




Impact of Smoking on COVID-19 Symptoms in Non-Vaccinated Patients: A Matched Observational Study from Qatar

Mohammad Z Haider ¹, Amna Al-Mannai¹, Sally Al-Sirhan¹, Ahmed Elsabagh¹, Nasser Nasser¹, Noora Al-Quraishi¹, Amr Ouda¹, Khadija Erradi¹, Anas A Ashour ², Ishita Gupta^{1,3}, Jazeel Abdulmajeed⁴, Hamad E Al-Romaihi⁴, Devendra Bansal⁴, Omran AH Musa⁴, Elmoubasher Abu Baker Abd Farag⁴, Mohammed HJ Al-Thani⁴, Ala-Eddin Al Moustafa ^{1,3,5}

¹College of Medicine, QU Health, Qatar University, Doha, Qatar; ²Department of Internal Medicine, Hamad Medical Corporation, Doha, Qatar; ³Biomedical and Pharmaceutical Research Unit, QU Health, Qatar University, Doha, Qatar; ⁴Ministry of Public Health, Doha, Qatar; ⁵Biomedical Research Centre, Qatar University, Doha, Qatar

Correspondence: Ala-Eddin Al Moustafa, College of Medicine, QU Health, Qatar University, PO Box 2713, Doha, Qatar, Tel +974 4403 7817, Fax +974 4403-3333, Email aalmoustafa@qu.edu.qa

Purpose: Predisposition to acute illness from COVID-19 is suggested to correlate with cigarette smoking as it augments the risk of developing cardiovascular and respiratory illnesses, including infections. However, the effects of smoking on COVID-19 symptoms are not well described and controversial. In this study, we aim to explore the associations between smoking and COVID-19 symptoms.

Subjects and Methods: A cross-sectional study using the Ministry of Public Health (MoPH), Qatar database was administered to a Qatari population with confirmed COVID-19 disease who filled in pre-defined phone-call questionnaire between 27th February 2020 and 31st December 2020. We analyzed 11,701 non-vaccinated COVID-19 individuals (2952 smokers and 8749 non-smokers) with confirmed RT-PCR test results. The association of smoking and the presence of symptoms as well as patient characteristics was calculated using Pearson's Chi-square and Fisher's exact tests, adjusting for potential covariates.

Results: Compared with the non-smokers, symptomatic COVID-19 infection is significantly higher in smokers. In addition, we found fever as the most common symptom developed in COVID-19 patients followed by cough, headache, muscle ache, and sore throat. As compared to other symptoms, association of smoking with chills and abdominal pain was less evident ($P < 0.05$ and $P < 0.001$, respectively). However, both groups showed similar rates of developing cough.

Conclusion: In conclusion, smoking is associated with COVID-19 symptoms frequency in non-vaccinated patients; nevertheless, further investigations are necessary to understand the mechanism of this association which could generate new targets for the management of COVID-19 in smoker patients.

Keywords: COVID-19, smoking, frequency, Qatar, symptoms

Introduction

Coronavirus disease 2019 (COVID-19), is a severe respiratory illness that is highly infectious, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).¹ It is evident that SARS-CoV-2 infection leads to multi-organ disease, with a high prevalence of acute respiratory distress syndrome (ARDS) and digestive tract complications.² COVID-19 has a wide range of clinical symptoms ranging from asymptomatic to multi-organ dysfunction, and is classified into mild, moderate, severe, and critical based on the severity of its manifestation.³ The most common symptoms of COVID-19 include fever, cough, diarrhoea, and fatigue.³ Moreover, aged individuals as well as those who are immunocompromised, comorbid patients, and smokers are at a higher risk of casualty.^{4,5}

Smoking is a known to trigger for respiratory tract inflammation, allergy, epithelial cells permeability, mucus development, and defective muco-ciliary clearance.⁶ Earlier studies reported that smoking practices elevate the risk of

several bacterial and viral respiratory infections and correlates with worst outcomes in infected individuals.^{7–9} Smoking is a well-recognized risk factor for various respiratory and cardio-metabolic diseases, including chronic obstructive pulmonary disease (COPD) and bronchial asthma.^{10,11} In comparison to non-smokers, acute or chronic smokers can develop infection, tuberculosis, bacterial pneumonia, ARDS^{12–14} with severe complications^{14–16} and present with several co-morbidities, including emphysema, atherosclerosis, and immune dysregulation,¹⁷ thus, promoting the onset and progression of COVID-19. Nevertheless, the role of smoking in COVID-19 remains controversial and understated.^{14,18–21} As some studies demonstrated an association between smoking and COVID-19 severity,^{16,22} while others failed to report such a correlation.^{23,24} As such, a previous report across acute care hospitals and associated outpatient clinics found smoking as an independent risk factor for COVID-19 hospitalization,²⁵ another meta-analysis described smoking as a risk factor for the development and progression of severe COVID-19.^{26,27} In contrast, a study by Farsalinos et al,²⁰ found smoking prevalence relatively lower in COVID-19 patients.

Although, the effects of smoking on COVID-19 symptoms vary and are not well-described in literature, especially in Qatar, despite the high prevalence of smoking; we herein explored the correlation between smoking and COVID-19 symptoms in the population of Qatar. Our study pointed out that smoking is associated with symptomatic COVID-19 infection. The results of this study can help in understanding the correlation between smoking and COVID-19 symptoms, however, further studies are needed to investigate the mechanism behind this association.

Materials and Methods

Sample Collection

This is a matched cross-sectional study conducted using the Ministry of Public Health (MoPH), Qatar database. MoPH gathers de-identified information from all confirmed COVID-19 patients and stores the data in their electronic database. Between 27th February 2020 and 31st December 2020, a total of 105,745 patients were confirmed to have COVID-19 and were included in the database. Our study included all adult patients (≥ 18 years) with RT-PCR-confirmed COVID-19 infection. The study was approved by the MoPH institutional review board (IRB: ERC-826-3-2020) with waiver of informed consent and Qatar University IRB. The authors had no direct contact with any of the participants.

All patients filled a pre-defined phone-call based forms that included “yes/no” questions about smoking status, COVID-symptoms, and comorbidities. COVID-19 symptoms included in the questionnaire were fever, chills, cough, shortness of breath, headache, muscle ache, sore throat, diarrhoea, and abdominal pain. Smoking status was defined as either active smoker or non-smoker with no further classification based on the number of cigarettes. All non-smokers were considered with no previous history of smoking. Subjects who identified themselves as smokers were matched in a 1:3 ratio with non-smokers based on age, gender, nationality, and known comorbidities. A total of 2952 smokers were extracted from the database and were matched with 8749 non-smokers. None of these patients had received any dose of the COVID-19 vaccine.

Subjects were excluded if COVID-19 was confirmed by methods other than RT-PCR, had active or prior cancer, were immunocompromised, were receiving immunosuppressive drugs or had missing demographic data (age, gender, nationality, smoking status, and symptoms).

Statistical Analysis

Pearson's Chi-square and Fisher's exact tests were used to compare the presence of symptoms and the characteristics between the two groups. Continuous variables were expressed as mean \pm standard deviation (SD) while categorical variables were presented by the count and percentage. All statistical analyses were carried out using Stata Statistical Software: Release 16 (College Station, TX: StataCorp LLC). Matching was performed using SPSS Fuzzy Case Control Matching extension. Two-tailed P-values of less than 0.05 was considered statistically significant.

Results

This study included 11,701 patients, of whom 2952 were smokers and 8749 were non-smokers. The two groups were matched based on age, gender, nationality, and comorbidities. Hence, both groups had similar characteristics. The mean

Table 1 Baseline Characteristics of Study Participants Based on Their Smoking Status. Data are Presented as Mean \pm Standard Deviation or as Number of Subjects (Percentage)

Characteristics	Smokers N= 2952 (25.23)	Non-Smokers N= 8749 (74.77)	P value
Age (years)	34.53 \pm 9.631	34.44 \pm 9.618	
Male sex	2872 (97.3)	8513 (97.3)	
Nationality			
Indian	745 (25.2)	2229 (25.5)	
Qatari	448 (15.2)	1327 (15.2)	
Other	2504 (59.6)	7422 (59.3)	
Comorbidities			
Diabetes	186 (6.3)	531 (6.1)	<i>0.650</i>
Cardiovascular	173 (5.9)	486 (5.6)	<i>0.534</i>
Asthma	32 (1.08)	79 (0.9)	<i>0.380</i>
Respiratory	13 (0.4)	32 (0.4)	<i>0.571</i>
Renal	8 (0.3)	15 (0.2)	<i>0.291</i>
Neurological	2 (0.1)	5 (0.1)	<i>0.839</i>
Hepatic	3 (0.1)	4 (0.05)	<i>0.283</i>
Thyroid	6 (0.2)	12 (0.1)	<i>0.428</i>
Prior surgeries	4 (0.1)	2 (0.02)	<i>0.03*</i>

Notes: P value is denoted in italics. *p < 0.05.

age of the study population was 34.5 years with the vast majority being males (97.3%). The most common nationality in this study was Indian which comprises around 25% of the population, followed by Qatari, Nepalese, and Bangladeshi. Diabetes and cardiovascular diseases were the most frequent comorbidities in the study population, each affecting around 6% of the patients. The rest of the comorbidities were rare. Four subjects from the smokers group underwent surgeries previously which was significantly higher than the non-smokers group, where only two had prior surgeries ($P < 0.05$) (Table 1).

As indicated in Table 2, our data revealed that a significantly higher proportion of smokers developed symptomatic COVID-19 infection (75.3%) compared to the non-smokers (62.8%; $P < 0.001$), indicating that smokers have a risk ratio of 1.2 (95% confidence interval: 1.17–1.23) to develop symptoms related to COVID-19 infection when compared to non-smokers (Figure 1).

On the other hand, and as demonstrated in Figure 2, the type of symptoms experienced in relation with smoking status show that fever is the most frequent symptom affecting 45% of confirmed COVID-19 cases, followed by cough, headache, muscle ache, and sore throat. Less frequent symptoms, present in less than 10% of patients, include chills, shortness of breath, diarrhoea, and abdominal pain. Smoking is associated with a significantly higher rate of developing all types of symptoms except cough, as both groups showed similar rates of developing cough (Table 2). On the other hand, the association of smoking with chills and abdominal pain was less evident when compared to the rest of the symptoms ($P < 0.05$ and $P < 0.001$; respectively) (Table 2).

Discussion

In this investigation we explored for the first time the correlation between smoking and COVID-19 symptoms frequency in the population of Qatar. Our data revealed that current smoking is associated with a risk of developing symptoms

Table 2 The COVID-19 Symptoms Based on Patients' Smoking Status. Data are Presented as Number of Subjects (Percentage)

Symptoms	Smokers N= 2952 (25.23)	Non-Smokers N= 8749 (74.77)	P value
Any symptom	2222 (75.3)	5495 (62.8)	< 0.001
Fever	1435 (48.6)	3784 (43.3)	< 0.001
Cough	936 (31.7)	2650 (30.3)	0.148
Headache	894 (30.3)	1899 (21.7)	< 0.001
Muscle ache	820 (27.8)	1796 (20.5)	< 0.001
Sore throat	653 (22.1)	1601 (18.3)	< 0.001
Chills	236 (8.0)	553 (6.3)	< 0.05
Shortness of breath	225 (7.6)	506 (5.8)	< 0.001
Diarrhea	174 (5.9)	358 (4.1)	< 0.001
Abdominal pain	151 (5.1)	357 (4.1)	< 0.05

Note: P value is denoted in italics.

Abbreviations: ACE2, angiotensin converting enzyme 2; ANG, ACE/angiotensin; ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IPF, idiopathic pulmonary fibrosis; MoPH, Ministry of Public Health; nAChRs, nicotinic acetylcholine receptors; qSOFA, quick sequential organ failure assessment; RAS, renin angiotensin system; RT-PCR, reverse-transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SPSS, Statistical Package for the Social Sciences; TNF- α , tumor necrosis factor-alpha; TMPRSS2, transmembrane serine protease 2.

suggestive of COVID-19, as well as a greater symptom burden, indicating an impact of smoking on COVID-19 disease frequency. Additionally, amongst patients positive for COVID-19, smokers had a higher symptom burden in comparison to non-smokers.

In our cohort, 97% of COVID-19 patients are males and 3% are females, which concurs with recent studies of COVID-19 infection.^{28–31} Furthermore, in this study, the estimated median age for patients is 34 years which is concordant with previous studies among COVID-19 patients in other countries^{32,33} as well as in Qatar and Saudi Arabia.^{29,30,34,35} As compared to other parts of the world, COVID-19 is found to affect younger populations in the Gulf Region.^{29,30,34} Such a trend is observed in our study, nevertheless, the age-groups effected with COVID-19 range from 15 to 87 years, indicating disease susceptibility across these ages. High infection and severity rates in adult patients are found to be associated with smoking, as seen in previous studies.^{36,37}

Approximately 15% of COVID-19 patients investigated here exhibited various comorbidities as reported in previous studies.^{27,29,38} In this study, we found that both smokers and non-smokers had diabetes (6%), followed by cardiovascular disease (6%) and asthma (1%). This is in concordance with other reports which showed diabetes and/or hypertension as the most common comorbidities.^{27,29,32,34,39–41} However, our findings revealed that smoking had no significant association with diabetes and cardiovascular comorbidities. Along with cardiac and chronic respiratory diseases, lung and chronic kidney diseases are reported as risk factors associated with worse outcomes in COVID-19 patients.^{42,43}

Similar to our data, various cohort studies revealed an association between smoking and COVID-19 disease comorbidity, incidence and mortality.^{14,16,22,27} In this context, smoking is known to damage the vascular endothelial,⁴⁴ a characteristic feature in COVID-19 pathophysiology. A meta-analysis of 13 published Chinese studies pointed out older age (age > 65 years), male gender, and smoking were risk factors for disease progression in COVID-19 patients.⁴⁵ On the other hand, a recent meta-analyses showed significant correlation between smoking and COVID-19 progression.^{27,46} Another meta-analysis based on 15 studies also reported concordant data where 22% of current and 46% of former smokers had severe COVID-19 complications.¹⁴ A recent study by Almazeedi et al⁴⁷ was performed based on a cohort of

Individuals with COVID-19 Symptoms and Smoking Status

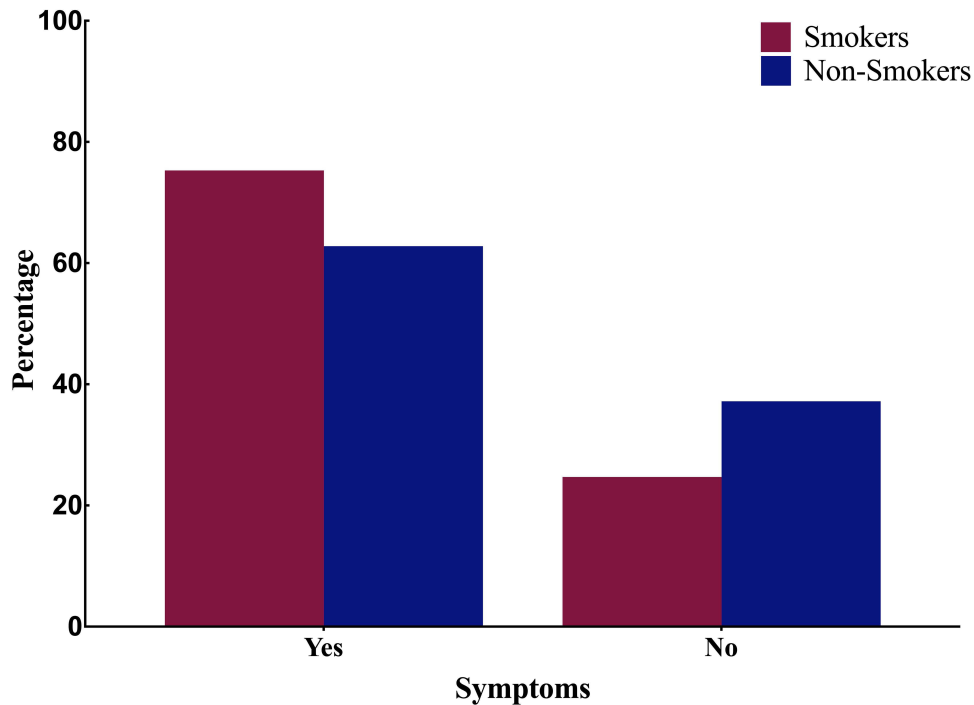


Figure 1 Bar chart showing the percentage of COVID-19 patients who experienced any COVID-19 related symptoms stratified based on their smoking status.

1096 COVID-19 patients in Kuwait and they reported that age > 50 years, smoking, elevated C-reactive protein (CRP) and prolactin levels as well as a quick sequential organ failure assessment (qSOFA) score greater than 0 as risk factors associated with COVID-19 severity. Likewise, a study on 10,713 COVID-19 patients from Brazil also reported smoking and pulmonary disease to augment the risk of COVID-19 severity.⁴⁸ In addition to studies carried out in larger cohorts, studies in small cohorts also showed similar results.^{49,50} Recently, Archie et al⁵¹ postulated a plausible role of smoking on cerebrovascular and neurological dysfunction in COVID-19 patients. Recently, Jiménez-Ruiz¹¹ performed a systematic review and meta-analysis and reported that smoking is a risk factor for a severe COVID-19 infection with a plausibility of developing a more critical condition. Similarly, another investigation showed a clear association between smoking and disease severity, with approximately 3% of deceased patients being smokers.⁵² Moreover, a meta-analysis that included 7 studies found that smokers had twice the risk of developing COVID-19 severity.⁵³

Although, smoking may not essentially elevate the risk of developing COVID-19, the underlying mechanisms involving the biological and inflammatory signaling pathways induced by COVID-19 infection can be severe for smokers.²¹ Likewise, earlier research showed increased susceptibility to COVID-19 infection is attributed to the overexpression of one of the key SARS-CoV-2 receptors, angiotensin converting enzyme 2 (ACE2) receptor.^{4,17,54} Smoking increases susceptibility to COVID-19 infection via the triggering of peripheral nicotinic acetylcholine receptors (nAChRs) present in various organ systems.⁵⁵ Nicotine disrupts homeostasis of the renin angiotensin system (RAS), and overexpresses the ACE/angiotensin (ANG)-II/ANG II type 1 receptor axis, resulting in cardiovascular and pulmonary diseases.⁵⁵ Hence, nicotine can affect the nAChRs and enhance the SARS-CoV-2 host entry.⁵⁶ Moreover, studies reported that smokers with diabetes, cardiovascular disease, COPD, asthma or cancer can enhance the expression pattern of ACE2; hence, they are more susceptible to develop COVID-19 infection and have worst prognosis.^{57,58} Diabetes can overexpress ACE2 expression via hyperinsulinemia along with other mechanisms.⁵⁹ During diabetes, the function of Treg cells is compromised and expression of tumor necrosis factor-alpha (TNF- α) is reduced, further enhancing infections.^{59,60} On the other hand, cardiovascular patients are also prone to COVID-19 disease severity. In hypertensive patients, ACE2 modulators (ACE1 inhibitors, ANG blockers, and thiazolidinediones)

Presence of Different COVID-19 Symptoms in Smokers v/s Non-Smokers

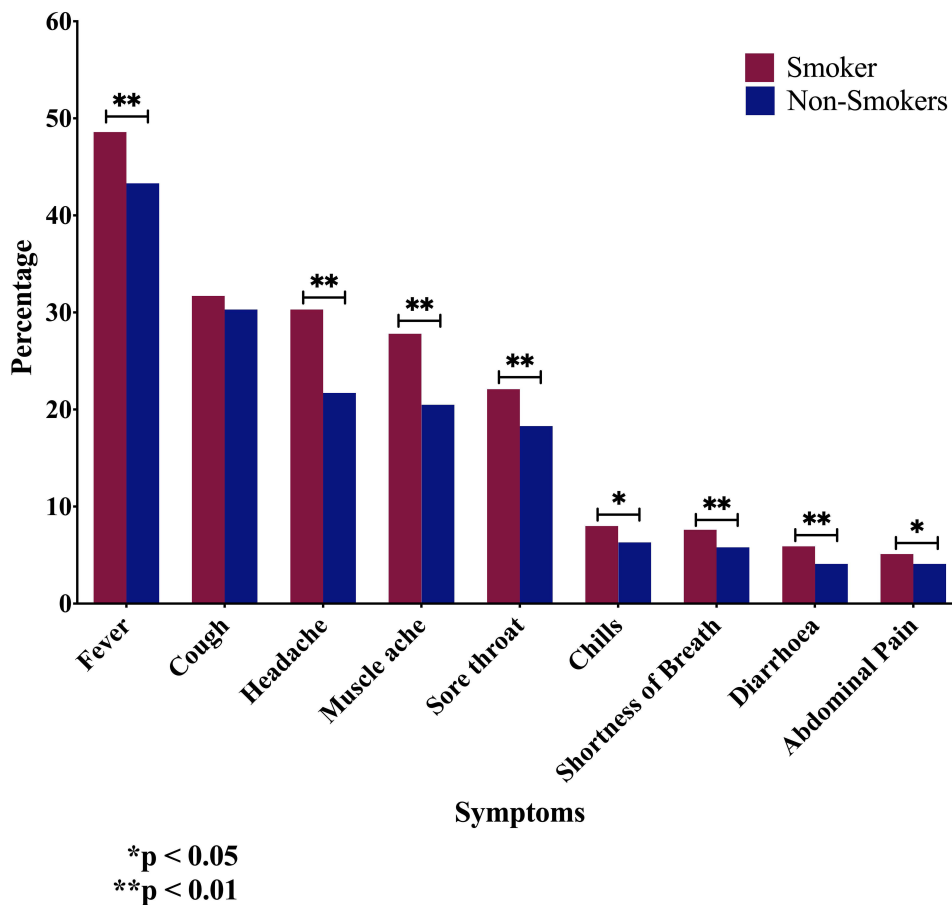


Figure 2 Bar chart showing the rate of developing known COVID-19 symptoms based on the patients' smoking status.

are often prescribed to treat hypertension and can overexpress ACE2;³⁹ a risk factor for the onset of COVID-19 disease. Likewise, the viral capsid of SARS-CoV-2 binds to the ACE2 surface and activates TMPRSS2, (Transmembrane serine protease 2, an androgen-responsive gene highly expressed in men), thus, increased TMPRSS2 expression in men increases their proneness to COVID-19 disease.⁶¹ Furthermore, it has been demonstrated that cigarette exposure can increase the expression pattern of ACE2 and TMPRSS2 in patients with COPD and idiopathic pulmonary fibrosis (IPF),^{17,62–66} in this context, it is important to highlight that COPD is reported as a major risk factor for COVID-19 infection.^{53,67} Smokers suffering from cancer are also found to be at a higher risk of developing COVID-19 infection due to compromised immunity, thus providing an effectual environment for viral replication.⁶⁸

On the contrary, while several studies reported an association between disease severity and smoking,^{16,22} few investigations found no difference or a negative correlation between smoking and COVID-19 severity.^{23,24} Moreover, a recent review reported that current smokers are at a comparatively lower risk of developing COVID-19 as compared to never smokers, however, these findings aim to analyse certain factors that could make the interpretation of these results more complex.¹⁹ Hence, it is necessary to conduct interventional studies in the general population and in patients post-COVID-19 disease. In addition to investigations analysing the correlation between smoking and COVID-19 severity, reports on behavioural changes in tobacco consumption during the pandemic found varying data. While, in USA there was an increase by 41% in tobacco consumption during the onset of COVID-19,⁶⁹ in Italy, smokers had considered quitting.⁷⁰ However, the same study found that former smokers and never smokers wanted to start smoking.⁷⁰ In China and England as well, there was an increase in smoking among smokers and relapsed smoking habits among former

smokers.^{71,72} As of currently, both epidemiological/clinical evidence and in-silico findings indicate that COVID-19 infection is a nAChR disease that could be prevented and may be controlled by nicotine.^{56,73} Smoking was suggested to exert a protective measure as its nicotine acts as a nAChR agonist and competes with the SARS-COV-2 for the binding site, hence leading to a decline in accessible viral adhesion sites.⁷⁴ Nevertheless, the plausibility of nicotine displaying protective effect against COVID-19 can be partially masked by smoking-related toxicity. In addition, abrupt cessation of nicotine consumption when smokers are hospitalized need further validation in laboratory studies using nicotine-based pharmaceutical products. Considering the limited and contradicting past investigations available on this topic, we hypothesized a strong association of smoking with the risk of developing respiratory diseases. However, coughing, which is the major respiratory depression symptom was reported in both smokers and non-smokers nearly equally, with only a non-statistically significant difference of 1.4% more for smokers. Moreover, significant differences were reported in other symptoms such as fever, muscle ache, abdominal pain, diarrhoea, headaches, and shortness of breath, all of which are also symptoms of nicotinic overstimulation of the cholinergic system⁷⁵ which is activated by the nicotine in cigarettes and triggers COVID-19 disease.^{76,77}

Although, our present study included a large sample size and points out a strong link between smoking and symptoms development among COVID-19 patients, there are several factors limiting the interpretation of our investigation. The present results remain limited by the available information. In particular, detailed data on possible sources of exposure to smoking are lacking. The data was self-reported by patients via phone-call based forms. The patients reported their symptoms through this form. Additionally, there was no classification based on the number of packs smoked per day. Thus, heavy smokers and light smokers were grouped together. Moreover, patients who reported as non-smokers are assumed to have no history of smoking and thus, we believe that further studies are needed to investigate the consequences and underlying mechanisms of smoking and its association with COVID-19 infection and its frequency in patients. In addition to cigarette smoking, effects of waterpipe and electronic cigarette use on COVID-19 transmission, clinical progression and frequency of COVID-19 should be further studied. Lastly, the association between COPD frequency and COVID-19 should be also analysed.

Conclusion

In conclusion, our present study demonstrates an association between smoking and COVID-19 symptoms frequency in non-vaccinated patients. While we believe that further studies in a larger cohort are required to clearly determine the association between smoking and COVID-19 symptoms which can help in controlling COVID-19 induced morbidity and mortality especially in smoker patients. Nevertheless, and based on our present study it is evident that discontinuing of smoking practices should be contemplated as a part of the strategies to address COVID-19 infection management in the international arena, as smoking increases both the likelihood of symptomatic disease and the frequency of disease.

Ethics Approval and Consent to Participate

Patient consent was waived as this was a matched cross-sectional study conducted using the Ministry of Public Health (MoPH), Qatar database. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Ministry of Public Health (IRB: ERC-826-3-2020).

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Disclosure

The authors report no conflicts of interest in this work.

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