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CORRELATION BETWEEN SMOKING AND SEVERITY OF SARS-COV-2 INFECTION AMONG IRAQI POPULATION

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Abstract:

Smoking regarded an important predisposing factor for cardiovascular and pulmonary disease and known risk factor for severe outcomes and death result from respiratory infection. This study aims to quantify the correlation between smoking and COVID-19 disease progression. This cross-sectional study done on 200 COVID-19 patients have been recruited from Al-Diwaniyah teaching hospital, Iraq in period of 1st of November, 2020 to the end of February, 2021, to assess the effect of smoking on susceptibility and/or clinical symptoms of SARS-COV2 infection. The study reveals no significant correlation between smoking and susceptibility nor with severity of disease (p = 0.231). During the time of this study, no strong evidence was available suggest that smoking have an effect on severity of SARS-COV2 infection. Smoking is not a risk factor for having bad COVID-19progression. even if one might have anticipated the opposite. Thus, the epidemiological data seem to question the role of coexisting active smoking as a risk factor for COVID-19 pneumonia.

Keywords: ACE-2 receptor; Active smoking; Iraqi population; SARS-COV2 infection

INTRODUCTION

During 2002-2003 the world have been threatened by emerging a new pandemic infectious disease caused by sever acute respiratory syndrome (SARS) virus that spread throughout the world, then in 2011 have been threatened again by middle east respiratory syndrome (MERS) virus (**Prompetchara E *et al.*, 2020)**. Both of these viruses were zoonotic in origin and were characterized as human coronavirus (HCoV) belongs to Beta-Coronavirus genus (**Ye Z *et al.*, 2020)**.

In 17th November, 2019 the world experienced other outbreaks of infectious disease due to emerging of SARS-COV2, the first identified in Wuhan, China. This virus causes respiratory illness with clinical symptoms close related to previous SARS and MERS viruses, rapidly characterized as a new member of Beta-coronavirus genus (**Faver G *et al.*, 2020)**. The virus expanded rapidly all over the world and in January 2020, the World Health Organization (WHO) declared this disease as a pandemic and officially named as 2019 novel coronavirus (2019-nCov) disease (**Keni R *et al.*, 2020)**.

Comparing SARS-COV2 with SARS and MERS, it appears to be more readily transmitted, it has been spread across the world and became an important health crisis and panic issue on a global level. COVID-19 disease was first documented in Wuhan, Hubei city, China at 17th December, 2019, then it had been extended more rapidly throughout the world in a dramatic manner causing a devastinting impact in most of the countries the World Health Organization (WHO) characterized this disease as a public health crises on 30 January, 2020 and declared the COVID-19 as a novel pandemic at 11th of March, 2020. Outbreak of COVID-19 is corrupt all over the world due to inadequate risk assessment, the pandemic disease has entered a new dangerous phase, since when it compared with sever acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), COVID-19 have been extended more rapidly and easy from human-to human (**Li Q, 2020)**. With this emerging health battle, the WHO has strategized to interrupt human to human contact, isolate patients at early stages and communicate information correctly to the public (**Coutard B 2020); Kannan U, 2020).** Pathological consequences of SARS-COV2 infection exhibit a wide variant of clinical symptoms that range from asymptomatic disease, mild or common cold, to moderate and severe outcomes (**Mo P *et al.*, 2020).** The most common sign and symptoms of COVID-19 are: fever, headache, dry cough, shortness of breath, myalgia and fatigue (**Chen N *et al.*, 2020).** Some patients presented with gastrointestinal outcomes such as: vomiting and diarrhea**.** Major complications that can be observed in severe cases are: SARD, acute lung injury (ALI), kidney injury, arrhythmia

and cardiomyopathy, multi-organ failure especially in elderly people, thrombosis and pulmonary embolism which always associated with higher level of fibrinogen and D-dimer (**Azer S, 2020)**.

Delta variant show a kind of different symptoms than that of wild stain, and may give a mistake hint as a bad cold and patients will not realize that they need to be isolated or hospitalization. The most common notable clinical signs include sore throat, headache, fever and runny nose without loss of smell and/or taste (**Hu Z *et al.,* 2022).** Infection with delta strain will increase the risk of hospitalization (about double of alpha) but with lower mortality rate and the patients are likely to develop pneumonia and require O2 more than the wild strain (**Ong S, 2021).** Regarding omicron variant's symptoms, are often less severe than with delta variant which often includes: fever, scratchy throat, general sickness and tiredness which often seen in common cold. These symptoms make it hard to be diagnosed **(Krishnan, A *et al*., 2021).** Severity of COVID-19 infection and risk of death is always correlated with several underlying risk factors like: age, gender and chronic disease that affect immune system function causing development of severe symptoms and eventually death (**Yang J. *et al*., 2020),** the comorbidities like; cardiovascular disease, diabetes, chronic lung and kidney disease, malignancy, obesity and immune compromised cases are the most common underlying factors have an association with deteriorated clinical outcomes and critical COVID-19 (**Richardson S. *et al*., 2020); Caussy C. *et al*., 2020).**

The smoking considered one of the important factors that causes a disease and contributed to eight million deaths around the world. Both SARS-COV2 infection and smoking affect primarily the respiratory system. Smoking affects nearly every organ of the body, causes various diseases. The smoker people may already have a respiratory and pulmonary illness or reduced lung capacity, which would greatly increase the risk of serious disease. For the smoker persons with a respiratory disease, the evidence has shown that the chance to get an infection is higher than in those who are non-smoker.

Regarding the smoking as a risk factor for predisposing a severe SARS-COV2 infection, the opinions split-up between supporters and oppose it. Many of recent observational reports found a low percentage of smokers have been infected with SARS-COV2. These observations have made the scientists to believe that smoking could be a protective behavior to face SARS-COV2 infection. On the other hand, there are studies that are opposed to these conclusions.

MATERIALS & METHODS

Study Design

This cross- sectional study was conducted on 200 patients (150 males and 50 females) were recruited from Al-Diwaniaya Teaching Hospital/Quarantine unit in Al-Qadisiyah governorate. The age ranged between 10-66 years old. The work was done during the period from 1st of November, 2020 to the end of February, 2021. The infected individuals with COVID-19 were divided into two groups depending on the severity of sign and symptoms; the 1st group involved 148 infected persons with mild/moderate sings, the 2nd group contained 52 persons who had been infected with severe symptoms as shown in fig. 1.

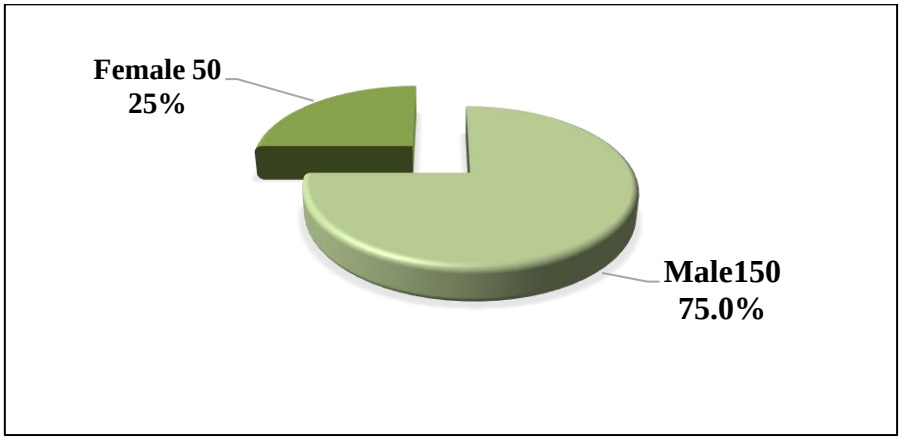

Figure 1: Pie chart of frequency distribution of SARS-Cov-2 patients according to gender

All the individuals who had been infected with SARS-COV2 were included within study and both genders had been involved. The study was corresponded with ethics of Al-Diwaniaya teaching hospital and verbal informed had been obtained from all patients participated in the study. Al demographic characteristics are illustrated in table 1.

Table 1: Mean age and frequency distribution regarding age and gender of SARS-COV2 patients among mild/moderate and severe clinical disease

	Mild/moderate ***n*** **= 148**	**Severe** ***n*** **= 52**	**Total** ***n*** **= 200**	***p***
Age (years)				
Mean ±SD	41.34 ±13.16	44.88 ±14.50	42.26 ±13.54	0.253 I NS
Range	10- 66	20- 64	10- 66	
≤ 20, *n* (%)	4(2.7 %)	2 (3.8 %)	6 (3.0 %)	0.769 C NS
21-40, *n* (%)	66 (44.6 %)	18 (34.6 %)	84 (42.0 %)	0.375 C NS
41-60, *n* (%)	68 (45.9 %)	22 (42.3 %)	90 (45.0 %)	0.748 C NS
> 60, *n* (%)	10 (6.8 %)	10 (19.2 %)	20 (10.0 %)	0.068 C NS
Gender				
Male, *n* (%)	118 (79.7 %)	32 (61.5 %)	150 (75.0 %)	0.065 C NS
Female, *n* (%)	30 (20.3 %)	20 (38.5 %)	50 (25.0 %)	

n: number of cases, SD: standard deviation, I: independent samples *t*-test, C: chi-square test, NS: not significant at $p > 0.05$

Inclusion and exclusion criteria

Persons who participate in this study involves both gender and aged were 10 years and above, who have been diagnosed with SARS-COV2 infection via laboratory confirmation of reverse-transcriptase-polymerase chain reaction (RT-PCR) test using nasopharyngeal and/or oro-pharyngeal swabs. The exclusion criteria of the patients include: 1) Uncooperative and not consenting individual. 2) Individuals with asthmatic or other atopic disease. 3) Subjects whom infected with SARS-COV2 and showed no symptoms. 4) Person whom infected with COVID-19 and show negative result of COVID-19 rapid test has been excluded (among mild cases).

Statistical analysis

The data were analyzed by using Statistical Package for Social Sciences (SPSS) software V20 in association with Microsoft Excel 2021. Chi-squared formula have been used to determine the significant associations of measured odd ratio (OR) and 95% of confidence interval (CI). All the statistics were inspected using bilateral probability and if the P value of such estimate were ≤ 0.05, so it is considered a significant value.

RESULTS

The results in table (2) reveals that active smoking was reported in 30 cases (15.0 %) and Ex-smoking was reported in 8 cases (4.0 %) whereas the non-smoker persons were 162 individuals there was no significant association between severity of the disease and smoking state ($p = 0.231$).

Table (2): Frequency distribution of patients regarding to smoking

Smoking	**Mild/moderate** ***n*** **= 148**	**Severe** ***n*** **= 52**	**Total** ***n*** **= 200**	***p***
Not smoker, *n* (%)	124 (83.8 %)	38 (73.1 %)	162 (81.0 %)	0.231 /C NS
Previous smoker, *n* (%)	6 (4.1 %)	2 (3.8 %)	8 (4.0 %)	
Active smoker, *n* (%)	18 (12.2 %)	12 (23.1 %)	30 (15.0 %)	

***n*: number of cases, C: chi-square test, NS: not significant at $p > 0.05$**

DISCUSSION

The smoking considered an interesting factor that exciting different opinions. The results in table 2 reveals that active smoking was reported in 30 cases (15.0 %) and Ex-smoking was reported in 8 cases (4.0 %). The results in this study shows no significant correlation between smoking and susceptibility nor with severity of disease ($p = 0.231$). Linking

with severity, the sever group include 52 patients, the percentage of non-smokers, active smokers and Ex-smokers was (73.1%, 23.1% and 3.8%), respectively comparing with (83.8%, 12.2% and 4.1%), respectively in mild/moderate group. Similar to this result, (Farsalinos et al., 2021) found that among 7162 COVID-19 patients there were 482 patients being smoker (OR = 0.24, 95% CI: 0.19-0.30). Also, they revealed no significant association between smoking and disease severity or with mortality rate (OR = 1.86, 95% CI: 0.88-3.94).

The same thing with (Karanasos et al., 2020), they suggested that no significant association links the smoking with SARS-COV2 severity (OR = 1.40, 95% CI: 0.98-1.98) or with mortality (OR = 1.86, 95% CI: 0.88- 3.94). Among other studies who agree with this original study is, (Vardavas et al., 2020), a reviewer study from China including 140 COVID-19 patients. The results found that among severe patients (n = 58), about 6.9% were former-smoker and 3.4% were active smoker in comparing with mild/moderate patients (n = 82) there was 3.7% a former smoker and no one was a current smoker 0% (OR= 2.23, 95% C: 0.65-7.63, $p = 0.2$). (Guan et al., 2020) also consistent with this result, a largest descriptive study of 1099 individuals with SARS2 infection. 178 patients had severe symptoms, among them 16.9% were smoker and 5.2% were previous smoker in apposite to 926 patients with mild/moderate symptoms: 11.8% were smokers and 1.3% former smokers.

To clarify why smoking considered a protective manner or even not associated with severe illness is; (Cai, 2020) found that smoking may affect the genes responsible for ACE2 receptor expression that causing upregulation of this pulmonary receptors compared with non-smoker patients and reported an increase in goblet cells that produce ACE2R in ever-smoker compared with never-smoker's lung, despite of these finding that seems to be in contrary with the epidemiological data indicating a low prevalence of active smokers among SARS-COV2 infected patients. The explanation of this is cigarette smoke induces epigenetic modifications of the bronchial epithelium causing metaplasia of mucous cells. Since that the mucus cell are the main source of ACE-2 receptor in the lung, this could justify the high level of ACE2 receptor in the lung of smoker individuals. The nicotine itself will stimulate structural changes in ACE2 alleles. These variants will interfere with intermolecular binding of S-protein of the virus with such variants of ACE2 receptor. The nicotine also will interact with many renin-angiotensin system components in many organs causing increase the expression and/or activity of Renin, ACE, AT-1R, while in the compensatory ACE2/Angiotensin (1-7) arm, the nicotine causing down regulation to the expression of ACE2R and AT2R. This action might counter balance the high level of ACE2 receptor that observed by Cai and his colleagues in the lung of the smoker persons. ACE2 knockout mice exposed to smoke of cigar shows increase pulmonary inflammation with activation of metalloprotease which could be in part responsible for activation or modification of ACE2 in smoker's lungs. Even it is possible that nicotine increases ACE2R by pulmonary epithelium and enhance SARS-COV2 entry inside the cell, this does not necessarily translate into a higher risk for COVID-19 pneumonia development (Polverino F, 2020). At the same time the nicotine could be protective against COVID-19 disease due to its anti-inflammatory proprieties to a potential direct interaction between SARS and nicotinic acetylcholine receptor (nACh). In addition to that the mucus cells act as a major source for mucous secretion that provide a primary essential host barrier to inhaled pathogen so prevent invasion of microbes and infection.

In contrast (Alqahtani et al., 2020) showed that the current smokers were at higher risk to develop intensive symptoms with higher mortality rate comparing with former smokers. The study includes 2473 COVID-19 patients, 22% of current smokers and 46% of previous smokers had severe symptoms and the current smokers were 1-45 times more likely to have hard clinical manifestations comparing with non-smokers (95% CI:1.03-2.04), even the mortality rate in current smokers reach up to 38.5%. (van Zyl-Smit et al., 2020) they provided a review and meta-analysis study, they reported that a higher risk to develop severe complications in correlation with smoking relative risk (RR = 1.4, 95% CI: 0.98-2.0) and increased mortality risk in association with current smoking (RR= 2.4, 96% CI: 1.43- 4.04). Another study that opposes our results provided by (Mohsin F et al., 2021) from Bangladesh included 2022 patients, 29.4% of them were heavily smokers. They found a strong relation between smoking and severity of symptoms ($x^2 = 38.88$, $p < 0.001$).

Smoking regarded an important predisposing factor for pulmonary disease thus, it was normal that studies suggest a highly severe case were being among smoker infected persons. This could be related to its important role in upregulation of ACE2 receptor as well as smoking contribute to make symptoms of COVID-19 more severe via activation of peripheral nACh receptor. Activation of nicotinic receptor might lead to enhance protease activation which in turn cause cleave and activation the S-protein of SARS-COV2 that is required for membrain fusion. On the level of immune system, nicotine will induce production of proinflammatory mediators and many studies have been investigated the association between smoking and auto-immune and chronic disease like; SLE, COPD, RA and psoriasis. Nicotine will bind to its nACh receptor on such immune cells like; macrophage and T+B cells and induce immunosuppression effect therefore smoking will alter the development and function of innate cell as well as adaptive immune cells (CD4, CD8, B cells and regT cell) leading to pro-inflammatory response that make the disease more worse. Another hypothesis indicating that smoking causes an increasing of TNF-α lead to increase reactive oxygen species (ROS) accumulation that result in tissue damage.

CONCLUSION

The impact of active smoking on COVID-19 severity is a delicate and complex topic that should be well assessed. The study reveals no significant association between severity of the disease and smoking state. Limitation of the study is low number of patients with severe infection (n=52), compared with patients suffering from mild/moderate infection (n= 148), therefore further study with larger sample size may be required for best evaluation of smoking effect on COVID-19 disease.

RECOMMMMENDATIONS

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