THE PARADOX OF THE LOW PREVALENCE OF CURRENT SMOKERS AMONG COVID-19 PATIENTS HOSPITALIZED IN NON-INTENSIVE CARE WARDS: RESULTS FROM AN ITALIAN MULTICENTER CASE-CONTROL STUDY

Simone Meini[a], Alberto Fortini[b], Roberto Andreini[c], Leonardo Alberto Sechi[d], Carlo Tascini[e]

[a]UOC Medicina Interna, Ospedale Santa Maria Annunziata, Firenze, Italy

[b]UOC Medicina Interna, Ospedale Nuovo San Giovanni di Dio, Firenze, Italy

[c]UOC Medicina Interna, Ospedale Felice Lotti, Pontedera, Italy

[d]Clinica Medica, Ospedale Santa Maria Misericordia, Udine, Italy

[e]SOC Malattie Infettive, Ospedale Santa Maria Misericordia, Udine, Italy

Corresponding author

Simone Meini

Internal Medicine Unit. Santa Maria Annunziata Hospital, Florence, Italy

simonemeini2@gmail.com

telephone number: +393288423317, and fax number: 0556936268

Abstract

Introduction. COVID-19, a respiratory illness due to SARS-CoV-2 coronavirus, was first described in December 2019 in Wuhan, rapidly evolving into a pandemic. Smoking increases the risk of respiratory infections; thus, cessation represents a huge opportunity for public health. However, there is scarce evidence about if and how smoking affects the risk of SARS-CoV-2 infection.

Methods. We performed an observational case-control study, assessing the single-day point prevalence of smoking among 218 COVID-19 adult patients hospitalized in 7 Italian non-intensive care wards and in a control group of 243 patients admitted for other conditions to 7 general wards COVID-19-free. We compared proportions for categorical variables by using the $\chi 2$ test and performed univariate and multivariate logistic regression analyses to identify the variables associated with risk of hospitalization for COVID-19.

Results. The percentages of current smokers (4.1% vs 16%, p=0.00003) and never smokers (71.6% vs 56.8%, p=0.0014) were significantly different between COVID-19 and non-COVID 19 patients. COVID-19 patients had lower mean age (69.5 vs 74.2 years, p=0.00085) and were more frequently males (59.2% vs 44%, p=0.0011). In the logistic regression analysis, current smokers were significantly less likely to be hospitalized for COVID-19 compared with non-smokers (Odds ratio 0.23; 95% CI, 0.11-0.48, p<0.001), even after adjusting for age and gender (OR 0.14; 95% CI, 0.06-0.31, p<0.001).

Conclusions. We reported an unexpectedly low prevalence of current smokers among COVID-19 patients hospitalized in non-intensive care wards. The meaning of these preliminary findings, which are in line with those currently emerging in literature, is unclear; they need to be confirmed by larger studies.

Implications

An unexpectedly low prevalence of current smokers among patients hospitalized for COVID-19 in some Italian non-intensive care wards is reported. This finding could be a stimulus for the generation of novel hypotheses on individual predisposition and possible strategies for reducing the risk of infection from SARS-CoV-2, and needs to be confirmed by further larger studies designed with adequate methodology.

Introduction

Starting in December 2019 in Wuhan (Hubei province, China), a novel coronavirus designated SARS-CoV-2 has caused an international outbreak of a respiratory illness (COVID-19), rapidly evolving into a pandemic. Most cases are asymptomatic or self-limiting, but the clinical spectrum extends to severe pneumonia and acute respiratory distress syndrome (ARDS), a life-threatening condition requiring mechanical ventilation and intensive care support.

It is well known that smoking increases the risk of respiratory infections (both bacterial and viral) and outcomes are generally worse in smokers and in patients with chronic lung diseases [1]. Smoking has also been reported as a risk factor both for infection and mortality due to MERS-CoV [2]. Smoking cessation at any time thus represents a huge opportunity for public health, and must always be encouraged. However, there is currently scarce evidence about if and how smoke exposure affects the risk of infection from SARS-CoV-2 [3-5]. It is therefore crucial to investigate the association between smoking and COVID-19 using real-life data.

In this study we evaluated the point prevalence of smoking in a cohort of patients hospitalized for COVID-19 in seven Italian non-intensive care wards, comparing it to that of patients admitted at the same time, for other conditions, in seven other COVID-19-free wards.

Methods

We performed an observational case-control study, conducted on a single day (between March 31 and April 6, 2020) on all adult patients hospitalized in 7 Italian general wards (4 Internal Medicine Units - IMUs, and 3 Infectious Disease Units - IDUs) for respiratory failure due to pneumonia, diagnosed as COVID-19 by reverse transcriptase-polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 on nasopharyngeal swab. The attending physicians directly assessed the smoking status in their patients, carefully asking the patient for the data necessary to define him/her as never smoker, former smoker or current smoker. The main demographic characteristics were also collected in a dedicated case record form.

At the same time, the same data was assessed in a control group of patients admitted for other conditions to 7 COVID-19-free wards (IMUs).

The aim of this study was to investigate the association between smoking status and the occurrence of COVID-19 among patients hospitalized in non-intensive care wards.

Current smokers were defined as people who smoked (even just one cigarette) at the time they presented the first symptoms related to COVID-19, or, for controls, related to the illness for which they had been hospitalized. Patients who reported smoking occasionally have been classified as current smokers, so as not to risk underestimating the habit of smoking. Former smokers were defined as people having completely quitted for at least one year. Patients who had stopped for less than one year were defined current smokers. In addition, the patients were asked about electronic cigarettes use. Patients with cognitive impairment, unlikely to answer reliably, were excluded from the study.

Continuous variables were presented as mean values and standard deviation (SD); categorical variables were presented as counts and percentages. We compared proportions for categorical variables by using the $\chi 2$ test. We performed univariate and multivariate logistic regression analysis to identify the variables associated with hospitalization for COVID-19. Predictors with a p-value less than 0.05 at the univariate logistic regression were considered for multivariate analysis. Odds ratios (OR) were used to compare the relative odds of the occurrence of the outcome of interest, given exposure to the variables of interest. We considered a p-value less than 0.05 to be statistically significant. We used for all analyses MedCalc® version 12.3.0 (MedCalc Software; Mariakerke, Belgium) and GNU PSPP Statistical Analysis Software PSPP program.

Results

We evaluated a total of 218 COVID-19 patients (cases), 126 enrolled from 4 IMUs and 92 from 3 IDUs: all patients were hospitalized for pneumonia with respiratory failure. We evaluated as controls 243 patients hospitalized for diseases other than COVID-19 in 7 IMUs. For an additional 13 cases and 21 controls we could not collect reliable data on their smoking status due to cognitive impairment, and they did not enter this study.

Table 1 summarizes key characteristics of the patients from the case and control groups. There were statistically significant differences in the proportion of males (59.2% vs 44%) and mean ages (69.5 vs 74.2 years) in COVID-19 patients and controls, respectively. Among COVID-19 patients, 9 (4.1%) were current smokers, 53 (24.3%) were former smokers and 156 (71.6%) had never smoked. Among the controls, 39 patients (16%) were current smokers, 66 (27.2%) were former smokers and 138 (56.8%) had never smoked. The prevalence of current smokers among patients hospitalized for COVID-19 was statistically significantly lower than among patients hospitalized for other conditions (4.1% vs 16%), while the proportion of never smokers was statistically significantly higher among the cases compared to the controls (71.6% vs 56.8%). No patient reported previous use of electronic cigarettes, in both case and control groups.

The mean age of COVID-19 patients hospitalized in IMUs was 73.5 years compared to 64.1 years for those admitted to IDUs. Of nine current smoking COVID-19 patients, 5 were from IMUs and 4 from IDUs; the prevalence of current smoking cases was similar in IMUs and IDUs (4% vs 4.3%), despite the difference in age.

The mean age of the 243 control patients hospitalized in 7 IMUs was about the same as that of 126 COVID-19 patients admitted to the 4 IMUs, 74.2 vs 73.5 years, respectively: despite the similar age and the same setting of hospitalization (IMU), the prevalence of current smokers was significantly different: 16% vs 4% ($p=0.0006$).

Among current smoking population, the 9 COVID-19 cases had a mean age of 67.1 years and 88.9% were males, while the 39 controls had a mean age of 63 years and 64.1% were males.

Table 2 shows the results of the univariate and multivariate logistic regression analysis to identify variables independently associated with hospitalization for COVID-19. Current smokers were significantly less likely to be hospitalized for COVID-19 compared with non-smokers (OR 0.23; 95% CI, 0.11-0.48, $p<0.001$), even after adjusting for age and gender (OR 0.14; 95% CI, 0.06-0.31, $p<0.001$).

Discussion

This study has been conducted on a population of patients hospitalized in Italian non-intensive care wards. We found that the prevalence of current smokers among patients hospitalized for COVID-19 was significantly lower than among controls hospitalized for other conditions (4.1% vs 16%), and there was a strong and statistically significant negative association between current smoking and hospitalization for COVID-19 after adjusting for age and gender (OR 0.14; 95% CI, 0.06-0.31).

An unexpectedly low prevalence of smoking among COVID-19 patients also emerged from the first data reported in Chinese studies. Wang et al. [6] did not report on smoking in their case series of COVID-19 patients hospitalized in Wuhan, but chronic obstructive pulmonary disease (COPD), a condition strongly associated with smoking, was reported in only 2.9% of patients. Neither was smoking reported in the study of Wu et al. [7], who assessed the risk factors for ARDS and death and reported chronic lung disease in only 2.5% of their population. Zhang et al. [8] reported a very low prevalence (1.4%) of both COPD and current smoking in 140 COVID-19 patients in Wuhan. Finally, Guan et al. [9] found 12.6% smoking prevalence and 1.1% COPD prevalence in a cohort of 1,099 COVID-19 patients, similar to a 1.5% COPD prevalence subsequently reported on a larger cohort of 1,590 cases, 7% of which were current or former smokers [10]. In a recent meta-analysis [11] including 5,960 Chinese patients hospitalized for COVID-19, the prevalence of current smoking observed from the pooled analysis was 6.5%, ranging from 1.4% to 12.6%; a secondary analysis, classifying former smokers as current smokers, found a pooled estimate of smoking prevalence of 7.3%.

The low prevalence of COPD reported in the Chinese studies may be an underestimate, reflecting the very low rate of spirometry testing, but the low prevalence of smoking among COVID-19 patients is remarkable considering that China has one of the highest smoking

prevalences in the world, ranging in men from 36.5% among people aged 15-24 years to 60% among those aged 45-64 years [12].

However, the low prevalence of smoking reported in this literature could be due, in part, to inadequate assessment, all too understandable in overwhelmed health systems. Our study is at less risk of misclassification of smoking status as assessment was carried out by directly asking the patient.

Our results and these previous findings collectively suggest smoking may be having a protective effect against SARS-CoV-2 infection. However, there are some possible biased that may be operating or alternative explanations for these findings.

One possible explanation is that smokers might have the same predisposition to be infected, but subsequently develop a less serious disease sparing them hospitalization. This seems neither rational nor endorsed by most of the available literature. For example, a recent meta-analysis [4] including a total of 11,590 COVID-19 patients showed that smokers have 1.91 times the odds of progression towards severe forms of COVID-19 than never smokers; so this directly contradicts this explanation of the findings.

A possible selection bias that can affect studies with hospital controls is that smokers are at higher risk of developing many diseases, so a hospitalized control group could have higher smoking prevalence than the community from where the COVID-19 cases are drawn. In recent population surveys among adults of similar ages to the cases and controls included in our study, smoking prevalence was 10.9% in the over 65 years age group in one Italian study [13] and 13.4% in 65-74 year olds and 8.2% among people aged >74 years in another European study [14]. The smoking prevalence observed in the cases in our study (4.1%) was therefore lower than expected in a general population sample, whilst it was higher than expected among controls (16%). This suggests that the strength of the negative association between smoking may have been exaggerated due to this selection bias affecting the controls, but it is unlikely to explain all of the association observed.

Another possible selection bias could occur if persons receiving COVID-19 tests were not fully representative of the general population and had a lower smoking prevalence than people who were not tested. This could occur for example if health care workers (who have a lower smoking prevalence) were more likely to be tested than other members of the community. However, we evaluated the smoking status among all patients, most of whom were relatively elderly, who tested positive for COVID-19 and who required hospitalization for severe respiratory impairment due to pneumonia, not in the general population in which most COVID-19 cases are asymptomatic or pauci-symptomatic. So this selection bias is less likely to be relevant in this study.

Finally, another possible bias could occur because we excluded COVID-19 patients hospitalized in intensive care units (ICUs). As smoking has been associated with greater severity [3,4], one could speculate that ICU-patients would have a higher prevalence of smoking, resulting in an apparently lower smoking prevalence among patients hospitalized with less severe disease in non-intensive care wards. However, in our study setting, non-invasive ventilation, which in certain hospitals is delegated to ICUs, was routinely performed in all the wards where cases were recruited; only patients needing invasive ventilation, or at very high risk of imminent orotracheal intubation, were admitted/transferred to ICUs. Therefore, only a small proportion of hospitalized cases would have been treated in ICUs, and this is unlikely to have greatly affected the association that we observed. Moreover, a higher prevalence of smoking among COVID-19 patients admitted to ICUs has not been definitively proven: in a study conducted on critically ill adults admitted to the ICUs of Wuhan [15], smoking was reported only in 4% of patients, as in our cohort, and among patients admitted to the ICUs in the Seattle-area hospitals [16] the percentage of never smokers was even higher than ours (78% vs 71.6%).

Our study has several important strengths. One is that smoking status was not investigated retrospectively from clinical records, but rather was assessed directly asking the patients, reducing the risk of misclassification of their smoking status. Another strength is that this study represents to the best of our knowledge the first detailed study of the association between smoking and COVID-19 from an Italian setting. A major limitation of the study is not having assessed comorbidities, in

particular we lack data on COPD prevalence due to the low rate of spirometry testing before the hospitalization.

Currently, evidence about if and how smoke exposure affects the risk of infection from SARS-CoV-2 is scarce, and the argument remains very complex. If smokers really were at a reduced risk to be infected by SARS-CoV-2, one would wonder why and what could be the plausible pathogenetic mechanism.

We know that Angiotensin-converting enzyme 2 (ACE2), which displays overall protective effects on the lungs [17], is the receptor that SARS-CoV-2 binds to enter the cells, subsequently downregulating it; therefore, any condition leading to reduced ACE2 levels could provide the virus with fewer binding sites. It has been reported that smoking can upregulate ACE2 [18], but it is also known from animal models that chronic cigarette exposure can reduce ACE2 expression in lung tissues [19]. Further evidence strongly suggests that nicotine affects the activity of the renin-angiotensin system by upregulating the ACE-mediated axis and downregulating the compensatory ACE2-mediated one [20]. Moreover, nicotine-induced increase of ACE activity could lead to an increased degradation of bradykinin, one of the most potent inflammatory mediators in humans, able to activate signaling pathways resulting in increased vascular permeability, edema, vasodilation, hypotension, pain and fever, all typical features of COVID-19 [21].

It has been proposed that COVID-19 could be a disease affecting the nicotinic cholinergic system, and many clinical characteristics could be explained by its dysregulation: nicotine (a cholinergic agonist) could exert protective effects by restoring and enhancing the cholinergic anti-inflammatory pathway during the systemic inflammatory response (cytokine storm), effectively contributing to maintaining a balanced immune response against SARS-CoV-2. Nicotine administration could thus be added to antiviral or other therapeutic options for COVID-19 [22].

In summary, current evidence does not seem to unequivocally support smoking as a predisposing factor for SARS-CoV-2 infection, and an unexpectedly low percentage of patients admitted to non-intensive care wards are current smokers. We are unable to give a

definitive explanation for this. These considerations should not under any circumstances lead to conclude that smoking has positive effects on human health, since smoking has undoubtedly deleterious respiratory and cardiovascular effects, and we believe that, in the face of this pandemic, it would be of utmost importance that all initiatives supporting smoking cessation be widely encouraged. Moreover, our data are preliminary and mainly descriptive, relate only to a relatively small population of patients, and need to be confirmed by further larger studies designed with adequate methodology. These considerations are meant solely as a stimulus for the generation of novel pathogenetic hypotheses on individual predisposition and possible strategies for reducing the risk of infection from SARS-CoV-2.

Conflict of interest statement

The authors declare they have no conflict of interest

Acknowledgments

All members of the Smokers-in-COVID-19 Collaborative Study Group* contributed to collecting clinical data. The authors thank Dr Anna Teresa Roberts for the linguistic revision of the manuscript.

*Smokers-in-COVID-19 Collaborative Study Group: Giancarlo Tintori, Edoardo Vitolo, Renato Bigazzi, Medicina Interna, Ospedali della Garfagnana e di Barga (non-COVID-19); Lino Mori, Medicina Interna, Ospedale di Pontremoli (non-COVID-19); Benedetta Longo, Susanna Giomi, Gabriella Sibilia, Valerio Vallini, Mauro Taccola, Luigi Venturini, Medicina Interna, Ospedale Felice Lotti, Pontedera (COVID-19 and non-COVID-19); Giovanni Grazi, Anna Teresa Roberts, Luciana Mangano, Elisabetta Rinaldi, Guido Vagheggini, Medicina Interna, Ospedale di Volterra (non-COVID-19); Gianni Taccetti, Michela Cameron Smith, Serena Sbaragli, Antonio Faraone, Laura Monsacchi, Francesca Baccetti, Medicina Interna, Ospedale Nuovo San Giovanni di Dio (COVID-19 and non-COVID-19), Firenze; Stefano Spolveri, Medicina Interna, Ospedale del Mugello, Borgo San Lorenzo (COVID-19); Fiorella Piani, Maria Teresa Passaleva, Anna Frullini, Cecilia Piga, Lucia Fani, Dario Mannini, Marco Fabbri, Gianni Giuntoli, Maria Pia Briganti, Caterina Fronzaroli, Stefania Bracci, Chiara Lombardo, Cinzia Lusini, Maria De Masi, Monica Galli, Medicina Interna, Ospedale Santa Maria Annunziata, Firenze (COVID-19); Pierluigi Blanc, Malattie Infettive, Ospedale Santa Maria Annunziata, Firenze (COVID-19); Giuseppe Fiorentino, Malattie Infettive, Ospedale Cotugno, Napoli (COVID-19); Chiara De Carlo, Elena Graziano, Maria Merelli, Nadia Castaldo, Emanuela Barbano, Malattie Infettive, Ospedale Santa Maria Misericordia, Udine (COVID-19); Cristiana Catena, Alessandra Cecotti, Clinica medica, Ospedale Santa Maria Misericordia, Udine (non-COVID-19).

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Table 1 - Characteristics of patients

	COVID-19	**Non-COVID-19**	**p-value**
Patients, n	218	243	-
Mean age (SD; range), years	69.5 (14.4; 18-96)	74.2 (15.1; 22-99)	0.00085
Males, n (%)	129 (59.2)	107 (44)	0.0011
Current smokers, n (%)	9 (4.1%)	39 (16.0%)	0.00003
Former smokers, n (%)	53 (24.3%)	66 (27.2%)	0.485
Never smokers, n (%)	156 (71.6%)	138 (56.8%)	0.00138

Table 2 - Univariate and multivariate logistic regression analysis to identify variables independently associated with hospitalization for COVID-19

	Univariate analysis			Multivariate analysis		
Variables	**Odds ratio**	**95% CI**	**p-value**	**Odds ratio**	**95% CI**	**p-value**
Age	0.98	0.97-0.99	0.001	0.97	0.96-0.99	0.001
Sex: females vs males	0.54	0.37-0.79	0.001	0.51	0.34-0.75	0.001
Smoking status: current smokers vs non-current smokers	0.23	0.11-0.48	<0.001	0.14	0.06-0.31	<0.001
Smoking status: current smokers vs former smokers	0.29	0.13-0.66	0.003			
Smoking status: current smokers vs never smokers	0.21	0.10-0.45	<0.001			
Smoking status: former smokers vs never smokers	0.73	0.48-1.13	0.156			