Original Article

Association between Smoking Habits and Outcomes of COVID-19 Patients in Persahabatan Hospital, Jakarta

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Abstract

Background: : Factors related to the severity and the outcome of coronavirus disease 2019 (COVID-19) are emerging subjects of interest to be studied. Smoking has long been known to have a negative impact on the response to infection. The purpose of this study was to determine the association between smoking habits with the severity, the length of hospitalization and the outcome of COVID-19 patients.

Methods: This study was a prospective cohort study of COVID-19 patients admitted at Persahabatan Hospital, Jakarta, Indonesia. Subjects were included by consecutive sampling from August to October 2021. Subjects were assigned into smokers and non-smokers group. All subjects were assessed for their severity, length of hospitalization and outcome; in smoking patients, the Brinkman Index (IB) and the Fagerström Test for Nicotine Dependent (FTND) score were also recorded. Statistical tests were then carried out to assess the significant association between smoking history and the degree of severity, length of hospitalization and outcome of COVID-19 in all patients and the FTND and IB scores with the degree of severity, length of hospitalization and outcome of COVID-19 in smokers.

Results: Authors found that 39/100 (39%) of participants were smokers. Smoking history had a correlation with the outcome (*P*=0.001) but not with the degree of severity (*P*=0.410) and length of hospitalization (*P*=0.780). Among subjects with smoking history, there were correlations found between FTND and the degree of severity and the outcome (*P*=0.022 and *P*=0.012), but not with the length of hospitalization (*P*=0.716). The Brinkman Index was correlated with only the degree of severity (*P*=0.020).

Conclusion: Our study found that smoking habits were correlated with the degree of severity and outcomes in COVID-19 patients.

Keywords: COVID-19, degree of severity, length of hospitalization, outcome, smoking habit

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INTRODUCTION

By the end of December 2019, a mysterious pneumonia case with symptoms of fever, dry cough, weakness and occasional gastrointestinal problems was found at a seafood market in Wuhan, China and infected around 66% of the staff there. As of January 2020, this disease had affected thousands of people in China and then spread to other countries, such as Thailand, Japan, Korea, Vietnam, Germany, United States and Singapore. As of 6 February 2020, a total of 28,276 confirmed cases with 565 deaths globally were documented by WHO, involving at least 25 countries. The pathogen causing this outbreak was later identified as a new beta-coronavirus called 2019 novel coronavirus (2019-nCoV) while the disease is known as coronavirus disease 2019 (COVID-19). In the last 20 years, COVID-19 is the third coronavirus pneumonia to cause a worldwide pandemic after severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).[1]

As COVID-19 is currently still a developing pandemic, there are still limited data on patients' clinical characteristics and prognostic factors. Smoking is commonly assumed to be associated with worse prognosis of disease. Various studies have proven the negative impact of tobacco use on lung health and respiratory diseases. Smoking also impairs the immune system and body's response to infection, rendering smokers more susceptible to infectious diseases. Previous studies have also shown that smokers are twice as likely as non-smokers to contract influenza, have more severe

symptoms and have also recorded higher mortality in previous MERS-CoV outbreaks.[2] Therefore, authors aimed to identify the association between smoking habits and prognosis of COVID-19. This study was conducted in COVID-19 patients at Persahabatan Hospital, Jakarta. The study result is expected to be used to highlight the danger of smoking especially in light to the new pandemic, thus assisting in the smoking cessation effort.

METHODS

This study was conducted by using prospective cohort method to determine the association between smoking habit and outcomes of the COVID-19 patients treated at Persahabatan Hospital, Jakarta. The inclusion criteria for this study were patients aged >18 years who were diagnosed with COVID-19 confirmed through reverse transcriptase polymerase chain reaction (RT-PCR) and chest radiography. Patients who had incomplete medical record, incomplete smoking history, refused or were unable to take part in this study were excluded.

The sampling of this study was conducted at COVID-19 isolation ward of Persahabatan Hospital, Jakarta from August to October 2021. Each subject signed the informed consent. A total of one hundred patients met the inclusion criteria and were willing to participate in the study. Among them, 39 were smokers and underwent thorough investigations regarding their smoking habits using Fagerström Test for Nicotine Dependent (FTND), Brinkman Index and types of cigarettes smoked. Degrees of severity and outcomes of each subject were recorded. The data were processed and analyzed using IBM SPSS software version 24.0 with a 95% confidence level and α=0.05.

RESULTS

The total number of subjects was 100 patients, 39 of whom were smokers and 61 non-smokers. In this study, it was found that the mean age was 53.05±13.582 years, with subjects belonging to the smoker group having a higher mean age (54.95±11.921) than non-smokers (51.84±14.926). Gender distribution showed that 35 (35%) of the subjects were female while 65 (65%) were male, 39 (60%) of which smoked. There were no smokers among the female subjects.

Among the 39 subjects who smoked, medium Fagerström scores were most commonly found, namely in 18 subjects (46.2%), while 16 subjects showed low scores (41.0%) and 5 subjects showed high (16.2%). A total of 32 subjects (82.1%) exclusively consumed conventional cigarettes while 7 subjects (17.9%) consumed both conventional cigarettes and e-cigarettes. There were no subjects who only consumed e-cigarettes or other types of cigarettes. In regard to the Brinkman index (IB), most subjects were found to have high IB (20 subjects, 51.3%) followed by 11 subjects medium (28.2%) and 8 subjects low (20.5%).

Assessment of comorbidities showed that hypertension was most commonly found in subjects (44 subjects), followed by diabetes mellitus (29 subjects) and cardiovascular disease (15 subjects). In addition, 43 subjects were known to have more than one comorbidity, 46 subjects only had one comorbidity and 11 had no comorbidities at all. Most of the chest radiography images showed bilateral infiltrates (54 subjects, 54%), with unilateral infiltrates found in 28 subjects (28%) and 18 subjects (18%) had no infiltrates at all.

The degree of severity of COVID-19 can be classified into mild, moderate, severe and critical, but this study found no subjects with mild disease. Most patients included in this study had moderate disease (57 subjects, 57%) followed by 32 subjects severe (32%) and critical (11 subjects, 11%). Most of the patients also had good outcomes as determined by them being discharged alive (86 patients) rather than dead (14 subjects). Patients in this study also had varying length of hospitalization, the shortest was 2 days and the longest was 41 days with a median of 12 days. Subjects with a history of smoking had a higher median length of hospitalization (13 subjects) than non-smokers (11 subjects).

Table 1. Characteristics of Subjects

Variables	Smoker (n=39)	Non-smoker (n=61)	Total (n=100)
Age (Mean±SD)	54.95±11.921	51.84±14.926	53.05±13.852
Gender			
Male	39 (60.0%)	26 (40.0%)	65 (100.0%)
Female	0 (0.0%)	35 (100.0%)	35 (100.0%)
Type of cigarette			
Conventional	32 (82.1%)	0 (0.0%)	32 (100.0%)
E-cigarette	0 (0.0%)	0 (0.0%)	0 (100.0%)
Conventional and e-cigarette	7 (17.9%)	0 (0.0%)	7 (100.0%)
Others	0 (0.0%)	0 (0.0%)	0 (100.0%)
Fagerström			
Mild	16 (41.0%)	0 (0.0%)	16 (100.0%)
Medium	18 (46.2%)	0 (0.0%)	18 (100.0%)
High	5 (12.8%)	0 (0.0%)	5 (100.0%)
Brinkman index			
Mild	8 (20.5%)	0 (0.0%)	8 (100.0%)
Medium	11 (28.2%)	0 (0.0%)	11 (100.0%)
High	20 (51.3%)	0 (0.0%)	20 (100.0%)
Type of comorbidities			
Diabetes mellitus	9 (31.0%)	20 (69.0%)	29 (100.0%)
Hypertension	15 (34.1%)	29 (65.9%)	44 (100.0%)
Cardiovascular	6 (40.0%)	9 (60.0%)	15 (100.0%)
Cerebrovascular	2 (28.6%)	5 (71.4%)	7 (100.0%)
Obstructive lung disease	2 (33.3%)	4 (66.7%)	6 (100.0%)
Tuberculosis	3 (50.0%)	3 (50.0%)	6 (100.0%)
Malignancy	3 (60.0%)	2 (40.0%)	5 (100.0%)
HIV	1 (20.0%)	4 (80.0%)	5 (100.0%)
Chronic kidney disease	2 (33.3%)	4 (66.7%)	6 (100.0%)
Others	15 (53.6%)	13 (46.4%)	28 (100.0%)
No comorbidities	2 (18.2%)	9 (81.8%)	11 (100.0%)
Number of comorbidities			
No comorbidities	2 (18.2%)	9 (81.8%)	11 (100.0%)
Single comorbidity	22 (47.8%)	24 (52.2%)	46 (100.0%)
Multiple comorbidities	15 (34.9%)	28 (65.1%)	43 (100.0%)
Infiltrates on chest radiograph			
Unilateral	13 (46.4%)	15 (53.6%)	28 (100.0%)
Bilateral	24 (44.4%)	30 (55.6%)	54 (100.0%)
No infiltrates	2 (11.1%)	16 (88.9%)	18 (100.0%)
Degree of severity			
Moderate	20 (35.1%)	37 (64.9%)	57 (100.0%)
Severe	10 (31.3%)	22 (68.7%)	32 (100.0%)
Critical	9 (81.8%)	2 (18.2%)	11 (100.0%)
Outcome			
Alive	27 (31.4%)	59 (68.6%)	86 (100.0%)
Dead	12 (85.7%)	2 (14.3%)	14 (100.0%)
Length of hospitalization [Median (min-max)]	13 (2-41)	11 (2-39)	12 (2-41)

In this study, the basic demographics of participants were also assessed for their significance on the degree of severity, length of hospitalization and outcome of COVID-19. During the statistical analysis, the degree of severity was classified into moderate and severe-critical, comorbidities into with and no comorbidities, and infiltrate in chest radiography and no infiltrate. It could be seen in the table, the variables of age and infiltrates in chest radiography had a significant association with the degree of severity but not with the length of hospitalization and outcome of COVID-19 patients.

Table 2. Association between General Characteristics with Degree of Severity, Length of Hospitalization and Outcome in COVID-19 Patients

Variables	Degree of severity		*P*	Length of Hospitalization (Mean Rank)	*P*	Outcome		*P*
	Moderate (n=57)	Severe-critical (n=43)				Alive (n=86)	Dead (n=14)	
Age	49.05±13.831	58.15±12.116	0.001[a]	-0.056	0.582[c]	52.09±13.900	58.93±12.437	0.087[a]
Gender								
Male	34 (52.3%)	31 (47.7%)	0.212[b]	45.40	0.016[d]	52 (80.0%)	13 (20.0%)	0.018[b]
Female	23 (65.7%)	12 (34.3%)		59.97		34 (97.1%)	1 (2.9%)	
Type of cigarette								
Conventional	15 (46.9%)	17 (53.1%)	0.407[b]	20.59	0.486[d]	21 (65.6%)	11 (34.4%)	0.403[b]
Conventional and e-cigarette	5 (71.4%)	2 (28.6%)		17.29		6 (85.7%)	1 (14.3%)	
Comorbidities								
With comorbidities	8 (72.7%)	3 (27.3%)	0.343[b]	40.82	0.240[d]	11 (100%)	0 (0.0%)	0.355[b]
Without comorbidities	49 (55.1%)	40 (44.9%)		51.70		75 (84.3%)	14 (15.7%)	
Infiltrates on chest radiography								
With infiltrates	14 (93.3%)	1 (6.7%)	0.002[b]	43.97	0.343[d]	14 (93.3%)	1 (6.7%)	0.687[b]
Without infiltrates	43 (50.6%)	42 (49.4%)		51.65		72 (84.7%)	13 (15.3%)	

Note: [a]*Independent t-test*; [b]*Fisher's exact test*; [c]*Spearman's rank-order correlation*; [d]*Mann-Whitney test*

On the opposite, gender appeared to have a significant association with outcome and length of hospitalization but not degree of severity. Both cigarette type and comorbidities didn't have significant association with the degree of severity, length of hospitalization and outcome of COVID-19 patients.

The association between smoking history and degree of severity, length of hospitalization and outcomes in COVID-19 patients was assessed in this study as well. The degree of severity was divided into moderate (57 subjects) and severe-critical (43 subjects). In the significance test, a value of *P*=0.410 was found, which indicates that there was no significant association between smoking history and the clinical grade of patients with COVID-19. Similar results were found regarding the length of hospitalization, in which patients with a history of smoking had a longer average length of hospitalization (mean rank 51.51 vs 49.85) but no significant association was found (*P*=0.780).

A different result was found while assessing the association between smoking history and the outcome of COVID-19 patients (life or death). It was found that out of 100 subjects, 86 were discharged from the hospital alive with 27 of them being smokers and 59 non-smokers. There were 14 subjects who died, with 12 being smokers and 2 non-smokers. In the significance test, a value of *P*=0.001 was found, which indicates that there is a significant association between smoking history and the outcome of patients with COVID-19.

The Fagerström Test for Nicotine Dependent (FTND) is a questionnaire used to assess someone's dependence on nicotine. Higher Fagerström score indicates the more cigarettes consumed every day. Statistical analysis in this study divided Fagerström scores into low and medium-high. Out of the 39 patients with a history of smoking, 16 of them had low Fagerström scores while the remaining 23 had medium-high scores. In the significance test, a value of *P*=0.022 was found, indicating that there is a significant association between the Fagerström score and the degree of severity of COVID-19 patients.

The assessment regarding outcomes yielded similar results, with 12 mortalities found among 39 patients with history of smoking, 11 of whom were patients with medium-high Fagerström scores. Significance test showed a value of *P*=0.012, which indicates that there is a significant association between the Fagerström score and the outcome of patients with COVID-19. On the other hand, no statistically significant difference was found (*P*=0.716) between the Fagerström score and length of hospitalization, however, the mean length of hospitalization was higher in patients with medium-high Fagerström scores (14.26±8.198) than low (13.38±6.087).

Table 3. Association between History of Smoking with Degree of Severity, Length of Hospitalization and Outcome in COVID-19 Patients

History of smoking	Degree of severity		*P*	Length of Hospitalization (Mean Rank)	*P*	Outcome		*P*
	Moderate (n=57)	Severe-critical (n=43)				Alive (n=86)	Dead (n=14)	
Smoker	20 (51.3%)	19 (48.7%)	0.410[a]	51.51	0.780[b]	27 (69.2)	12 (30.8)	0.001[b]
Non-smoker	37 (60.7%)	24 (39.3%)		49.85		59 (96.7)	2 (3.3)	

Note: [a]*Fisher's exact test*; [b]*Mann-Whitney test*

Table 4. Association between Fagerström Score with Degree of Severity, Length of Hospitalization and Outcome in COVID-19 Patients

Fagerström score	Degree of severity		*P*	Length of Hospitalization (Mean±SD)	*P*	Outcome		*P*
	Moderate (n=20)	Severe-critical (n=19)				Alive (n=27)	Dead (n=12)	
Low	12 (75.0%)	4 (25.0%)	0.022[a]	13.38±6.087	0.716[b]	15 (93.8%)	1 (6.2%)	0.023[b]
Medium-high	8 (34.8%)	15 (54.2%)		14.26±8.198		12 (52.2%)	11 (47.8%)	

Note: [a]*Fisher's exact test*; [b]*Independent t-test*

Table 5. Association between Brinkman Index with Degree of Severity, Length of Hospitalization and Outcome in COVID-19 Patient

Brinkman index	Degree of severity		*P*	Length of Hospitalization (Mean±SD)	*P*	Outcome		*P*
	Moderate (n=20)	Severe-critical (n=19)				Alive (n=27)	Dead (n=12)	
Low	6 (100.0%)	0 (0.0%)	0.020[a]	12.17±4.956	0.537[b]	6 (100.0%)	0 (0.0%)	0.151[b]
Medium-high	14 (42.4%)	19 (57.6%)		14.21±7.700		21 (63.6%)	12 (36.4%)	

Note: [a]*Fisher's exact test*; [b]*Independent t-test*

This study also assessed the association between BI and the length of hospitalization for COVID-19 patients. The mean length of hospitalization in patients with medium-high IB was higher (14.21±7,700) than low (12.17±4.956) but no statistically significant difference was found (*P*=0.537). Similar results were found in regards of outcome (*P*=0.151), with 12 from 33 subjects in the medium-high IB group passed away, while no deaths were recorded in the low IB group.

The Brinkman index (the number of cigarettes consumed per day multiplied by the number of years of smoking) was used to measure the cumulative dose of cigarette consumption. The risk of experiencing higher degree of COVID-19 increases with higher IB score. Statistical analysis in this study divided IB into low and medium-high. This study showed that among the 39 smokers, 6 had low IB with all of them suffering moderate COVID-19, while 33 had medium-high IB with 14 of them being in the moderate degree and 19 being critical-severe. In the significance test, a value of *P*=0.020 was found, which indicates that there is a significant association between IB and the degree of severity in patients with COVID-19.

DISCUSSION

This study's main objective was to determine the association between smoking habits and clinical grade, length of hospitalization and outcomes of COVID-19 patients. The study involved 100 participants who met the inclusion criteria, the FTND and IB were recorded on the smokers and then all subjects were assessed in regards of degree of severity, length of hospitalization and outcomes.

In this study, the overall mean age of the subjects was 53.05 years, with the smoker group having a higher mean age (54.95±11.921) than non-smokers (51.84±14.926). This is similar to a meta-analysis study by Qian et al which reported that the average age of COVID-19 patients was more than 50 years (52.4 years).[3] Study by Lowe et al also reported that the average age in the smoker group was higher than non-smokers (56.5±17.2 vs 47.8±19.3).[4] The higher mean age of smokers compared to non-smokers can be caused by higher level of education and greater awareness of the dangers of smoking in younger populations as mentioned in the research of Ciftci et al and Vieira et al[5,6] This study also found that the risk of experiencing more severe disease and mortality increases with age. This is because elderly patients often have comorbidities and lower immune response compared to the younger ones.[7]

There were more male than female subjects included in this study (65% vs 35%). Meta-analysis by Qian et al provided a similar picture of more male patients (62.1%) contracting COVID-19 than females,[3] while another study by Li et al in Wuhan did

not find a significant difference between genders (56% males).[8] This study also found that gender had a significant correlation with patient's degree of severity, in accordance with study by Surendra et al and Varidy et al which linked male gender to the worse prognosis for COVID-19.[7,9]

This could be caused by the higher number of comorbidities and smoking habits in males, but several studies have also found differences in the expression of the ACE-2 receptor and the cellular protease enzyme TMPRSS2 which play a role in virus entry and attachment. Females are also known to have greater T cell activation than males so they are able to fight viruses better. [9] Study by Takahashi et al also found higher levels of pro-inflammatory cytokines and chemokines such as IL-8, IL-18 and CCL5 in men which is associated with progression and more severe disease.[10]

The type of cigarette consumed needs to be considered when analyzing smoking habits. In this study, it was found that most smokers (82.1%) consumed only conventional cigarettes, while 17.9% consumed both conventional cigarettes and e-cigarettes. This is in accordance with data from the Tobacco Control Support Center which states that >50% of smokers in Indonesia consume conventional cigarettes.[11] However, no significant differences were found between the type of cigarette consumed with clinical symptoms and patient outcomes. This is because e-cigarettes also contain dangerous ingredients such as nicotine, volatile organic compounds, carbonyl and particulate matter. Qasim et al stated that e-cigarettes can cause airway irritation and oxidative stress which trigger a series of inflammatory reactions. Study in mice also shows a decrease in the immune system due to e-cigarette exposure. It can be concluded that there is no evidence that e-cigarettes are safer for health than conventional cigarettes.[12]

Analysis of comorbidities in participants showed the most common comorbidities were hypertension (44 cases), diabetes mellitus (29 cases) and cardiovascular diseases (15 cases). This is similar to the study by Sanyaolu et al. and meta-analysis by Yang et al which stated that those three diseases are the biggest comorbidities in COVID-19.[13,14] The presence of comorbidities such as hypertension, diabetes mellitus, respiratory tract disease and cardiovascular disease may be linked to the pathogenesis of COVID-19. Chronic diseases have several conditions in common with infectious diseases such as proinflammatory states and weakened immune responses. For example, diabetes occurs due to the accumulation of activated immune cells in metabolic tissue, thereby releasing a number of inflammatory mediators such as IL-1ß and TNF-α which cause systemic insulin resistance and damage to ß cells. Metabolic diseases can also suppress immune function by disrupting the function of macrophages and lymphocytes.[14]

The presence of comorbidities in this study did not yield a significant difference in degree of severity, length of hospitalization and outcomes, which contradicts the study by Surendra et al, in which worse prognosis was generally shown in patients with comorbidities.[7] This is because this study only analyzed the presence of comorbidities without considering the types of comorbidities most associated with mortality rates. Furthermore, data regarding comorbidities was only obtained through secondary data without identifying other factors such as disease stages, control and management of those conditions.[15]

Another characteristic assessed in this study was the presence of infiltrates on chest radiography. Most of the subjects (54%) had bilateral infiltrates, 28% unilateral and 18% had no infiltrates. This result supports the study by Kaleemi et al which reported that there were more bilateral than unilateral infiltrates on the chest radiography of COVID-19 patients (92% vs 8%). The presence of infiltrates had a significant association with the subject's degree of severity but not the outcome and length of hospitalization. The result is also comparable with the study by Kaleemi et al which confirmed that patients with bilateral infiltrates had worse prognosis and mortality rate. This is because bilateral infiltrates generally indicate more severe disease and worse cytokine storms.[16]

A total of 39 patients with a history of smoking and 61 patients without a history of smoking were included in this study. Statistical tests showed that there was a significant association between smoking history with the outcome of patients with COVID-19 (*P*=0.001) but not with degree of severity (*P*=0.410) and length of hospitalization (*P*=0.780).

Smoking is known to affect the degree of severity and prognosis of COVID-19 through several mechanisms, namely impairing the immune system, increasing the regulation of ACE-2 receptors, causing comorbidities and easing the transmission of the virus to the body by frequently touching the facial area when smoking.[11] Smoking is associated with various changes in the function of the cellular and humoral immune systems. These changes include decreased levels of circulating immunoglobulins, decreased antibody responses to certain antigens, decreased numbers of CD4+ lymphocytes, increased numbers of CD8+ lymphocytes, suppressed phagocyte activity and decreased release of proinflammatory cytokines. The pathogenesis of the effects of smoking on the body's immune system is not fully understood. Nicotine is also known to stimulate the release of catecholamines and corticosteroids. These mediators may increase CD8+ lymphocytes in a cellular-mediated immune response and suppress the body's defense against infection.[17]

Smoking can also increase the expression of angiotensin converting enzyme-2 (ACE-2), which is the receptor for 2019-nCoV. The ACE-2 receptor provides the S protein binding site for human coronaviruses especially SARS-CoV-2 which has a higher affinity for ACE-2 and has a 10-20 times greater probability of binding to ACE-2 in human cells than the S protein from other SARS-CoV. This increased affinity allows easier spread of the virus from person to person than previous SARS viruses.[18]

The ACE-2 receptor is thought to be upregulated in the airway epithelium of smokers. Zhao et al found that ACE-2 is expressed explicitly in type 2 pneumocytes containing genes that regulate viral reproduction and transmission. This suggests that smokers may be more susceptible to SARS-CoV-2 infection and possibly COVID-19.[19] Previous studies using an in vivo mice model showed that attachment of SARS-CoV-2 to ACE-2 can also down-modulate ACE-2 expression so that it eventually increases the production and activation of other ACE related enzymes. Impaired modulation and drastic reduction of ACE-2 might cause severe acute respiratory failure.[20,21]

Smoking is also known to be associated with various comorbidities such as diabetes, hypertension and cardiovascular disease which can also affect the degree of severity and prognosis of COVID-19. In hypertension and cardiovascular disorders, dysregulation of the renin-angiotensin-aldosterone system and immune system dysfunction occur. Dysfunction of CD8+ lymphocytes can reduce the body's ability to fight viral infections and cause cytokine dysregulation, which plays a role in the incidence of systemic inflammatory response syndrome (SIRS) and acute respiratory distress syndrome (ARDS) in severe COVID-19. In diabetes, immune system dysfunction and increased expression of pro-inflammatory cytokines might occur, which lead to cytokine storms commonly found in severe cases of COVID-19.[22]

Although in theory smoking may deteriorate the clinical severity and prognosis of COVID-19, several studies on this matter have yielded conflicting results. Zhang et al's study stated that a history of smoking is associated with the emergence of severe and critical degree of severitys in COVID-19 as well as increasing the rate of ICU admission and mortality.[23] Similar things were expressed by Vardavas et al and Lowe et al who reported that smoking can increase the risk of hospitalization and poor prognosis.[4,24] On the other hand, a preliminary meta-analysis by Lippi et al found that smoking did not increase the risk of progression to severe COVID-19.[25]

Research by Zhou et al also did not find a significant difference in mortality rates in patients with and without a history of smoking.[26] Various descriptive studies also showed a relatively low number of COVID-19 patients with a history of smoking.[27] Regarding the length of hospitalization, Khalil et al found that a history of smoking was

associated with a longer length of hospitalization (12.0±7.8 vs 10.8 days; *P*<0.001). Our study also found longer length of hospitalization in smoking patients compared to non-smokers (mean rank 51.51 vs 48.95) but there was no statistically significant difference.[28]

Differences in results from various studies can be caused by several factors. Until now, the effect of smoking on COVID-19 has yet to be determined with certainty. Cigarettes contain various toxic chemicals possessing no protective effect against COVID-19. However, one of the main components of cigarettes is nicotine. Nicotine was found to prevent acute lung injury in animal models of ARDS and to inhibit TNF expression in airway epithelial cells in vitro. Nicotine also exhibits anti-inflammatory properties in vivo in humans exposed to endotoxin.[28,29]

Nicotine is an agonist of the cholinergic anti-inflammatory pathway which regulates the immune and inflammatory responses of host cells so that it can inhibit the production of pro-inflammatory cytokines such as TNF, IL-1 and IL-6 without inhibiting the production of anti-inflammatory cytokines such as IL-10. This is known to provide a protective effect against cytokine-mediated diseases such as sepsis and endotoxemia, including cytokine release syndrome (cytokine storm) which plays a role in the pathophysiology of severe COVID-19 and can lead to mortality.[28,29]

As mentioned previously, cigarette smoke can increase the expression of ACE-2 which is the receptor for SARS-CoV-2. This is hypothesized to increase the number of virus attachments and can lead to a more severe degree of disease. However, on the other hand, ACE-2 reduces the bad effects of angiotensin II by breaking down angiotensin I and II into angiotensin which possesses good vasodilator, anti-inflammatory and antioxidant properties. Studies show that this can prevent ARDS in mice. It can be concluded that the increase in ACE-2 expression can paradoxically protect patients from disease progression to severe disease and lung injury. The potential of nicotine as an immunomodulator and its complex interaction with the renin-angiotensin-aldosterone system can explain why smoking does not always aggravate disease severity and mortality rates in COVID-19.[28,29]

The Fagerström Test for Nicotine Dependance (FTND) or Fagerström questionnaire is a test to measure someone's dependence on nicotine. The higher the Fagerström score, the higher a person's dependence on nicotine and the greater the likelihood of consuming cigarettes. This can affect the degree of severity, length of hospitalization and outcome of COVID-19. In this study, a significant association was found between the Fagerström score with degree of severity and outcome of COVID-19 patients (*P*=0.022 and *P*=0.012; respectively) although not with length of hospitalization (*P*=0.716) but the author has not found other studies about this matter. A study by Fidanci et al found that there was a decrease in cigarette addiction levels after the onset of the COVID-19 pandemic, so it is hoped that this pandemic can become a momentum to increase awareness regarding smoking cessation.[30]

The Brinkman Index or IB (the number of cigarettes consumed per day multiplied by the number of years of smoking) is used to assess the cumulative dose of cigarette consumption. In general, IB is divided into mild (<200), moderate (200-600) and severe (>600). In this study, it was found that IB also had a significant association with clinical grade (*P*=0.020). The result supports a study by Goto et al which states that a higher IB is associated with more severe degree of disease.[31] On the other hand, IB in this study did not have a significant association with COVID-19 outcomes (*P*=0.151) and length of hospitalization (*P*=0.537). This is inconsistent to studies by Vardavas et al and Lowe et al which found the increasing risk of worsening prognosis and hospitalization rates in subjects with higher rates of cigarette consumption.[4,24] This could be caused by the protective and immunomodulatory effects of nicotine on the respiratory system.[27]

LIMITATION

The research study appears to have certain limitations that ought to be considered. Firstly, the study did not involve patients with mild Covid, thus

possibly limiting its scope. Secondly, the study did not evaluate laboratory parameters, which could have provided additional and more objective data. It is recommended that these limitations be acknowledged and addressed in future studies.

CONCLUSION

In the study, it was found that there were 39 subjects with a history of smoking and 61 without a history of smoking, with all of the smoking patients being men and the non-smoking patients consisting of 26 men and 35 women. Statistically, age increases the risk of contracting critical-severe COVID-19 but not the risk of mortality. A history of smoking does not affect the degree of severity of COVID-19, but there may be a higher risk of mortality in smokers. Subjects with higher Fagerström score are at risk of experiencing COVID-19 with more severe degree of severity and a higher risk of mortality. Patients with higher IB are at risk of contracting severe COVID-19 but the risk of mortality is not significantly different. In this study, the history of smoking, higher Fagerström score or IB are generally associated with a higher length of hospitalization but this isn't significantly different statistically.

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CONFLICT OF INTEREST

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