Journal of Iranian Medical Council, Volume 6, Issue no. 2
http://dx.doi.org/10.18502/jimc.v6i2.12231

Review Article

The Impact of Smoking on COVID-19 Severity: A Multi-Analysis Study

Mariwan Ahmed Hama Saeed[1]*, Ayad M Ali[2], Kameran M Ali[3] and Hassan Muhammad Rostam[4]

1. College of Basic Education, University of Halabja, Halabja, Kurdistan Region, Iraq
2. Department of Chemistry, College of Sciences, University of Garmian, Kalar, Kurdistan Region, Iraq
3. Department of Medical Lab Technology, Kalar Technical College, Sulaimani Polytechnic University, Kalar, Kurdistan Region, Iraq
4. Immunology & Immuno-bioengineering Group, School of Life Sciences, Faculty of Medicine & Health Sciences, University of Nottingham, Nottingham, UK

Abstract

Background: Smoking is considered to be one of the main risk factors that may affect the severity of coronavirus disease 2019 (COVID-19). Previously, several meta-analyses with a limited or small sample size and insufficient methodology have been conducted investigating the impact of smoking on disease severity. Here, we use a more accurate method to identify the effect of smoking on COVID-19 disease severity.

Methods: BMC, PubMed, Science Direct, Wiley, Springer, and Google Scholar websites were used to search for and select reliable articles to be included in the current analysis. Research articles that mentioned the relationship between smoking and COVID-19 severity were included.

Results: Twenty-six research articles detailing 15,713 confirmed COVID-19 cases comprising patients who smoke were selected to be included in this analysis. The analysis showed a relationship between smoking, severe COVID-19, and non-severe COVID-19 (OR=0:11; 95%CI: 0.10–0.11; p<0.00001). Only 15% (2407) of the smokers suffered severe COVID-19, with the other 85% (13306) of smokers experiencing non-severe COVID-19.

Conclusion: The current analysis found that only 15% of severe COVID-19 cases were smokers. Therefore, smoking is not significantly correlated with severe covid19.

Keywords: COVID-19, Humans, Smokers, Smoking

*** Corresponding author**
Mariwan Ahmed Hama Saeed, MSc
College of Basic Education, University of Halabja, Halabja, Kurdistan Region, Iraq
Tel: +96 477 0191 5519
Email: mariwan.hamasaeed@uoh.edu.iq

Received: 7 Jun 2022
Accepted: 29 Aug 2022

Citation to this article:
Saeed MAH, Ali AM, Ali KM, Rostam HM. The Impact of Smoking on COVID-19 Severity: A Multi-Analysis Study. *J Iran Med Counc.* 2022;6(2):229-39.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has infected approximately 200 million people worldwide (1), causing a considerable public health threat and posing an immediate risk to the health of the global population (2). A number of factors have emerged that may cause an increased risk of severe outcomes and death from coronavirus disease 2019 (COVID-19) (3), including older age, male sex, smoking, race/ethnicity, nutrition, and having specific comorbid conditions such as hypertension, cardiovascular diseases, diabetes, liver diseases, pregnancy, and autoimmune disease (4-6).

There has been some argument regarding the impact of smoking on SARS-CoV-2 infection and subsequent COVID-19 severity, although it is well established that smokers face an increased risk of both viral and bacterial respiratory infections (7,8). Smoking tobacco causes cardiovascular disease and induces lung diseases, increasing the risk of respiratory infections, and the WHO has also highlighted smokers' hand-to-mouth action as another factor that may cause smokers to be more susceptible to SARS-CoV-2 infection and development of COVID-19 (9,10). Available data concerning the effect of smoking on disease progression and death amongst COVID-19 patients is contradictory (11). Early in the pandemic, it was argued that higher mortality among males in China may reflect and be partly explained by the gender disparity in smoking prevalence (12). Smokers were not, however, identified as a vulnerable group within the UK Government's COVID-19 guidance on social distancing (13).

A large study based on electronic health records from the United Kingdom identified a counterintuitive lower risk of COVID-19 mortality among smokers than among ex-smokers (14). A smaller French study also suggested that there were fewer smokers among COVID-19 patients than among the general French population (15). Conversely, other studies have linked the infection and severity of COVID-19 to smoking (16,17). In addition, smoking status, pack-years, and smoking intensity were correlated with hospitalizations in COVID-19 patients and smoking intensity was linked to ICU admission (18). Regarding these conflicting issues related to smoking and COVID-19, this study aims to determine the impact of smoking on COVID-19 severity, as well as the association between COVID-19 outcome and age in smokers that pave a way for COVID-19 treatment guidelines and further research in this area.

Materials and Methods

Ethical approval and informed consent were not required for this study because it was conducted using published studies.

Search

We used search machines on the BMC, PubMed, ScienceDirect, Wiley, Springer, and Google Scholar websites to select a number of appropriate papers to be included in the current analysis. To find studies for the analysis, papers published between January 1, 2020 and July 1, 2021 were searched using the key-words/phrases 'coronavirus and smoking', 'smoking and COVID-19 severity', 'COVID-19 and health conditions', 'smoking and risk of COVID-19', and 'relationship between smoking and COVID-19'.

Paper inclusion and exclusion

Papers that met the following conditions were included in the analysis: 1) described the relationship between COVID-19 and smoking; 2) were written in English; 3) were published between January 1, 2020 and July 1, 2021; 4) mentioned the severity of COVID-19 due to smoking. Papers were excluded from this study if they: 1) were not written in English; 2) did not clearly explain the relationship between severities of COVID-19 and smoking; and/or 3) were case reports or editorial letters.

Data extraction

Article titles and abstracts were scanned to find appropriate studies to be included in the next step, in which the full text of the selected the articles were evaluated to determine if they would be included in or excluded from the study. The following features were extracted from all the papers: title, authors, publication date, location, age, sample size, and if COVID-19 was described as severe (critical, severe, ICU, non-survivors) or non-severe (mild, common type, non-ICU, survivors). Patient numbers from a study by Bhaskaran *et al* (19) were adjusted (divided by 1000) to be closer to the range of the other papers.

Ethics declarations

All methods were used in accordance with relevant guidelines and regulations. The current study analysed other studies without involving any COVID-19 patient.

Statistical analysis

Revman version 5.4 was used to calculate odds ratios with 95% confidence intervals, which were depicted using a forest plot. For evaluating heterogeneity between studies, chi-square and I-square were used. Python 3.8.8 was used for data management and study plots.

Results

The initial search identified 489 articles, but after removing the duplicates, 309 articles remained. Based on the abovementioned exclusion criteria, 283 of these articles were excluded from the study, resulting in 26 articles remaining to be included in the quantitative analysis (Figure 1). These articles included 15,713 hospitalised COVID-19 patients; 2,704 severe cases and 13,306 non-severe cases (Figure 2).

Three studies (20-22) were conducted on COVID-19 populations of fewer than 10 patients; 14 studies involved population studies of 10–100 patients (23-36); four studies (37-40) consisted of 100–1000 COVID-19 patients; and five studies (19,41-44) included thousands of patients.

The current study included 10 studies (20-24,26,31, 32,37,38) from China, which consisted of 619 patients; 119 severe cases and 427 non-severe. Five studies included here occurred in the US (30,39,41,43,44) comprising 4,168 COVID-19 patients; 1,564 severe and 2,604 non-severe. The UK offered the largest sample size, 8,716 patients (11 severe and 8,705 non-severe) (19). A single study was included from each of the following countries: Spain (1,221 samples; 336 severe and 885 non-severe) (42); Italy (567 samples; 167 severe and 391 non-severe) (40); Qatar (98 samples; 30 severe and 68 non-severe) (36); Pakistan (72 samples; 13 severe and 59 non-severe) (35); Iraq (71 samples; 28 severe and 43 non-severe) (34); Turkey (68 samples; eight severe and 60 non-severe) (33); Brazil (38 samples; 18 severe and 16 non-severe) (29); Israel (33 samples; 10 severe and 23 non-severe) (28); Japan (29 samples; 12 severe and 17 non-severe) (27); and Egypt (17 samples; nine severe and eight non-severe) (25) (Table 1).

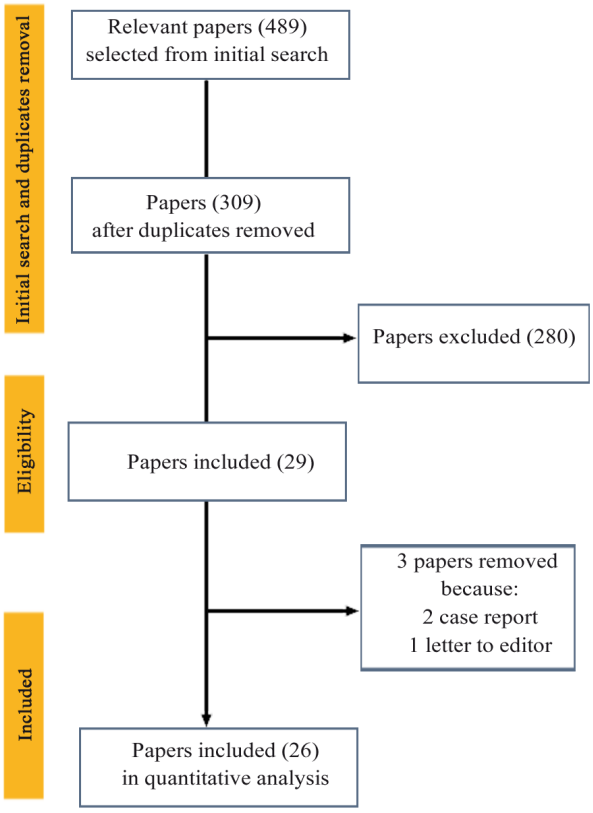

Figure 1. Flowchart for studies selected in review of COVID-19 patients with smoking.

The ages of patients ranged from 29 years 35 to 70 years (29). Eight studies (23,25-27,30,38,39,42) involved patients between 60 and 69 years of age; seven studies (24,28,31-33,41,43) included patients between 50 and 59 years of age; and another seven articles (19,21,22,34,37,40,44) had patients between 40 and 49 years of age. The mean age of samples in two studies were 38 (20) and 32 years (34) (Figure 3).

In our multi-analysis study, we found that 15% of the COVID-19 patients with smoking habits had experienced severe symptoms, whereas the rest experienced non-severe symptoms (Figure 4).

Discussion

In this review, data from the BMC, PubMed, ScienceDirect, Wiley, Springer, and Google Scholar websites were analysed to show the impact of smoking on COVID-19 severity. This review evaluated literature concerning the link between smoking and COVID-19, including the likelihood of SARS-CoV-2

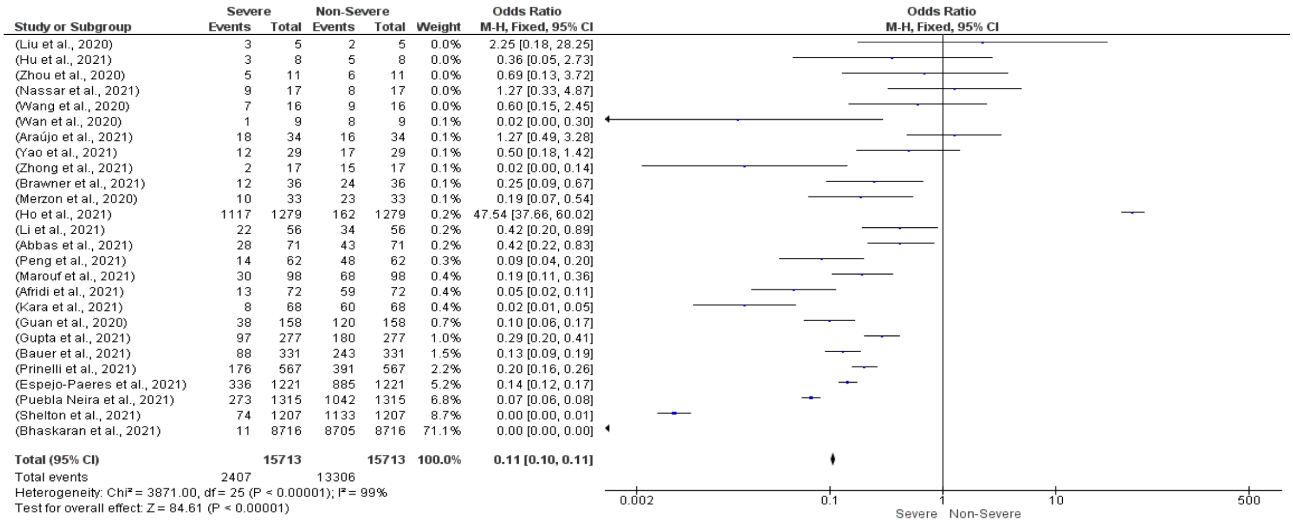

Figure 2. Prevalence of smoking in severe and non-severe COVID-19 patients. Bhaskaran *et al* (19) cases have been divided by 1000.

Table 1. The Table shows the summary and features of the selected papers to include in the analysis. Bhaskaran *et al* 18 cases have been divided by 1000

Author	Study	Publication date	Location	Age	Sample size (N)	Severe	non-severe
Prinelli *et al*	Association between smoking and SARS-CoV-2 infection: cross-sectional study of the EPICOVID19 internet-based survey 39	April/2021	Italy	48	567	176	391
Guan *et al*	Clinical characteristics of coronavirus disease 2019 in China 36	Feb/2020	China	40	158	38	120
Abbas *et al*	Presenting the characteristics, smoking versus diabetes, and outcome among patients hospitalized with COVID-19, 33	Jan/2021	Iraq	48	71	28	43
Nassar *et al*	Outcomes and risk factors for death in patients with coronavirus disease-2019 (COVID-19) pneumonia admitted to the intensive care units of an Egyptian University Hospital: A retrospective cohort study 24	June/2021	Egypt	60	17	9	8
Merzon *et al*	Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes 27	Sept/2020	Israel	59	33	10	23
Gupta *et al*	SARS-CoV-2 infection and smoking: what is the association? A brief review 37	March/2021	China	65	277	97	180
Shelton *et al*	Trans-ancestry analysis reveals genetic and non-genetic associations with COVID-19 susceptibility and severity 40	April/2021	USA	51	1207	74	1133

Cont. table 1.

Afridi *et al*	Elemental concentrations in biological samples of coronavirus disease (COVID-19) and other pulmonary disease patients 34	May/2021	Pakistan	32	72	13	59
Marouf *et al*	Association between periodontitis and severity of COVID-19 infection- A case–control study 35	April/2021	Qatar	29	98	30	68
Li *et al*	Tobacco smoking confers risk for severe COVID-19 unexplainable by pulmonary imaging 30	March/2021	China	58	56	22	34
Bauer *et al*	Hypertension medications and risk of severe COVID-19 -A Massachusetts community-based observational study 38	Jan/2021	USA	61	331	88	243
Hu *et al*	Predictive value of the prognostic nutritional index for the severity of coronavirus disease 2019 20	Dec/2020	China	44	8	3	5
Zhong *et al*	Which factors, smoking, drinking alcohol, betel quid chewing, or underlying diseases, are more likely to influence the severity of COVID-19? 25	Jan/2021	China	64	17	2	15
Espejo-Paeres *et al*	Impact of smoking on COVID-19 outcomes: a HOPE registry sub analysis 41	June/2021	Spain	66	1221	336	885
Puebla Neira *et al*	Smoking and risk of COVID-19 hospitalization 43	April/2021	USA	42	1315	273	1042
Ho *et al*	Controversy over smoking in COVID-19—A real world experience in New York city 42	Dec/2020	USA	58	1279	1117	162
Araújo *et al*	Health conditions of potential risk for severe COVID-19 in institutionalized elderly people 28	Jan/2021	Brazil	70	34	18	16
Kara *et al*	Grip strength as a predictor of disease severity in hospitalized COVID-19 patients 32	June/2021	Turkey	55	68	8	60
Bhaskaran *et al*	Factors associated with deaths due to COVID-19 versus other causes-population-based cohort analysis of UK primary care data and linked national death registrations within the Open SAFELY platform 18	May/2021	UK	49	8716	11	8705
Peng *et al*	Smoking is correlated with the prognosis of coronavirus disease 2019 (COVID-19) patients an observational study 31	March/2021	China	55	62	14	48
Zhou *et al*	Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China a retrospective cohort study 22	March/2020	China	61	11	5	6

Cont. table 1.

Wang *et al*	Epidemiological and clinical features of 125 Hospitalized Patients with COVID-19 in Fuyang Anhui China 23	April/2020	China	50	16	7	9
Brawner *et al*	Inverse relationship of maximal exercise capacity to hospitalization secondary to coronavirus disease 2019, 29	Oct/2020	USA	65	36	12	24
Yao *et al*	Experience of 101 patients with coronavirus infectious disease 2019 (COVID-19) at a tertiary care center in Japan 26	Dec/2020	Japan	60	29	12	17
Liu *et al*	Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease 19	May/2020	China	38	5	3	2
Wan *et al*	Clinical features and treatment of COVID?19 patients in northeast Chongqing 21	April/2020	China	46	9	1	8

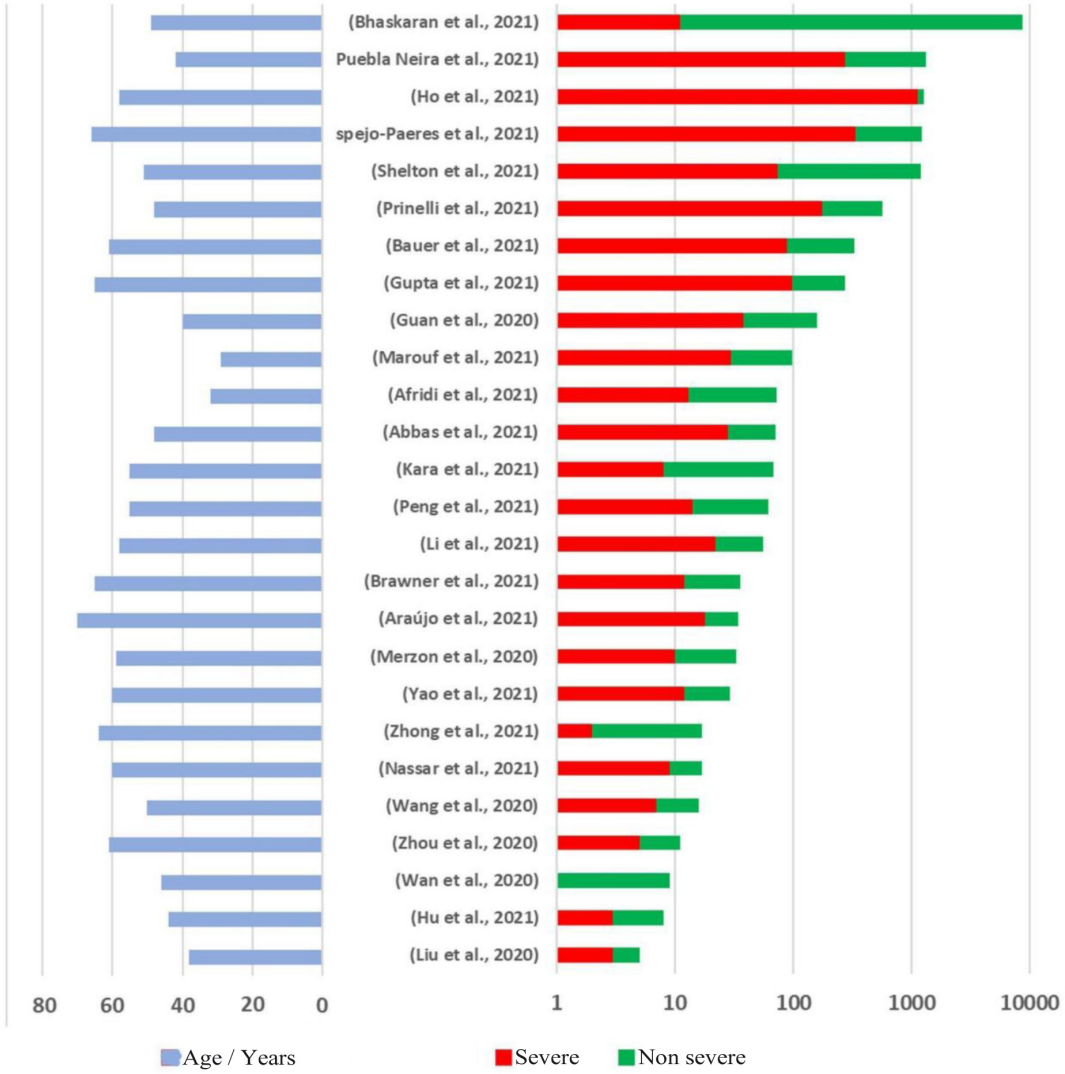

Figure 3. Characteristics of the selected papers by Age-Group and COVID-19 Severity; Right X_Axis shows COVID-19 severity, Left X_Axis demonstrates age group. Bhaskaran *et al* (19) cases have been divided by 1000.

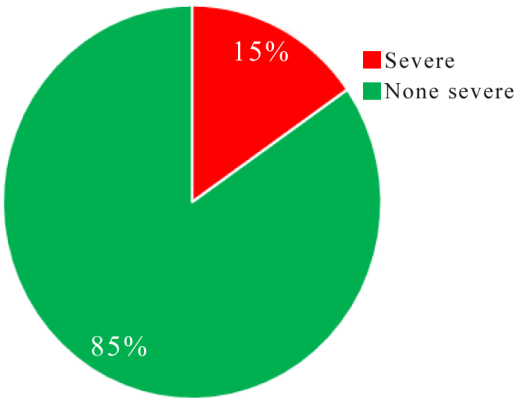

Figure 4. Relationship between smoking and COVID-19 severity (%).

infection and COVID-19 hospitalisation, and the severity of COVID-19 outcomes among hospitalised patients, such as admission to critical care units.

The 26 studies analysed are presented in table 1. Overall, 8,723,756 COVID-19 patients with smoking habits from around the world were selected for inclusion in this analysis. A total of 16,280 of these patients were hospitalised. The results of our meta-analysis represented that smoking patients might face a lower risk of developing severe or mortal COVID-19, as 85% (13,306 patients) experienced non-severe COVID-19, with only 15% (2,407 patients) suffering increased severity of disease (OR =0.11; 95%CI: 0.10–0.11; p<0.00001).

Generally, fever, cough, and sputum are the most prevalent clinical symptoms in COVID-19 patients. Normal body temperature may be a sign of a poor immune response in a patient. Shortness of breath, often known as dyspnoea, indicates a shortage of oxygen and poor lung function. As a result, if the patient has trouble breathing but no temperature, it is important to remain on the lookout for future deterioration of the patient's condition (45).

Even though, limitations add to misclassification errors in number of studies, which can lead to biased results toward the null and underestimates the risk of smoking in increasing COVID-19 severity (46).

The findings of our meta-analysis may be useful in determining the impact of smoking status on illness progression, complications, and death in COVID-19 patients who are hospitalised. Two recent studies used univariate analysis to find a link between smoking and poor outcomes in COVID-19 patients who were hospitalised, although the links were not always statistically significant (16,17).

SARS-CoV-2 attaches to the receptor for Angiotensin-Converting Enzyme 2 (ACE2), which has generally protective effects on the lungs, and then downregulates it; hence, any condition that causes ACE2 levels to drop may supply the virus with fewer binding sites. It has been reported that smoking can upregulate ACE2 (47), but it is also known from animal models that chronic cigarette exposure can reduce ACE2 expression in lung tissues (48). More data show that nicotine alters the renin-angiotensin system's function by upregulating the ACE-mediated axis while downregulating the compensatory ACE2-mediated axis (49). Moreover, a nicotine-induced increase of ACE activity could lead to an increased degradation of bradykinin, one of the most potent inflammatory mediators in humans, which is able to activate signalling pathways resulting in increased vascular permeability, oedema, vasodilation, hypotension, pain, and fever, all typical features of COVID-19 (50).

Our findings indicate that smoking increases the progression of COVID-19 severity, in line with previous meta-analysis studies that have clearly demonstrated a significant relationship between smoking and patients with severe COVID-19 (51-54). Although no clear conclusions can be drawn regarding the particular effects of smoking on the risk of COVID-19 hospitalisation, tobacco cigarette smoke contains numerous toxins and other substances that are not known to have any immunomodulatory or antiviral characteristics that might protect against COVID-19. Nicotine, however, is a major component of tobacco cigarette smoke, and was reported to protect acute lung damage and decrease TNF expression in airway epithelial cells in vitro in an animal Acute Respiratory Distress Syndrome (ARDS) model (55). Nicotine is a cholinergic anti-inflammatory agonist that controls the immunological and inflammatory responses of the host, and has also been shown to have anti-inflammatory effects in individuals who have been exposed to endotoxins *in vivo* (55). Nicotine suppresses the production of pro-inflammatory cytokines like TNF, IL-1, and IL-6 while not suppressing the production of

anti-inflammatory cytokines like IL-10 (57). In addition, smoking increases the severity and mortality of both bacterial and viral infections through the induction of mechanical and structural changes in the respiratory tract and alteration of cell- and humoral-mediated immune responses (58,59).

In contrast, antibodies against cytokine-mediated illnesses such as sepsis and endotoxemia, which cause organ damage and death, have been discovered. The condition known as 'cytokine storm' is characterised by an enhanced production of pro-inflammatory cytokines in response to infections, which can develop to ARDS. This phenomenon appears to have a role in the pathophysiology of severe COVID-19 and might explain the histological findings in a COVID-19 patient after death (60,61). Medicines that target pro-inflammatory cytokines, such as IL-1 or IL-6 inhibitors, have therefore been proposed for and are now being investigated in clinical studies to treat COVID-19 patients by neutralising these important inflammatory mediators (62). The US FDA recently approved a Phase III clinical trial of an IL-6 inhibitor for the treatment of COVID-19 (63). As a result, the cytokine storm has been identified as a therapeutic target in COVID-19 patient clinical trials, and nicotine's effects on the immune system may be useful in decreasing the severity of the cytokine storm.

Conclusion

To conclude, our analysis demonstrated that smoking was not contributed to increased severity of COVID-19, as 15% of COVID-19 cases among smokers were severe. This is a higher percentage than that among the whole COVID-19 patient population, most likely due to the effect of smoking on COVID-19 disease pathology, which requires further studies.

Conflict of Interest

Not applicable.

References

1. WHO. WHO Coronavirus (COVID-19) Dashboard: World Health Oranazation; 2021 [Available from: https://covid19.who.int/?gclid=Cj0KCQjwweyFBhDvARIsAA67M703RW_Ot4bPRwGTcP_GSFoRJwZl4u2UIHZK0SgQf_wR7KPuVjMwi5MaApSJEALw_wcB accessed 12/06/2021 2021.

2. Grundy EJ, Suddek T, Filippidis FT, Majeed A, Coronini-Cronberg S. Smoking, SARS-CoV-2 and COVID-19: a review of reviews considering implications for public health policy and practice. Tob Induc Dis 2020 Jul 3;18:58.

3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 28;395(10229):1054-62.

4. Salter A, Fox RJ, Newsome SD, Halper J, Li DK, Kanellis P, et al Outcomes and risk factors associated with SARS-CoV-2 infection in a north American registry of patients with multiple clerosis. JAMA Neurol 2021 Jun 1;78(6):699-708.

5. Fadl N, Ali E, Salem TZ. COVID-19: risk factors associated with infectivity and severity. Scand J Immunol 2021 Jun;93(6):e13039.

6. Mehta HB, Li S, Goodwin JS. Risk Factors Associated With SARS-CoV-2 Infections, Hospitalization, and Mortality Among US Nursing Home Residents. JAMA Netw Open 2021 Mar 1;4(3):e216315.

7. Lawrence H, Hunter A, Murray R, Lim WS, McKeever T. Cigarette smoking and the occurrence of influenza – Systematic review. J Infect 2019 Nov;79(5):401-6.

8. Bagaitkar J, Demuth DR, Scott DA. Tobacco use increases susceptibility to bacterial infection. Tob Induc Dis 2008 Dec 18;4(1):12.

9. Haddad C, Bou Malhab S, Sacre H, Salameh P. Smoking and COVID-19: a scoping review. Tob Use Insights 2021 Feb 15;14:1179173X21994612.

10. WHO. Coronavirus disease (COVID-19): Tobacco: World Helth Organization; 2020 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/coronavirus-disease-COVID-19-tobacco accessed 07/08/2021 2021.

11. Prats-Uribe A, Xie J, Prieto-Alhambra D, Petersen I. Smoking and COVID-19 infection and related mortality: a prospective cohort analysis of UK biobank data. Clin Epidemiol 2021 May 25;13:357-65.

12. Cattaruzza MS, Zagà V, Gallus S, D'Argenio P, Gorini G. Tobacco smoking and COVID-19 pandemic: old and new issues. A summary of the evidence from the scientific literature. Acta Biomed 2020 May 11;91(2):106-12.

13. GOV.UK. Coronavirus: how to stay safe and help prevent the spread: United Kingdom Government; 2021 [Available from: https://www.gov.uk/guidance/COVID-19-coronavirus-restrictions-what-you-can-and-cannot-do accessed 07/08/2021 2021.

14. Williamson EJ, Walker AJ, Bhaskaran K, Glowacki F, Couchoud C, Lapidus N. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020 Aug;584(7821):430-6.

15. Miyara M, Tubach F, Pourcher V, Morelot-Panzini C, Pernet J, Haroche J. Low incidence of daily active tobacco smoking in patients with symptomatic COVID-19. MedRxiv. 2020 Jun 12:2020-06.

16. Lippi G, Henry BM. Active smoking is not associated with severity of coronavirus disease 2019 (COVID-19). European J Inter Med 2020;75:107-08.

17. Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. Tob Induc Dis 2020 Mar 20;18:20.

18. Mahabee-Gittens EM, Mendy A, Merianos AL. Assessment of severe COVID-19 outcomes using measures of smoking status and smoking intensity. Int J Environ Res Public Health 2021 Aug 25;18(17):8939.

19. Bhaskaran K, Bacon S, Evans SJW, Bates CJ, Rentsch CT, MacKenna B, et al Factors associated with deaths due to COVID-19 versus other causes: population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. Lancet Reg Health Eur 2021 Jul;6:100109.

20. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, et al Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J (Engl) 2020 May 5;133(9):1032-8.

21. Hu X, Deng H, Wang Y, Chen L, Gu X, Wang X. Predictive value of the prognostic nutritional index for the severity of coronavirus disease 2019. Nutrition 2021 Apr;84:111123.

22. Wan S, Xiang Y, Fang W, Zheng Y, Li B, Hu Y, et al Clinical features and treatment of COVID-19 patients in northeast Chongqing. J Med Virol 2020 Jul;92(7):797-806.

23. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020 Mar 28;395(10229):1054-62.

24. Wang R, Pan M, Zhang X, Han M, Fan X, Zhao F, et al Epidemiological and clinical features of 125 hospitalized patients with COVID-19 in Fuyang, Anhui, China. Int J Infect Dis 2020 Jun;95:421-428.

25. Nassar Y, Mokhtar A, Elhadidy A, Elsayed M, Mostafa F, Rady A, et al Outcomes and risk factors for death in patients with coronavirus disease-2019 (COVID-19) pneumonia admitted to the intensive care units of an Egyptian University Hospital. A retrospective cohort study. J Infect Public Health 2021 Oct;14(10):1381-8.

26. Zhong R, Chen L, Zhang Q, Li B, Qiu Y, Wang W, et al Which factors, smoking, drinking alcohol, betel quid chewing, or underlying diseases, are more likely to influence the severity of COVID-19? Front Physiol 2021 Jan 18;11:623498.

27. Yao K, Hasegawa S, Tagashira Y, Takamatsu A, Uenoyama Y, Shimizu K, et al Experience of 101 patients with coronavirus infectious disease 2019 (COVID-19) at a tertiary care center in Japan. J Infect Chemother 2021

Feb;27(2):413-7.

28. Merzon E, Green I, Shpigelman M, Vinker S, Raz I, Golan-Cohen A, et al Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes. Diabetes Metab Res Rev 2021;37(5):e3398-e98.

29. Araújo MPD, Nunes VMA, Costa LA, Souza TA, Torres GD, Nobre TT. Health conditions of potential risk for severe COVID-19 in institutionalized elderly people. PLoS One 2021 Jan 14;16(1):e0245432.

30. Brawner CA, Ehrman JK, Bole S, Kerrigan DJ, Parikh SS, Lewis BK, et al Inverse relationship of maximal exercise capacity to hospitalization secondary to coronavirus disease. Mayo Clin Proc 2021 Jan;96(1):32-9.

31. Li J, Long X, Zhang Q, et al Tobacco smoking confers risk for severe COVID-19 unexplainable by pulmonary imaging. J Intern Med 2021 Apr;289(4):574-83.

32. Peng F, Lei S, Zhang Q, Zhong Y, Wu S. Smoking is correlated with the prognosis of coronavirus disease 2019 (COVID-19) patients: an observational study. 2021 Mar 3;12:634842.

33. Kara Ö, Kara M, Akın ME, Özçakar L. Grip strength as a predictor of disease severity in hospitalized COVID-19 patients. Heart Lung 2021 Nov-Dec;50(6):743-7.

34. Abbas HM, Nassir KF, Al Khames Aga QA, Al-Gharawi AA, Rasheed JI, AL-Obaidy MW, et al Presenting the characteristics, smoking versus diabetes, and outcome among patients hospitalized with COVID-19. J Med Virol 2021 Mar;93(3):1556-67.

35. Afridi HI, Kazi TG, Talpur FN, Baig JA, Chanihoon GQ, Lashari A, et al Elemental concentrations in biological samples of coronavirus disease (COVID-19) and other pulmonary disease patients. Am J Analytic Chemist 2021 May 18;12(5):162-87.

36. Marouf N, Cai W, Said KN, Daas H, Diab H, Chinta VR, et al Association between periodontitis and severity of COVID-19 infection: A case-control study. J Clin Periodontol 2021 Apr;48(4):483-91.

37. Guan WJ, Ni ZY, Hu Y, et al Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020 Apr 30;382(18):1708-20.

38. Gupta I, Sohail MU, Elzawawi KE, Amarah AH, Vranic S, Al-Asmakh M, et al SARS-CoV-2 infection and smoking: What is the association? A brief review. Comput Struct Biotechnol J 2021;19:1654-60.

39. Bauer AZ, Gore R, Sama SR, Rosiello R, Garber L, Sundaresan D, et al Hypertension, medications, and risk of severe COVID-19: a Massachusetts community-based observational study. J Clin Hypertens (Greenwich) 2021 Jan;23(1):21-7.

40. Prinelli F, Bianchi F, Drago G, Ruggieri S, Sojic A, Jesuthasan N, Molinaro S, et al Association between smoking and SARS-CoV-2 infection: cross-sectional study of the EPICOVID19 internet-based survey. JMIR Public Health Surveill 2021 Apr 28;7(4):e27091.

41. Shelton JF, Shastri AJ, Ye C, Weldon CH, Filshtein-Sonmez T, Coker D, et al Trans-ancestry analysis reveals genetic and nongenetic associations with COVID-19 susceptibility and severity. Nat Genet 2021 Jun;53(6):801-8.

42. Espejo-Paeres C, Núñez-Gil IJ, Estrada V, Fernández-Pérez C, Uribe-Heredia G, Cabré-Verdiell C, et al Impact of smoking on COVID-19 outcomes: a HOPE Registry subanalysis. BMJ Nutr Prev Health 2021 Jun 17;4(1):285-92.

43. Ho KS, Narasimhan B, Sheehan J, Wu L, Fung JY. Controversy over smoking in COVID-19-A real world experience in New York city. J Med Virol 2021 Jul;93(7):4537-43.

44. Neira DP, Watts A, Seashore J, Polychronopoulou E, Kuo YF, Sharma G. Smoking and risk of COVID-19 hospitalization. Respir Med 2021;182:106414.

45. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020;395(10223):497-506.

46. Patanavanich R, Glantz SA. Smoking is associated with worse outcomes of COVID-19 particularly among

younger adults: a systematic review and meta-analysis. BMC Public Health 2021 Aug 16;21(1):1554.

47. Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. Smoking upregulates angiotensin-converting enzyme-2 receptor: a potential adhesion site for novel coronavirus SARS-CoV-2 (COVID-19). J Clin Med 2020 Mar 20;9(3):841.

48. Yuan YM, Luo L, Guo Z, Yang M, Ye RS, Luo C. Activation of renin-angiotensin-aldosterone system (RAAS) in the lung of smoking-induced pulmonary arterial hypertension (PAH) rats. J Renin Angiotensin Aldosterone Syst 2015 Jun;16(2):249-53.

49. Oakes JM, Fuchs RM, Gardner JD, Lazartigues E, Yue X. Nicotine and the renin-angiotensin system. Am J Physiol Regul Integr Comp Physiol 2018 Nov 1;315(5):R895-R906.

50. Meini S, Zanichelli A, Sbrojavacca R, Iuri F, Roberts AT, Suffritti C, et al Understanding the pathophysiology of COVID-19: could the contact system be the key? Frontiers Immunol 2020 Aug 11;11:2014.

51. Gülsen A, Yigitbas BA, Uslu B, Dromann D, Kilinc O. The effect of smoking on COVID-19 symptom severity: systematic review and meta-analysis. Pulm Med 2020 Sep 8;2020:7590207.

52. Zhang J, Ding N, Ren L, Song R, Chen D, Zhao X, et al COVID-19 reinfection in the presence of neutralizing antibodies. Natl Sci Rev 2021 Jan 11;8(4):nwab006.

53. Reddy RK, Charles WN, Sklavounos A, Dutt A, Seed PT, Khajuria A. The effect of smoking on COVID-19 severity: A systematic review and meta-analysis. J Med Virol 2021 Feb;93(2):1045-56.

54. Karanasos A, Aznaouridis K, Latsios G, et al Impact of smoking status on disease severity and mortality of hospitalized patients with COVID-19 infection: a systematic review and meta-analysis. Nicotine Tob Res 2020 Aug 24;22(9):1657-9.

55. Farsalinos K, Barbouni A, Niaura R. Systematic review of the prevalence of current smoking among hospitalized COVID-19 patients in China: could nicotine be a therapeutic option? Intern Emerg Med 2020 Aug;15(5):845-52.

56. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. J Clin Invest 2007 Feb;117(2):289-96.

57. Ulloa L. The vagus nerve and the nicotinic anti-inflammatory pathway. Nat Rev Drug Discov 2005 Aug;4(8):673-84.

58. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med 2004 Nov 8;164(20):2206-16.

59. Huttunen R, Heikkinen T, Syrjänen J. Smoking and the outcome of infection. J Intern Med 2011 Mar;269(3):258-69.

60. Conti P, Ronconi G, Caraffa A, et al Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents 2020;34(2):327-31.

61. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2020 May;55(5):105954.

62. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020 Mar 28;395(10229):1033-4.

63. Feldmann M, Maini RN, Woody JN, Holgate ST, Winter G, Rowland M, et al Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet 2020;395(10234):1407-09.