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Less disease severity of COVID-19 among smokers: An indication of investigating nicotine as preventive measure

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Abstract: The study was aimed to mention the epidemiology of smoking in Pakistani COVID-19 infected patients along with the disease severity, oxygen dependency and fatality rate. A cross sectional epidemiological study was carried out on 555 confirmed cases of COVID-19 infection. The median age was 47±16 years. 59% were male and 41% were female. Most of the patients (97.5%) survived, while only 2.5% expired. 25.6% patients required the oxygen. Total 17 (3%) COVID-19 patients with age 20-75 years were identified as smokers. No mortality was observed in smokers. The 1.4% smokers presented with mild disease, 1.2% with moderate disease and 0.4% had severe disease. According to Chi-Square test, there existed an insignificant difference (p- value: 0.38649) between smokers and non-smokers in disease severity levels. Smoking is a precursor for countless diseases, but it behaved differently in COVID-19 infected patients, as its prevalence was significantly low. We found no significant variation of the disease severity among the smokers and non-smokers. Profound experiments should be conducted to recommend whether nicotine can be used as a protective agent to negate COVID-19 infection.

Keywords: COVID-19 infection, nicotine, nitric oxide (NO), cigarette smoking, fatality rate.

INTRODUCTION

Smoking is a known public health issue worldwide (Elders *et al.,* 1994). Intake of tobacco can lead to 8 million deaths each year. It is a risk factor for a number of non-communicable diseases like cardiovascular problems (Erhardt, 2009), peripheral vascular diseases, cerebrovascular accidents (Chitrah *et al.,* 2019), diabetes (Chang, 2012), hypertension, chronic obstructive pulmonary diseases (Chatila *et al.,* 2008) and many malignancies (Doll *et al.,* 2004). This is the reason why smoking cessation leads to countless health benefits. In the recent days, many unique features about the COVID-19 virus, its impact on human body and human behaviors including smoking are being discussed (Xiao *et al.,* 2020; Mattiuzzi and Lippi, 2020). According to WHO (World Health Organization) estimates, over 1.1 billion people worldwide are smokers. The current study was aimed to assess the frequency of smokers in Pakistani COVID-19 infected patients along with the disease severity, oxygen dependency and fatality rate. There are many hazardous components in cigarette. Nicotine is among 95 chemicals of the cigarette (Fowles *et al.,* 2000). This component is also used as a medication to aid quit smoking, though it is an addictive substance depending upon the levels in the body (Benowitz and Jacob, 1986). In the ongoing SARS-COV-2 pandemic, there are queries that what will be the fate of smokers, because this infection mainly affects the lungs. Will they have to face more severe form of COVID-19 infection, or would they remain in the same status as would be the nonsmokers? Will nicotine in their body can help them in fighting COVID-19 infection, as it has an effective role in down-regulating the angiotensin-converting enzyme2 (ACE2) receptors? (Yue *et al.,* 2018; Oakes *et al.,* 2018). The ACE2 receptors are responsible for entry of SARS-CoV-2 infection in the body through lungs (Oakes *et al.,* 2018). Cattaruzza *et al.,* (2020) discussed the tobacco smoking as a risk factor linked with COVID-19 infection. They have mentioned that tobacco smoking is a risk factor because it can cause a 'dose-dependent' up-regulation of ACE2. The real question is that some studies are reporting a lower incidence of smokers with COVID-19 infection (Tsigaris *et al.,* 2020; Farsalinos *et al.,* 2020). The down/up regulation roles of ACE2 receptors in COVID-19 disease severity and susceptibility are under discussion (Blake *et al.,* 2020; Cai and Bulk, 2020; Imai *et al.,* 2008; Imai *et al.,* 2005). These ACE2 receptors are also present in small intestine, kidney, heart, blood, spleen, bone marrow, brain and many more places. Another important aspect is that these ACE2 receptors are up-regulated by the hormone estrogen, which is more prevalent in females and children. Therefore, less severity of SARS-CoV-2 disease is reported in females and children (Bukowska *et al.,* 2017).

As a cholinergic agonist, the nicotine also plays an important role in the actions of proinflammatory markers that act through the cholinergic anti-inflammatory pathways (Xu *et al.,* 2020), like tumor necrosis factor (TNF), Interleukin -1(IL-1) and Interleukin-6 (IL-6), which are the causes of cytokine storm in SARS-CoV-2.

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The treatment with anti-IL-6 and anti TNF are already mentioned in clinical trials (Zhou *et al.,* 2012; Feldmann *et al.,* 2020; Zhao, 2020). Besides nicotine, there is another component called nitric oxide (NO), which is present in cigarette smoke (in concentration of 250-1,350 ppm). It is a potent pulmonary vasodilator and also being recommended to lessen the risk of severe COVID-19 in smokers (Hedenstierna *et al.,* 2020). The favorable impacts of inhaled nitric oxide in the spontaneously breathing patients of COVID-19 infection have been noted by Parikh *et al.,* (2020).

MATERIALS AND METHODS

A cross sectional epidemiological study was carried out during 1st June to 30th June, 2020 and included confirmed COVID-19 (n=555) infected patients presented in the outpatient clinic of Jinnah Hospital Lahore, Pakistan. The sampling was non-probability consecutive sampling. All patients' data was included with informed consents.

Inclusion & exclusion criteria

The patients of both genders, with age between 18 to 85 years who diagnosed with COVID-19 infection via. PCR /antibody tests were included. The patients with critical condition of COVID-19 were excluded who required the ICU care at presentation.

Clinical information

The clinical information of patients (smokers/non-smokers) was recorded on a standardized proforma about smoking habits (present/past smokers & number of pack years), severity of disease (mild/moderate/severe), requirement of oxygen at the time of first presentation, fatalities, rate of recovery. The severity of COVID-19 disease was assessed according to WHO interim guidelines (2020).

Ethical approval

A prior ethical approval was taken before the conduction of the study. The study was conformed to the Institutional Ethical Standards

STATISTICAL ANALYSIS

The data was collected, compiled and analyzed statistically on IBM SPSS Version 24. The quantitative data like age, were expressed in mean. The qualitative variables like gender and history of smoking were expressed in frequency and percentage. The stratification was done for age, gender, history of smoking and fatalities. A Chi-square test was applied to see the significance or non-significance of diseases severity (mild/moderate/severe) between smokers and non-smokers. The p-value less than 0.050 was considered statistically significant.

RESULTS

Age & gender distribution

Among 555 patients, the majority of the patients (118) were between 40 to 49 years. The median age of the patients was 47±16 years. Out of 555 cases 327 patients (59%) were male, while remaining 228 (41%) were female. Most of them are alive that is, 541 (97.5%) patients, while 14 (2.5%) have been expired. Among the expired patients, the 2 patients were female, while rest 10 patient were male.

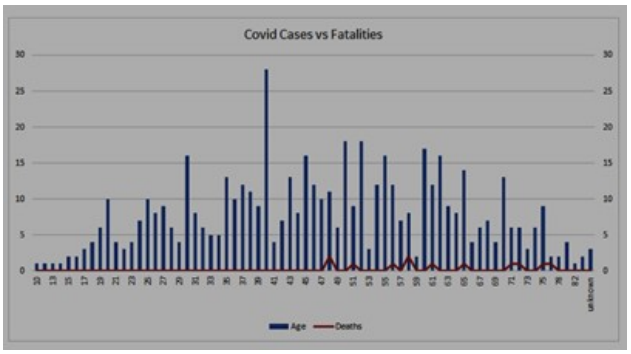

Fig. 1: COVID -19 Cases vs. Fatalities

COVID-19 disease severity and oxygen requirement

On the basis of severity, overall, 246 cases (44.3%) had mild disease, 170 cases (30.6%) had moderate disease and 139 (25%) had severe SARS-CoV-2 infection. The 142 patients (25.6%) required the oxygen at the time of presentation. Maximum recovery was observed in following age groups: 10-19 years, 20-29 years & 30-39 years (table 1).

Distribution of smokers & non-smokers with covid-19 disease

A total of 17 patients (3%) with age from 20-75 years were identified as cigarette smokers. Among them, the 13 patients (2.3%) were identified as chain smokers and 4 patients (0.7%) had a history of smoking. Four cases (0.7%) had history >20 pack years and 13 cases (2.3%) had <20 pack years. Among the cigarette smokers, 15 patients (2.7%) were male and 2 patients (0.4%) were female. There was no fatality among the cigarette smokers (n=17). Eight smokers (1.4%) presented with mild disease, 7 (1.2%) smokers presented with moderate disease and 2 (0.4%) had severe disease and required oxygen at the time of presentation (table 2). Out of the 12 patients that expired, all were non-smokers with age ranged from 48 to 76 years who were presented with severe symptoms prior to death. Average age of deceased patients was 63.3 years. fig. 1 shows the COVID -19 cases vs. fatalities.

Chi-Square (χ^2) Test

The data of COVID-19 diseases severity (mild/moderate/severe) was stratified in two groups, i.e.,

Table 1: COVID-19 cases according to age groups, number of cases, fatalities and recovery rates

Age Groups (years)	No. of Cases (n=555)	No. of Fatalities	Recovery Rate (%)
10-19	21	0	100
20-29	65	0	100
30-39	95	0	100
40-49	118	2	98.26
50-59	105	4	96.19
60-69	97	2	97.94
70-79	47	4	91.49
80+	7	0	95

Table 2: Background Information of COVID-19 among cigarette smokers (n=17, 3%)

No. of Active Smoker	No. of Past Smoker	No. of Male Patients	No. of Female Patients	Fatality
13 (2.3%)	4 (0.7%)	15(2.3%)	2(0.7%)	None

Table 3: Distribution of COVID-19 severity in smokers & non-smokers

	Mild	Moderate	Severe	p value	Chi-Square (χ^2)
Smokers (n=17; 3%)	8 (1.4%)	7 (1.2%)	2 (0.4%)	0.38649 (the result is not significant at $p<0.05$)	1.9013
Non Smokers (n=538; 97%)	238 (44.2%)	163 (30.3%)	137 (25.4%)		
Total (n=555)	246 (44.3%)	170 (30.6%)	139 (25%)		

smokers and non-smokers and applied Chi-Square test. There existed an insignificant difference (p- value: 0.38649) between smokers and non-smokers in disease severity levels (table 3).

DISCUSSION

In the current pandemic of COVID-19, it has been hypothesized that smokers are more vulnerable and may suffer more due to their baseline lungs status. The study was aimed to determine the frequency of cigarette smoking in Pakistani COVID-19 cases including disease severity and influence on outcome in terms of fatality. Our study setting reported only 3% cigarette smokers mainly in mild condition among 555 cases of COVID-19. No fatality was reported among the cigarette smoker patients of COVID-19 infection. Overall, among all smoker & non-smoker patients (n=555), the recovery rate was good (97.5%), more male patients (59%) were infected in mild condition (44.3%) and only 25.6% required the oxygen at the time of presentation. Guan *et al.,* (2020) also reported that more male patients (59%) were infected from COVID-19. Similarly, up to 66%, the male predisposition was also found in epidemics SARS (2003) and MERS (2012) (Walter and McGregor, 2020). In China, it was also found that more men was infected with COVID-19 as compared to women (Cattaruzza1 *et al.,* 2020). In male patients, the fatality rate was 22% and in female patients, it was found 13% (Schurz *et al.,* 2019). The exact reason of low fatality rate in females is still needed to be ascertained but some studies explained that due to the hormonal differences, as the X chromosome contains more genes regarding immune system (Schurz *et al.,* 2019). Interestingly, the gene is responsible for ACE2 receptors expression is also present on X chromosome (Patel *et al.,* 2014). The outcome of COVID-19 shows a wide range of impacts depending upon the disease severity. We reported fatality rate of 2.1% in all patients. The variation in the outcome of disease is usually based mainly on the initial presentation. If the patient is presenting in severe disease initially and is oxygen dependent with high inflammatory markers (CRP, LDH, and serum ferritin levels), higher body temperatures or respiratory failures, there will be more chances of an adverse outcome.

Smoking and nicotine play an important role in the ACE2 receptors expression in the lungs and these act as physiologically relevant receptor for a cellular entry for SARS-CoV-2 S protein, which have an impact on efficiency of virus infectivity (Zhou *et al.,* 2020). During COVID-19 pandemic, the issue of smoking and respiratory illnesses is a debatable issue as corona virus is an RNA virus, which predominantly affects the lungs. Many studies done on COVID-19 declared that there is a great danger to smokers (Liu *et al.,* 2020; Reddy *et al.,* 2020; Gülsen *et al.,* 2020). Reddy *et al.,* (2020) mentioned that the smoking leads to structural, mechanical (mucociliary) and alteration in the immunological response of the respiratory tract and this all make the patient more vulnerable to both bacterial as well as viral infections. Many studies reported a low

prevalence of smokers with COVID-19 infection (Tsigaris *et al.,* 2020; Farsalinos *et al.,* 2020). We also did not find a statistically significant difference between smokers and non-smokers in disease severity levels. Lippi and Henry (2020) mentioned that the active smoking was not associated with the severity of COVID-19 infection. The results of current study also showed that there was no significant difference in the disease pattern and severity among the present or past smokers. We found no effect of difference of number of pack years of smoking between active and past smokers. Most of our smokers COVID-19 patients were found in the mild conditions. We found no significant variation of the diseases among the smokers, because, we found zero fatality rate in them. Alqahtani *et al.,* (2020) has reported a low incidence of COPD cases in COVID-19, although, this infection is also linked with the severity of the disease as well as mortalities. However, the active smokers have been mentioned as more vulnerable to COVID-19 infection as compared to the former smokers. Patanavanich and Glantz (2020) mentioned that smoking is a risk factor of pulmonary and other infectious diseases. Although, some studies reported a low prevalence of smokers with COVID-19 infection, however, the meta-analysis of Patanavanich and Glantz (2020) reported a significant association between the smoking and the progression of COVID-19. They also mentioned that the smokers can have higher odds of COVID-19 infection as compared to non-smokers. Therefore, this prevalence is debatable and needs an urgent attention for further research. A European study investigated the association between the incidence of smokers and COVID-19 infections. Tsigaris *et al.,* (2020) identified a negative association between smoking and incidence of COVID-19 in 38 European countries. They also mentioned that this association may not be a true causal and nevertheless smoking is not recommended to use it as any preventive measure. It is also possible that several studies found the under-representation of the numbers of smokers among COVID-19 cases. Therefore, more large studies are required to affirm the facts. Although, we, as well as other scientists are not recommending or supporting the idea of smoking as treatment modality, but, some profound and potential experiments can be conducted to recommend the use of nicotine as a protective agent to negate the impacts of COVID-19 infection.

CONCLUSION

A considerable difference was observed in the number of cases as smokers (3%) versus non-smokers (97%). The exact reason for this difference needs to ascertain. Cigarette smoking was not found associated with the disease severity, however, nothing concludes the favors of smoking. We should investigate the role of nicotine or nitric oxide (NO) as a drug-treatment in the COVID-19 virus infection.

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