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COVID-19 and smoking: A systematic review of the evidence

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COVID-19 is a coronavirus outbreak that initially appeared in Wuhan, Hubei Province, China, in December 2019, but it has already evolved into a pandemic spreading rapidly worldwide[1,2]. As of 18 March 2020, a total number of 194909 cases of COVID-19 have been reported, including 7876 deaths, the majority of which have been reported in China (3242) and Italy (2505)[3].

However, as the pandemic is still unfortunately under progression, there are limited data with regard to the clinical characteristics of the patients as well as to their prognostic factors[4]. Smoking, to date, has been assumed to be possibly associated with adverse disease prognosis, as extensive evidence has highlighted the negative impact of tobacco use on lung health and its causal association with a plethora of respiratory diseases[5]. Smoking is also detrimental to the immune system and its responsiveness to infections, making smokers more vulnerable to infectious diseases[6]. Previous studies have shown that smokers are twice more likely than non-smokers to contract influenza and have more severe symptoms, while smokers were also noted to have higher mortality in the previous MERS-CoV outbreak[7,8].

Given the gap in the evidence, we conducted a systematic review of studies on COVID-19 that included information on patients' smoking status to evaluate the association between smoking and COVID-19 outcomes including the severity of the disease, the need for mechanical ventilation, the need for intensive care unit (ICU) hospitalization and death.

The literature search was conducted on 17 March 2020, using two databases (PubMed, ScienceDirect), with the search terms: ['smoking' OR 'tobacco' OR 'risk factors' OR 'smoker*'] AND ['COVID-19' OR 'COVID 19' OR 'novel coronavirus' OR 'sars cov-2' OR 'sars cov 2'] and included studies published in 2019 and 2020. Further inclusion criteria were that the studies were in English and referred to humans. We also searched the reference lists of the studies included. A total of 71 studies were retrieved through the search, of which 66 were excluded after full-text screening, leaving five studies that were included. All of the studies were conducted in China, four in Wuhan and one across provinces in mainland China. The populations in all studies were patients with COVID-19, and the sample size ranged from 41 to 1099 patients. With regard to the study design, retrospective and prospective methods were used, and the timeframe of all five studies covered the first two months of the COVID-19 pandemic (December 2019, January 2020).

Specifically, Zhou et al.[9] studied the epidemiological characteristics of 191 individuals infected with COVID-19, without, however, reporting in more detail the mortality risk factors and the clinical outcomes of the disease. Among the 191 patients, there were 54 deaths, while 137 survived. Among those that died, 9% were current smokers compared to 4% among those that survived, with no statistically significant difference between the smoking rates of survivors and non-survivors (p=0.21) with regard to mortality from COVID-19.

Similarly, Zhang et al.[10] presented clinical characteristics of 140 patients with COVID-19. The results showed that among severe patients (n=58), 3.4% were current smokers and 6.9% were former smokers, in contrast to non-severe patients (n=82) among which 0% were current smokers and 3.7% were former smokers , leading to an OR of 2.23; (95% CI: 0.65–7.63; p=0.2).

Huang et al.[11] studied the epidemiological characteristics of COVID-19 among 41 patients. In this study, none of those who needed to be admitted to an ICU (n=13) was a current smoker. In contrast, three patients from the non-ICU group were current smokers, with no statistically significant difference between the two groups of patients (p=0.31), albeit the small sample size of the study.

The largest study population of 1099 patients with COVID-19 was provided by Guan et al.[12] from multiple regions of mainland China. Descriptive results on the smoking status of patients were provided for the 1099 patients, of which 173 had severe symptoms, and 926 had non-severe symptoms. Among the patients with severe symptoms, 16.9% were current smokers and 5.2% were former smokers, in contrast to patients with non-severe symptoms where 11.8% were current smokers and 1.3% were former smokers. Additionally, in the group of patients that either needed mechanical ventilation, admission to an ICU or died, 25.5% were current smokers and 7.6% were former smokers. In contrast, in the group of patients that did not have these adverse outcomes, only 11.8% were current smokers and 1.6% were former smokers. No statistical analysis for evaluating the association between the severity of the disease outcome and smoking status was conducted in that study.

Finally, Liu et al.[13] found among their population of 78 patients with COVID-19 that the adverse outcome group had a significantly higher proportion of patients with a history of smoking (27.3%) than the group that showed improvement or stabilization (3.0%), with this difference statistically

Indexes

significant at the p=0.018 level. In their multivariate logistic regression analysis, the history of smoking was a risk factor of disease progression (OR=14.28; 95% CI: 1.58–25.00; p= 0.018).

We identified five studies that reported data on the smoking status of patients infected with COVID-19. Notably, in the largest study that assessed severity, there were higher percentages of current and former smokers among patients that needed ICU support, mechanical ventilation or who had died, and a higher percentage of smokers among the severe cases[12]. However, from their published data we can calculate that the smokers were 1.4 times more likely (RR=1.4, 95% CI: 0.98–2.00) to have severe symptoms of COVID-19 and approximately 2.4 times more likely to be admitted to an ICU, need mechanical ventilation or die compared to non-smokers (RR=2.4, 95% CI: 1.43–4.04).

In conclusion, although further research is warranted as the weight of the evidence increases, with the limited available data, and although the above results are unadjusted for other factors that may impact disease progression, smoking is most likely associated with the negative progression and adverse outcomes of COVID-19.

Table 1

Overview of the five studies included in the systematic review

Title	Setting	Population	Study design and time horizon	Outcomes	Smoking rates by outcome
Zhou et al.[9] (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study	Jinyintan Hospital and Wuhan Pulmonary Hospital, Wuhan, China	All adult inpatients (aged ≥18 years) with laboratory confirmed COVID-19 (191 patients)	Retrospective multicenter cohort study until 31 January 2020	**Mortality** 54 patients died during hospitalisation and 137 were discharged	Current smokers: n=11 (6%) Non-survivors: n=5 (9%) Survivors: n=6 (4%) (p=0.20) Current smoker vs non-smoker Univariate logistic regression (OR=2.23; 95% CI: 0.65–7.63; p=0.2)
Zhang et al.[10] (2020) Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China	No. 7 Hospital of Wuhan, China	All hospitalised patients clinically diagnosed as 'viral pneumonia' based on their clinical symptoms with typical changes in chest radiology (140 patients)	Retrospective 16 January to 3 February 2020	**Disease Severity** Non-severe patients: n=82 Severe patients: n=58	**Disease Severity** Former smokers: n=7 Severe: n=4 (6.9%) Non-severe: n=3 (3.7%) (p= 0.448) Current smokers: n=2 Severe: n=2 (3.4%) Non-severe: n=0 (0%)
Guan et al.[12] (2019)	552 hospitals in 30	Patients with		**Severity and admission to an ICU, the use of**	**By severity** Severe cases 16.9% current smokers 5.2% former smokers 77.9% never smokers Non-severe cases 11.8% current smokers 1.3% former smokers 86.9% never smokers

Clinical Characteristics of Coronavirus Disease 2019 in China	provinces, autonomous regions, and municipalities in mainland China	laboratory-confirmed COVID-19 (1099 patients)	Retrospective until 29 January 2020	**mechanical ventilation, or death** Non-severe patients: n=926 Severe patients: n=173	**By mechanical ventilation, ICU or death** Needed mechanical ventilation, ICU or died 25.8% current smokers 7.6% former smokers 66.7% non-smokers No mechanical ventilation, ICU or death 11.8% current smokers 1.6% former smokers 86.7% never smokers
Huang et al.[11] (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China	A hospital in Wuhan, China	Laboratory-confirmed 2019-nCoV patients in Wuhan (41 patients)	Prospective from 16 December 2019 to 2 January 2020	**Mortality** As of 22 January 2020, 28 (68%) of 41 patients were discharged and 6 (15%) patients died	Current smokers: n=3 ICU care: n=0 Non-ICU care: n=3 (11%) Current smokers in ICU care vs non-ICU care patients (p=0.31)
Liu et al.[13] (2019) Analysis of factors associated with disease outcomes in hospitalised patients with 2019 novel coronavirus disease	Three tertiary hospitals in Wuhan, China	Patients tested positive for COVID-19 (78 patients)	Retrospective multicentre cohort study from 30 December 2019 to 15 January 2020	**Disease progression** 11 patients (14.1%) in the progression group 67 patients (85.9%) in the improvement/stabilization group 2 deaths	Negative progression group: 27.3% smokers In the improvement group: 3% smokers The negative progression group had a significantly higher proportion of patients with a history of smoking than the improvement/stabilisation group (27.3% vs 3.0%) Multivariate logistic regression analysis indicated that the history of smoking was a risk factor of disease progression (OR=14.28; 95% CI: 1.58–25.00; p= 0.018)

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PROVENANCE AND PEER REVIEW

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