31/34]	[185/207]	[379/404]			
Median (IQR)	38 (1.6)	37.9 (1.3)	38 (1.6)	38 (1.5)	0.088	0.247	0.258

TABLE 1 (Continued)

	All patients (N = 645)	Current smoker (N = 34) (5.3%), G1	Ex-smoker (N = 207) (32.1%), G2	Never smoker (N = 404) (62.6%), G3	p value (G1 vs. G3)	p value (G1 vs. G2)	p value (G2 vs. G3)
Abnormal lung auscultation	543/600 (90.5)	23 (85.2)	181/198 (91.4)	339/375 (90.4)	0.382	0.297	0.690
Dyspnoea/tachypnoea	466/600 (77.7)	19/27 (70.4)	165/198 (83.3)	282/375 (75.2)	0.576	0.102	0.025
General weakness	457 (70.8)	21 (61.8)	142 (68.6)	294 (72.8)	0.170	0.430	0.280
Cough	451 (69.9)	19 (55.9)	140 (67.6)	292 (72.3)	0.043	0.180	0.233
Shortness of breath	435 (67.4)	19 (55.9)	152 (73.4)	264 (65.4)	0.268	0.037	0.042
Diarrhea	182 (28.2)	11 (32.4)	48 (23.2)	123 (30.5)	0.817	0.249	0.059
Myalgia	122 (18.9)	7 (20.6)	25 (12.1)	90 (22.3)	0.820	0.175	0.002
Nausea	86 (13.3)	4 (11.8)	26 (12.6)	56 (13.9)	0.733	0.896	0.655
Headache	84 (13.0)	5 (14.7)	22 (10.6)	57 (14.1)	0.924	0.485	0.225
Ageusia	53 (8.2)	1 (2.9)	15 (7.3)	37 (9.2)	0.216	0.350	0.423
Anosmia	45 (7.0)	1 (2.9)	9 (4.4)	35 (8.7)	0.243	0.703	0.051
Sore throat	28 (4.3)	1 (2.9)	8 (3.9)	19 (4.7)	0.636	0.792	0.633
Laboratory measures admission							
Lymphocytes (g/L), median (IQR), Reference range: 1–4, [n/N] ^a	0.97 (0.68), [603/645]	1.08 (0.93), [33/34]	0.88 (0.69), [194/207]	0.98 (0.67), [376/404]	0.154	0.027	0.077
Monocyte (g/L), median (IQR), Reference range: 0.2–0.9, [n/N] ^a	0.47 (0.36), [603/645]	0.65 (0.47), [33/34]	0.47 (0.34), [194/207]	0.47 (0.36), [376/404]	0.005	0.011	0.881
CRP (mg/L), median (IQR), Reference range: <5, [n/N] ^a	68.8 (106.8), [561/645]	69 (89.6), [30/34]	76.2 (98.5), [180/207]	66.4 (111.8), [351/404]	0.799	0.591	0.555
Creatinine (μmol/L), median (IQR), Reference range: 45–104, [n/N] ^a	83 (39), [601/645]	84 (44), [32/34]	90 (53), [195/207]	80 (36), [374/404]	0.185	0.493	<0.001
Outcome^a							
Death, n (%)	122 (18.9)	3 (8.8)	61 (29.5)	58 (14.4)	0.371	0.012	<0.001

Note: Categorical variables were described as number (%) and compared by X² test or Fisher's exact test. Continuous variables were described as median (IQR) and compared by Mann–Whitney U test [n/N]. Abbreviations: CRP, C reactive protein; ICU, intensive care unit; IQR, interquartile range.

^aNumber of available data compared to total patients and for each group.

TABLE 2 Multiple logistic regression analysis of variables independently associated with severe outcome in confirmed COVID-19 hospitalized patients according to the smoking status (Lyon, France)

	Adjusted OR	95% CI	p value
Smoking status			
Never smoker	1.0	-	-
Ex-smoker	1.71	1.12–2.63	0.013
Smoker	0.54	0.20–1.47	0.225
Signs at admission			
Dyspnoea	3.06	1.81–5.18	<0.001
Duration of symptoms (days)	1.04	1.03–1.06	<0.001
Temperature (°C)	1.25	1.01–1.53	0.038
Comorbidities			
Renal diseases	2.67	1.55–4.60	<0.001
Laboratory parameters			
CRP > 100 mg/L	2.05	1.36–3.09	<0.001
Monocytes < 0.3 g/L	3.09	1.88–5.07	<0.001

Note: 1: reference group.

Abbreviations: CRP, C reactive protein; 95% CI, 95% confidence interval; OR, odds ratio.

meta-analysis did not compare the risk of disease severity between current and ex-smokers.

No strong evidence exists to support an increased risk of severe SARS-CoV-2 infection in ex-smokers compared to active smokers. Older age (> 65 years) is a recognized risk factor of SARS-CoV-2 severity¹³ and could explain the observed adverse outcomes in older ex-smokers. The higher prevalence of tobacco-related disease such as cardiovascular and renal diseases in ex-smokers might also further weaken this population. A misclassification bias of smokers as ex- or nonsmokers may have occurred as we investigated the smoking status from clinical records. Lack of information on the duration of smoking and interval time since smoking cessation in the ex-smoker group is another limitation. Finally, the relatively small sample size of the study population could have had an impact on 95% CI of aOR of current smoking compared to nonsmoking.

Conflicting hypotheses on a potential protective effect of nicotine by competition with angiotensin-converting enzyme II (ACE2), the primary receptor of SARS-CoV-2, have been published.¹⁴ Absence of nicotine exposure in ex-smokers provides more site availability for SARS-CoV-2 and could explain more severe clinical presentation with higher rate of ICU admission and mortality observed in the present study. Nicotine has also been suggested to limit the commonly called “cytokine storm” due to its anti-inflammatory properties through the cholinergic anti-inflammatory system.¹⁵ Current smoking has also been shown to have a protective effect in patients with ulcerative colitis.¹⁶ There is also another hypothesis implicating the cholinergic system and the cholinergic anti-inflammatory pathway.^{17,18} This hypothesis implicates a direct interaction between the

spike glycoprotein of SARS-CoV-2 and $\alpha 7$ nicotinic cholinergic receptors. This could result in dysfunction of the receptors, which form a major part of the cholinergic anti-inflammatory pathway, and could disrupt the immune homeostasis. If validated, this hypothesis goes far beyond nicotine, since other cholinergic agonists could be used therapeutically.

High levels of CRP and monocytopenia were associated with an increased risk of severity in our study. High level of CRP was significantly associated with severe infection in the initial phases of the SARS-CoV-2 infection.¹⁹

As reported by others,^{7,8} smoking prevalence in the French population was much higher (24% overall and 10% in individuals >65 years old) than the recorded prevalence in our study population (5.3%).

The results of this study suggest differing effects of smoking on the severity of COVID-19 in hospitalized patients. Past smoking was associated with enhanced risk of progressing toward severe COVID-19 disease, whereas current smoking showed rather a nonsignificant protective trend against severe disease. The date of smoking cessation was available for one third of our study population. However, it is known that many smokers quit as soon as the occurrence of underlying diseases, which is parallel to aging. The relative advanced aged of our study population suggests that there it is unlikely that they have stopped smoking just before developing COVID symptoms. High likelihood of misclassification bias, worse health-seeking behaviors, and self-treating in smokers²⁰ and misreporting on the part of the patient by fear of stigmatization¹¹ may explain, at least partly, the observed lack of an association between current smoking and adverse outcomes. Furthermore, the cross-sectional design of our study precludes definite information about cause-and-effect relationships.

There is a need for further evaluation of the complex relationship between smoking history and COVID-19 severity taking into account confounders such as age or obesity. Whether nicotinic agents such as nicotine patches could be used in the treatment of severe SARS-CoV-2 infection is being investigated in a double-blind randomized controlled clinical trial in France (NCT04608201).

The majority of cigarette smoke compounds have known oxidative stress properties and are therefore unlikely to have any potential protective. Consequently, any evidence of a potential protective impact of smoking should be interpreted cautiously as it could counterbalance the well-known deleterious effect of smoking on health.

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CONFLICT OF INTERESTS

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AUTHOR CONTRIBUTIONS

Conceptualization: Mitra Saadsatian-Elahi and Philippe Vanhems. *Data acquisition:* Christelle Elias, Laetitia Henaff, and Cédric Dananché. *Statistical analysis and validation:* Mitra Saadsatian-Elahi, Sélim Amour, and Philippe Vanhems. *Writing-original draft:* Mitra Saadsatian-Elahi and Philippe Vanhems. *Writing-review and editing:* All

DATA AVAILABILITY STATEMENT

Data will be available upon reasonable request from the corresponding author (M. S. E.).

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