Impact of smoking on COVID-19 outcomes: a HOPE Registry subanalysis

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ABSTRACT

Background Smoking has been associated with poorer outcomes in relation to COVID-19. Smokers have higher risk of mortality and have a more severe clinical course. There is paucity of data available on this issue, and a definitive link between smoking and COVID-19 prognosis has yet to be established.

Methods We included 5224 patients with COVID-19 with an available smoking history in a multicentre international registry Health Outcome Predictive Evaluation for COVID-19 (NCT04334291). Patients were included following an in-hospital admission with a COVID-19 diagnosis. We analysed the outcomes of patients with a current or prior history of smoking compared with the non-smoking group. The primary endpoint was all-cause in-hospital death.

Results Finally, 5224 patients with COVID-19 with available smoking status were analysed. A total of 3983 (67.9%) patients were non-smokers, 934 (15.9%) were former smokers and 307 (5.2%) were active smokers. The median age was 66 years (IQR 52.0–77.0) and 58.6% were male. The most frequent comorbidities were hypertension (48.5%) and dyslipidaemia (33.0%). A relevant lung disease was present in 19.4%. In-hospital complications such sepsis (23.6%) and embolic events (4.3%) occurred more frequently in the smoker group (p<0.001 for both). All cause-death was higher among smokers (active or former smokers) compared with non-smokers (27.6 vs 18.4%, p<0.001). Following a multivariate analysis, current smoking was considered as an independent predictor of mortality (OR 1.77, 95% CI 1.11 to 2.82, p=0.017) and a combined endpoint of severe disease (OR 1.68, 95% CI 1.16 to 2.43, p=0.006).

Conclusion Smoking has a negative prognostic impact on patients hospitalised with COVID-19.

What this paper adds

► It has been described that a history of smoking is associated with higher rates of mortality and complications in patients with COVID-19. Contrastingly, it has been suggested that tobacco may have a 'protective' role in COVID-19 infections.

► The strengths of this study are the large sample size and adjusting for confusion factors to evaluate the independent role of tobacco in the course of SARS-CoV-2 infections. We included former smokers as well in our analysis since both current and former smokers share characteristics and underlying respiratory comorbidities.

► Main limitations of this study are that some variables such as packs-year of smoking or smoke-free years were not recorded, as well as the bias given the observational nature of the study.

INTRODUCTION

COVID-19 was declared a pandemic on 11 March 2020 by the WHO.[1] COVID-2019 has a wide spectrum of manifestations ranging from subclinical infection to acute respiratory distress syndrome (ARDS) and multiorgan failure.[2][3] Although some poor prognostic factors have been observed,[4][5] its clinical course remains unpredictable.

Since pulmonary alveolar epithelial cells are one of the targets of SARS-CoV-2, underlying respiratory risk factors may play a role in modifying respiratory response. Available findings regarding smokers are inconsistent, and the impact of smoking on SARS-CoV-2 infection is uncertain.[4–7]

A large case series from China reported a higher prevalence of active smokers in severe COVID-19 infections, in comparison to milder cases.[4] Nevertheless, some studies failed to demonstrate a link between smoking and poorer prognosis of the disease. Even some previous series suggested a theoretical 'protective' effect of smoking habit.[7][8] This last hypothesis can be deduced from the lower rates of smoking observed in patients
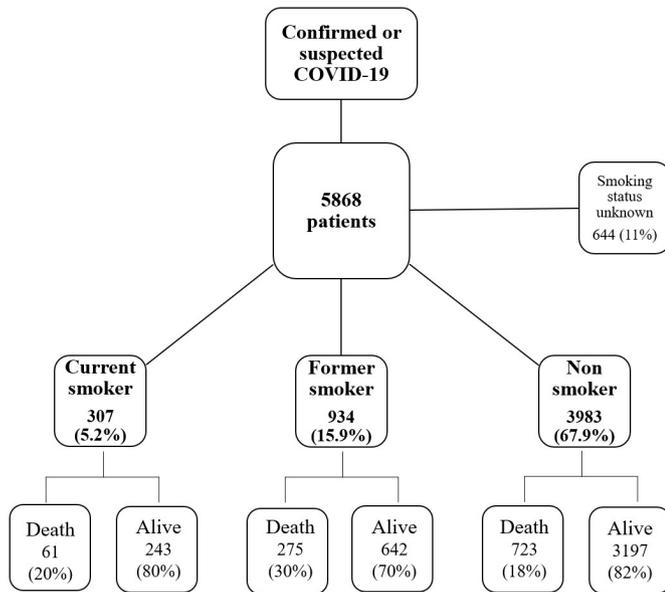
Figure 1 Study flow diagram.

with COVID-19 in comparison with the general population. The prevalence of smokers among SARS-CoV-2-infected patients has been estimated between 1.4% and 12.5% according to different studies.[5–15] These rates are notably lower than those recorded in the Chinese general population (25.2%).[16]

The pathophysiology of lung damage has not been fully understood. It has been suggested that high levels of proinflammatory cytokines in serum can induce the hyperinnate inflammatory response. This cascade produces a 'cytokine release syndrome' with an overproduction of immune cells and cytokines, which leads to an ARDS and septic shock.[17–20] Smoking may modulate the immune response and smokers could present an attenuated immune response presenting lower levels of inflammation markers compared with non-smokers.[21 22]

On the one hand, the ACE2 protein is known to play a role in the infection's mechanism. The ACE2 protein is expressed on the surface of lung type 2 pneumocytes and is the principal receptor molecule for SARS-CoV-2.[23–25] On the other hand, some authors have described decreased levels of ACE2 in smokers.[26 27] Conversely, it has been suggested that ACE2 is upregulated on the airway epithelium of smokers. In a study in resected lung specimens, Leung and coworkers found an increase of ACE2 gene expression in patients with chronic obstructive pulmonary disease (COPD). Likewise, a higher ACE2 gene expression was observed in smokers when compared with non-smoker individuals.[28 29] The question of whether smokers are more prone to contract SARS-CoV-2 infection remains unresolved.

Based on the aforementioned, we aimed to assess if smokers are more likely to die or develop more severe forms of COVID-19.

METHODS
Study design and population
We conducted a cohort study of 5868 consecutive patients who were hospitalised with confirmed or highly suspected COVID-19 infection. Smoking history was available in the 5224 patients included in the final analysis (figure 1). The patients were entered in the Health Outcome Predictive Evaluation for COVID-19 Registry (NCT04334291), a multicentre international registry without conflicts of interest, designed as an ambispective cohort. In this multicentre registry, we included the data from 40 centres from seven countries. From 23 March 2020 to 5 May 2020, patients discharged from the hospital (deceased or alive) with COVID-19 diagnosis were included in the registry. Epidemiological and clinical data were obtained from electronic medical records, and the data were stored in an anonymised fashion.

Definitions and study endpoints
We assessed the impact of smoking on the prognosis of 5224 patients with COVID-19. We defined three study groups according to smoking status. Patients were classified in active smokers, former smokers and non-smokers. We evaluated the differences in baseline characteristics, clinical presentation and treatment, according to these groups. Likewise, we performed an age-stratified analysis of mortality and complications in each smoking group. Age groups were divided into quartiles as follows: (1) <52 years old, (2) 52–66 years old, (3) 66–77 years old and (4) >77 years old.

The primary endpoint was defined as all-cause in-hospital death. A combined secondary endpoint was established as a composite of intensive care unit (ICU) admission, need of prone position or death. Other secondary outcomes assessed included in-hospital complications such as ICU admission, respiratory insufficiency, pneumonia, sepsis, systemic inflammatory response syndrome (SIRS) and embolic events.

Patient and public involvement
The research question and outcome measures were informed according to experience. Due to the pandemic situation, it was not appropriate to involve patients or the public in the design of our research and recruitment to or conduct of the study. Results may be disseminated on reasonable request.

Statistical analysis
The data are presented as mean (SD) for continuous variables with a normal distribution, median (IQR) for continuous variables with a non-normal distribution and as frequency (%) for categorical variables. Student's t-test and the Mann-Whitney U test were used to compare continuous variables with normal and non-normal distributions, when needed. The χ^2 test or Fisher's exact test was used to compare categorical variables. Univariate analysis was performed for qualitative variables and reported as ORs with 95% CIs. Given the multiplicity of variables, only

factors with a p value of <0.01 on the mentioned univariate analysis in the smoker cohort were entered into the multivariate analysis (binary logistic regression) to define independent risk factors for the principal outcome and focusing on the smoking status (current, former or never). Mortality analysis was performed using Kaplan-Meier estimates and log-rank tests to compare factors. Two-sided p values of <0.05 were accepted as statistically significant. Likewise, in order to eliminate potential confounding factors, propensity scores for mortality and the combined endpoint were performed. Statistical analysis was performed using SPSS V. 22.0 and STATA V. 14.0.

RESULTS

A total of 5224 patients with COVID-19 were included in this analysis. The majority patients, 3983 (67.9%), were non-smokers, while 934 (15.9%) were former smokers and only 307 (5.2%) were active smokers. Smoking habits were not available in 644 patients (11%); thus, finally, 5224 patients were entered in the study (figure 1). The median age was 66 years (IQR 52.0–77.0) and 3060 (58.6%) were male. Most individuals were Caucasian (4333, 82.9%) followed by Hispanic ethnicity (710, 13.6%).

In the overall cohort, the most frequent comorbidities were hypertension (2626, 48.5%) and dyslipidaemia (1716, 33.0%). Other conditions included heart disease (of any form; 1191, 23%) and obesity (981, 22.1%). A relevant lung disease was present in 1012 patients (19.4%). The most frequent lung disease was COPD (39.4%) followed by asthma (26.9%).

Comparing smoking patterns, we found that former smokers were older and had a higher comorbidity burden compared with both active and non-smoker groups. Ex-smokers had higher rates of hypertension (64.3%), dyslipidaemia (48.6%) and obesity (30.6%), as well as a higher prevalence of lung disease (39.3%) and heart disease (38.3%) (p<0.001 for all). Ex-smokers presented the highest prevalence of COPD (24.6%) compared with smokers (16.3%) and non-smokers (3%) (p<0.001). Asthma was predominantly observed among non-smokers (5.7%). Consequently, cardiovascular medications such as ACE inhibitor/angiotensin receptor blockers, antiplatelets or inhaled beta agonist were more prevalent among former smokers. Differences in baseline characteristics and previous treatment are displayed in table 1.

Regarding clinical manifestations, current smokers presented with different symptoms complaining of anosmia, dysgeusia and sore throat to a higher degree than the two other groups. The most common symptoms were fever (73%) and cough (65.6%), whereas dyspnoea was less frequently described among smokers. It is worth noting that acute-phase reactants such as C reactive protein, lactate dehydrogenase and ferritin were less frequently elevated in the smoking group, while white cell count was higher than in non-smokers or ex-smokers. Clinical presentation and analytical results are described in online supplemental table S1.

The current smoker group received more beta interferon but less antibiotics or prophylactic anticoagulation compared with both non-smoker and ex-smoker groups (p<0.001) (online supplemental table S2). In line with this, in-hospital complications such as sepsis (23.6%) and embolic events (4.3%) occurred more frequently in the smoker group (p<0.001 for both) (online supplemental table S3).

The secondary endpoint of ICU admission was greater among the active-smoker group in comparison with the former-smoker group and the non-smoker patients (p<0.001), while the prone position was more frequently used among ex-smokers (online supplemental table S3).

In the univariate analysis, all-cause death was higher in smokers (20.1%) when compared with non-smokers (18.4%) (p<0.001), while the highest mortality was observed among the former-smoker group (30.0%) (p<0.001). Mortality according to age groups is shown in figure 2 and online supplemental table S4.

The impact of a smoking history was then compared with the absence of a smoking history. All-cause in-hospital mortality and the combined endpoint (ICU admission, prone, death) are depicted in online supplemental table S5.

Following this, a multivariate analysis was performed. After adjusting for confounding factors, current smokers presented a greater risk of death from all causes (OR 1.77, 95% CI 1.11 to 2.82, p=0.017) when compared with non-smokers. Likewise, former smokers had an increased risk of death compared with non-smokers (OR 1.32 95% CI 1.0 to 1.73 p=0.049), but this independent risk was not as strong as that observed in the current smokers' group.

Other independent predictors of mortality were older age, hypertension, previous heart disease and elevated LDH. Moreover, we performed a multivariate analysis for a combined endpoint of death, ICU admission or need of prone position. As well, the highest risk for the combined endpoint was observed among active smokers when compared with non-smokers (OR 1.68, 95% CI 1.16 to 2.43, p=0.006). There were no significant differences in the combined endpoint between former smokers and non-smokers after adjusting for comorbidities (OR 1.09, 95% CI 0.86 to 1.39, p=0.467). The multivariate analysis is presented in the table 2.

In online supplemental table S6 propensity scores for mortality and the combined endpoint are depicted. In propensity scores, any kind of smokers (former or current) were compared with non-smokers.

Kaplan-Meier survival curve for all-cause mortality is displayed in figure 3.

DISCUSSION

The main finding in our study was the fact that current smoking was independently associated with a twofold increased risk of mortality compared with non-smoking, after adjusting for confounding factors in a large international cohort admitted with COVID-19.

Table 1 Baseline characteristics and previous treatment

Baseline characteristics	Smoker (n=307)	Ex-smoker (n=934)	Non-smoker (n=3983)	P value
Female	95 (30.9)*	160 (17.1)	1909 (47.9)*†	<0.001
Male	212 (69.1)	774 (82.9)†‡	2074 (52.1)	
Hypertension	171 (55.9)‡	597 (64.3)†‡	1758 (44.2)	<0.001
Dyslipidaemia	100 (32.9)	450 (48.6)†‡	1166 (29.4)	<0.001
Type 1 diabetes mellitus	2 (0.7)	6 (0.6)	22 (0.6)	<0.001
Type 2 diabetes mellitus	61 (19.9)	255 (27.3)†‡	623 (15.6)	
Insulin therapy	63 (20.5)	261 (27.9)†‡	645 (16.2)	<0.001
Obesity	74 (28.1)‡	228 (30.6)‡	679 (19.8)	<0.001
Renal failure	30 (9.8)‡	100 (10.7)‡	204 (5.1)	<0.001
Lung disease	93 (30.3)‡	367 (39.3)†‡	552 (13.9)	p<0.001
Atrial fibrillation	7 (2.3)	53 (5.7)†‡	136 (3.4)	0.02
HIV	6 (2)‡	6 (0.6)	8 (0.2)	<0.001
Heart disease	82 (27)‡	355 (38.3)†‡	754 (19.1)	<0.001
Cerebrovascular disease	17 (5.6)	104 (11.4)†‡	277 (7.1)	<0.001
Connective disease	12 (4)	29 (3.2)	107 (2.7)	0.389
Liver disease	29 (9.6)‡	56 (6.1)‡	105 (2.7)	<0.001
Cancer	49 (16.2)‡	210 (22.8)†‡	431 (11)	<0.001
Immunosuppression	41 (14.4)‡	99 (11.2)‡	235 (6.3)	<0.001
Partially dependent	19 (6.2)	95 (10.2)†	366 (9.2)	0.036
Totally dependent	4 (1.3)	40 (4.3)†	164 (4.1)†	
Home oxygen therapy	11 (3.6)	68 (7.3)†‡	81 (2.0)	0.036
Aspirin	70 (23.3)‡	239 (26.2)‡	462 (11.7)	<0.001
Other antiplatelet	17 (5.7)‡	63 (7.0)‡	110 (2.8)	<0.001
Anticoagulants	28 (9.3)	143 (15.7)†‡	358 (9.1)	<0.001
ACEI/ARB	124 (41.5)‡	447 (48.4)†‡	1263 (32.0)	<0.001
Beta blockers	69 (23.0)‡	230 (25.1)‡	530 (13.4)	<0.001
Beta2 agonist	43 (14.4)‡	198 (21.8)†‡	287 (7.3)	<0.001
Glucocorticoids	28 (9.4)	180 (19.7)†‡	258 (6.5)	<0.001
Vitamin D supplement	36 (12.0)	113 (12.3)	401 (10.2)	0.119
Benzodiazepines	55 (18.5)‡	155 (16.9)‡	564 (14.3)	0.027

Values are n (%). All p values were determined by using an analysis of variance with Bonferroni method.
*P<0.05 compared to ex-smokers.
†P<0.05 compared to smoker subjects.
‡P<0.05 compared to non-smoker subjects.
ACEI, ACE inhibitor; ARB, angiotensin receptor blocker.

As well, active smokers presented a higher risk for critical illness (combined endpoint of death, prone position and ICU admission) in comparison with non-smokers (1.7-fold). Interestingly, in spite of the fact that former smokers were sicker, the risk of mortality was not as strong as the risk of current smokers after adjusting for comorbidities.

According to previous series, smoking has been associated with higher mortality and complication rates in patients with COVID-19.[4–7] Our aim was to clarify if the detrimental effect of smoking was independently associated with poor prognosis in COVID-19 after adjusting for other factors.

SARS-CoV-2 targets pulmonary alveolar epithelial cells and can cause severe pneumonia and respiratory distress.[2–5] Thus, underlying respiratory risk factors such as previous lung disease or smoking may alter the respiratory response. Some studies have shown that COPD is associated with a worse prognosis of COVID-19.[5 15]

The pathogenesis of acute lung injury remains largely unknown. It has been suggested that high levels of proinflammatory cytokines in serum can induce the hyperinnate inflammatory response. The hyperinnate inflammatory response leads to the activation of Th1 cell-mediated immunity and accumulation of alveolar macrophages and neutrophils. This cascade produces a 'cytokine release syndrome'
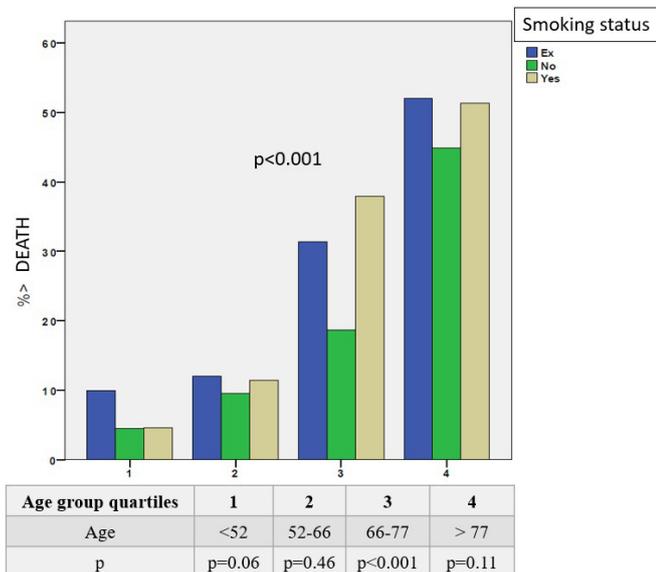
Espejo-Paeres C, et al. bmjnph 2021;4:e000269. doi:10.1136/bmjnph-2021-000269

Figure 2 All-cause in-hospital death according to smoking status, stratified by age.

Table 2 Multivariate analysis for in-hospital mortality and for secondary combined endpoint

	Multivariate analysis for in-hospital mortality		
	OR	**95% CI**	**P value**
Current smoker	1.77	1.11 to 2.82	**0.017**
Former smoker	1.32	1.00 to 1.73	**0.049**
Age 52–66 years old	1.74	1.10 to 2.79	**0.020**
Age 66–77 years old	4.56	2.90 to 7.19	**<0.001**
Age >77 years old	10.63	6.78 to 16.66	**<0.001**
Hypertension	1.71	1.33 to 2.2	**<0.001**
Lung disease	1.06	0.81 to 1.39	0.679
Any cardiac disease	1.38	1.08 to 1.76	**0.010**
Elevated CRP	2.11	1.23 to 3.63	0.007
Elevated LDH	2.61	1.91 to 3.58	**<0.001**
Elevated ferritin	1.22	0.96 to 1.53	0.101
	Multivariate analysis for the composite endpoint*		
	OR	**95% CI**	**P value**
Current smoker	1.68	1.16 to 2.43	**0.006**
Former smoker	1.09	0.86 to 1.39	0.467
Age 52–66 years old	1.33	1.01 to 1.77	**0.044**
Age 66–77 years old	1.77	1.31 to 2.40	**<0.001**
Age >77 years old	2.64	1.95 to 3.57	**<0.001**
Hypertension	1.65	1.35 to 2.03	**<0.001**
Lung disease	1.26	1.00 to 1.58	0.054
Any cardiac disease	1.53	1.23 to 1.91	**<0.001**
Elevated CRP	2.27	1.50 to 3.44	**<0.001**
Elevated LDH	2.16	1.70 to 2.75	**<0.001**
Elevated ferritin	1.61	1.32 to 1.96	**<0.001**

Statistically significant p value: p <0.05.
*Composite endpoint of intensive care unit admission, prone position or death.
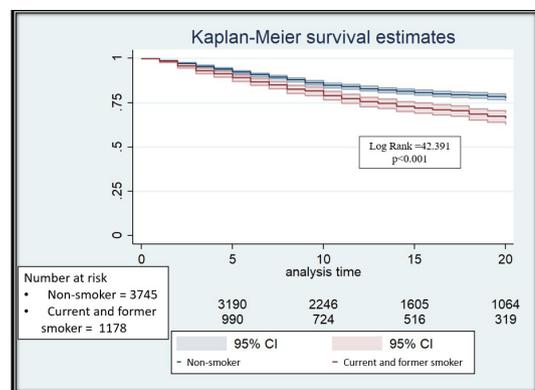CI, Confidence interval; CRP, C reactive protein; LDH, lactate dehydrogenase.

with an overproduction of immune cells and cytokines, which leads to an ARDS and septic shock.[17–20] Smoking may alter and attenuate immune response by lowering inflammatory marker levels.[21 22] In line with this, smokers in our cohort presented lower levels of C reactive protein, ferritin and dehydrogenase lactate when inflammatory marker levels were compared between groups (online supplemental table S1). Likewise, SIRS was less frequently observed in the current smoker group (online supplemental table S3).

Despite these findings, globally, smoking has detrimental effects on the immune system and infectious response, and has been associated with a worse prognosis of pulmonary disease.[17 18] Moreover, smokers were noted to have higher mortality in the previous MERS-CoV outbreak compared with non-smokers (37% vs 19%, OR=3.14, 95% CI 1.10 to 9.24, n=146).[30]

Concerning SARS-CoV-2 infection, previous studies have suggested that active smokers and former smokers are more prone to develop severe COVID-19 infections. Despite the apparent logical link between smoking and COVID-19 prognosis, this relationship has not been fully established. In some previous studies, statistical significance was not reached; sample sizes were small; and results were not entirely adjusted for other confounding factors.[4–7]

Reviewing the available previous data, Guan *et al* described clinical characteristics and outcomes of 1099 patients with COVID-19 from China. This study reported a higher prevalence of active-smokers in severe COVID-19 (16.9%) compared with non-severe disease (11.8%). However, no statistical analysis for evaluating any association was performed.[4]

Moreover, Zhao *et al* conducted a meta-analysis with 11 case series. They studied the impact of smoking on the severity of COVID-19 among 2002 patients. This study concluded that active smoking increases the risk of severe COVID-19 (fixed effect model, OR=1.98, 95% CI 1.29 to

Figure 3 Kaplan-Meier survival curve free from all-cause death, according to smoking status.

3.05) by around twofold.[5] Results were heavily influenced by one study[4] and after removing it from analysis, association was not reached with the OR of 1.55 (95% CI 0.83 to 2.87).[5]

In a similar fashion, Liu *et al* studied 78 patients with COVID-19. They found a higher proportion of smokers (27.3%) among adverse outcome group, compared with the group that showed improvement or stabilisation (3.0%) (p=0.018). In their multivariate logistic regression analysis, the history of smoking was a risk factor of disease progression (OR=14.28, 95% CI 1.58 to 25.00, p=0.018).[6]

Furthermore, in a meta-analysis conducted by Patanavanich and Glantz, a total of 11 590 patients with COVID-19 from 19 studies were included. In the overall cohort, 18.4% of the patients developed disease progression. Afterwards, results between smokers and non-smokers were compared. Smokers presented a higher rate of disease progression (29.8%) in contrast with non-smokers (17.6%) with a twofold increased risk for smokers (OR 1.91, 95% CI 1.42 to 2.59, p=0.01).[31]

In our cohort, pernicious effects of smoking have been observed by the finding of a relationship between smoking and worse outcomes in patients with COVID-19. Mortality was significantly higher among patients with a smoking history (both former and current) than in the non-smoker group (27.6 vs 18.4%, p<0.001). Likewise, a more severe disease was associated to both present and past smoking history (composite endpoint: 36.2 vs 26.1%, p<0.001; online supplemental table S5).

Our results are in line with those found in a meta-analysis conducted by Jiménez-Ruiz *et al*. This study analysed data from 34 studies including a total of 6487 patients with SARS-CoV-2 infections. This meta-analysis showed a worse clinical course in current and former smokers (OR 1.96, 95% CI 1.36 to 2.83), as well as a greater risk of critical illness (OR 1.79, 95% CI 1.19 to 2.70), when compared with non-smokers.[32]

Moreover, Lowe *et al* evaluated the association between cumulative smoking exposure, as measured by pack-years, with COVID-19 outcomes. They studied a cohort of 7102 patients recovered in Cleveland Clinic who tested positive for COVID-19. Eighty-five per cent (6020) of them were non-smokers; 2.4% (172) were current smokers; and 12.8% (910) were former smokers. As well, they compared non-smokers with patients smoking 0–10, 10–30 and more than 30 pack-years, respectively. They found an association between the risk of bad outcomes and the number of pack-years, with a 1.89 and 2.25-fold increased risk of mortality and hospitalisation, respectively, among those patients smoking more than 30 pack-years. This relationship was dose-dependent with a progressive increment of risk according to the number of pack-years. They conclude that smoking is an independent risk factor for hospital admission and mortality in COVID-19.[33]

Likewise, a meta-analysis conducted by Vardavas reviewed five studies on COVID-19. All studies included patients' smoking status with sample sizes ranging from 41 to 1099 patients. In all these studies, there was a higher prevalence of both current and former smokers among more severe cases (patients who needed ICU support, mechanical ventilation or who had died; relative risk (RR): 2.4, IQR 1.43–4.04).[34]

Another retrospective study conducted by Adrish *et al* analysed 1173 patients with COVID-19 and smoking habit available. Among them, 837 patients never smoked while 336 were either current or past smokers. In this analysis, smokers developed more critical illness requiring mechanical ventilation (47% vs 37% p=0.005). Univariate Cox model for survival showed that only current smokers had higher risk of death compared with never smokers (HR 1.61, 95% CI 1.22 to 2.12, p<0.001).[35]

In our cohort, to clarify if the impact of smoking on COVID-19 outcome is rather linked to the smoking-related comorbidities, a multivariate logistic regression analysis was performed. After adjusting by confounding factors, mortality and severity (defined as the composite endpoint) were still higher among smokers compared with never smokers (multivariate analysis in table 2). Indeed, one of the most interesting findings in this work is the fact that active smokers, even if they presented less comorbidities than former smokers, presented the greatest risk of mortality and severity, once confounding factors were adjusted. Current smoking was found to be an independent predictor of mortality and poor prognosis in COVID-19. Former smokers presented a slightly increased risk of mortality (1.3-fold), but there were no statistically significant differences for the combined endpoint in contrast with non-smokers.

In our study, ex-smokers had a greater burden of comorbidities compared with the other two groups. It might explain a higher crude mortality rate among ex-smokers in comparison with active smokers.

Unlike our cohort, other studies did not include ex-smokers in their analysis.[9] It is worth highlighting the importance of including ex-smokers, since both current and former smokers share characteristics and underlying respiratory comorbidities. Moreover, both groups have a similar expression of ACE2 receptors. Cai observed a higher ACE2 gene expression in the airway epithelia of healthy patients with a current or previous history of smoking compared with non-smokers.[28]

Contrastingly, it has been widely questioned whether a history of smoking contributes to an increased risk of contracting COVID-19. An important mechanism of SARS-COV2 infection relates to the levels of ACE 2 proteins that are produced. While the hyperinnate inflammatory response is mainly related to the clinical course of the disease, this second mechanism may play a role in the susceptibility to infection. The ACE2 protein is expressed on the surface of lung type 2 pneumocytes and is the principal receptor molecule for SARS-CoV-2. Some authors have described decreased levels of ACE2 in smokers,[26 27] which proposes a protective role of smoking. This mechanism suggests that in the ACE/ANG II/AT1R arm, nicotine increases the expression and activity of renin, ACE and AT1R, whereas in the compensatory

ACE2/ANG-(1–7)/MasR arm, nicotine downregulates the expression and activity of ACE2 and AT2R, thus suggesting a possible contribution of acetylcholine receptors in ACE2 regulation (nicotine).[27]

A theoretical 'protective' role of tobacco in COVID-19 infection has been suggested. It is worth noting the lower rates of smoking observed in patients with COVID-19 in comparison with the general population. This may indicate a lower susceptibility to the infection in individuals with a smoking history.

Previous Chinese studies have shown low rates of current smokers among SARS-CoV-2-infected patients (1.4%–12.5%),[5–15] lower than the reported prevalence of smoking in China (25.2%).[16] Moreover, possible selection biases need to be considered. It is remarkable the median age of patients ranged from 38 to 59.7 years in the previously mentioned series.[6 9–14] These ages are strikingly lower than expected results and differ notably from our cohort with a median age of 66 years (IQR 52.0–77.0).

Similarly, Miyara *et al* studied 482 patients with COVID-19 to evaluate smoker's susceptibility to develop SARS-CoV-2 infection. In their cohort, 4.4% of the hospitalised patients and 5.3% of outpatients were daily smokers. Finally, they compared these results with the French general population (daily smokers' rate of 25.4%). An increased susceptibility to SARS-COV2 infection in smokers was suggested.[8]

Since our study population is predominantly Spanish, we reviewed data regarding current smokers in Spain. These data have been reported by the Instituto Nacional de Estadística in 2017. The survey involved 29 195 individuals interviewed between October 2016 and October 2017. They were classified in daily smokers, occasional smokers, former smokers and non-smokers. Smoking prevalence in 2017 among men was approximately 25.6% and 18.8% in women. It is worth pointing out that these rates are notably higher than the smoking rates recorded in our Spanish cohort (5%). Although this imbalance draws attention, it should be considered that smoking status has been assessed only in hospitalised patients with COVID-19, thus symptomatic individuals fulfilling admission criteria. Since most COVID-19 studies have been performed in symptomatic patients, the smokers' lower susceptibility to have COVID-19 infection cannot be extrapolated from these data. Moreover, considering ex-smokers, the prevalence of current and former smokers reaches 21% in our cohort. This percentage approaches those observed in the general population.

Conversely, it has been suggested that ACE2 is upregulated in the airway epithelium of smokers.[23] As previously stated, increased levels of ACE2 gene expression have been reported in samples taken from smokers in comparison with non-smokers[28]; thus, smokers may be more susceptible to SARS-CoV-2 infection. Similarly, in a study in resected lung specimens, Leung *et al* found an increased rate of ACE2 gene expression in smokers.[29]

It remains to be seen if smokers are more prone to contracting SARS-CoV-2. Despite its relevance, the current data do not answer this question. It is also worth noting that the true prevalence of COVID-19 infection rates in the general population is likely underestimated.

Limitations

In our study, only hospitalised patients with COVID-19 were evaluated; therefore, it is clear that these patients had a more severe clinical course.

Moreover, as this study is an observational study, there is the potential for bias, given the nature of the study design. It must be considered that many individuals may be asymptomatic, and it is not currently possible to establish the real prevalence of smoking among all COVID-19 cases.

Furthermore, another limitation of our study was the fact that the number of pack-years of smoking was not recorded in our database and, therefore, it was not possible to classify the patients following this interesting criterion. Likewise, the number smoke-free years was not available, which would have provided a more accurate classification of previous risk in former smokers.

CONCLUSIONS

In conclusion, current smoking has a detrimental impact on COVID-19 prognosis. A history of active smoking is related to worse COVID-19 outcomes, with increased risk of mortality and the combined event, after adjusting for comorbidities. Likewise, a greater risk of mortality was still found among former smokers, compared with non-smokers.

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