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Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

ASSOCIATION OF SMOKING AND SEVERITY OF COVID-19 INFECTION AMONG 5,889 PATIENTS IN MALAYSIA: A MULTI-CENTER OBSERVATIONAL STUDY

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ARTICLE INFO

Article history:

Received 23 April 2021

Revised 16 December 2021

Accepted 5 January 2022

Keywords:

Smoking
COVID-19
severity
complications
disease outcome
Malaysia

ABSTRACT

Objective: This study aims to investigate the association between smoking and the severity of COVID-19 infection during the initial wave of this pandemic in Malaysia.

Methods: This is a multi-center observational study using secondary hospital data collected retrospectively from February 1, 2020, until May 30, 2020. Clinical records of all real-time polymerase chain reaction (RT-PCR)-confirmed COVID-19 cases with smoking status, co-morbidities, clinical features, and disease management were retrieved. Severity was assessed by the presence of complications and outcomes of COVID-19 infection. Logistic regression was used to determine the association between COVID-19 disease severity and smoking status.

Results: A total of 5,889 COVID-19 cases were included in the analysis. Ever smokers had a higher risk of having COVID-19 complications, such as acute respiratory distress syndrome (odds ratio [OR] 1.69; 95% confidence interval [CI] 1.09–2.55), renal injury (OR 1.55; 95% CI 1.10–2.14), and acute liver injury (OR 1.33; 95% CI 1.01–1.74), compared with never smokers. However, in terms of disease outcomes, there were no differences between the two groups.

Conclusion: Although no significant association was found in terms of disease outcomes, smoking is associated with a higher risk of having complications owing to COVID-19 infection.

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1. Background

Coronavirus is a large family of viruses that can infect both animals and humans. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold

to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (World Health Organization 2019). The most recently discovered coronavirus is known as SARS-CoV-2 that was reported in Wuhan, Hubei Province, China, in December 2019. This virus spread worldwide extremely fast evolving into a pandemic that affected many countries. In Malaysia, the first wave of the COVID-19 epidemic began in late January whereby only 22 confirmed cases were reported (Ng et al., 2020). The second wave of infections broke out in late February 2020 and grew rapidly in the first three weeks,

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where Malaysia reported three-digit cases in a day. By the end of August 2020, 9,340 confirmed cases were recorded. The Malaysian Prime Minister announced a nationwide Movement Control Order (MCO) that went into effect on March 18, 2020. The main aim was to reduce social mixing, and approximately three weeks after the MCO, disease transmissibility (R_t) had reduced substantially from 3.1 to 1.0 and remained below 1.0 for the remaining period (Ng et al., 2020). However, in October 2020, Malaysia entered the third wave of COVID-19 and up until 16th April 2021, there were about 370,528 cases with 1,365 deaths reported.

Smoking is one of the biggest causes of illness and contributed to 8 million deaths around the world. Both smoking and COVID-19 infection affect primarily the respiratory system. In Malaysia, the burden of smoking remains high where the prevalence of smokers in adults aged 15 years and older was 21.3% (Institute for Public Health 2019) and in adolescents aged 13–15 years was 13.2% (Institute for Public Health, 2017). Smoking harms nearly every organ of the body, causes many diseases, and reduces the health of smokers in general. Smokers may already have lung disease or reduced lung capacity, which would greatly increase the risk of serious illness. In respiratory diseases, when a person smokes, evidence has shown that the chance of getting an infection is higher and the infection is more severe (van Zyl Smit et al., 2010). The respiratory diseases are due to tobacco smoke, which causes the deposition of particles in the airways and damages the protection mechanisms of the respiratory system at different levels, altering the function of the ciliary mucus and the clearance of inhaled substances. It also enables the adherence of microorganisms to airway epithelial cells, increases alveolar permeability, and decreases cellular and humoral immunity (Feng et al., 2011; Murin and Bilello, 2005). Smoking also affects the immune system and its response to infection, making smokers more vulnerable to infectious diseases (Zhou et al., 2016). Through these effects on the immune system, smoking may facilitate influenza virus infection, its severity, and its most frequent complications, such as pneumonia (Almirall et al., 2008; Epstein et al., 2010). Previous studies have shown that smokers are twice more likely to contract influenza, presented with more severe symptoms, and had a higher mortality rate in the previous Middle East Respiratory Syndrome coronavirus (MERS-CoV) outbreak (Park et al., 2018; Arcavi and Benowitz, 2004). Owing to this, smoking is shown to be associated with poor prognosis, as most evidence highlighted the negative impact of tobacco use on lung health and its causal association with an abundance of respiratory diseases (Tonnesen et al., 2019).

In recent studies, researchers found that those with a history of smoking had a higher risk of getting severe COVID-19 progression compared with those who never smoked (Liu et al., 2020; Patanavanich and Glantz, 2020). A systematic review conducted in March 2020 concluded that smokers were 1.4 times more likely to have severe symptoms of COVID-19 and approximately 2.4 times more likely to be admitted to an Intensive Care Unit (ICU), need mechanical ventilation, or die compared with non-smokers (Vardavas and Nikitara, 2020). In addition, those with existing Chronic Obstructive Pulmonary Disease (COPD) and had ongoing smoking history were more likely to have worse progression and outcome of COVID-19 (Zhao Q et al., 2020). As the COVID-19 pandemic is still a rapidly evolving topic and major health concern around the world, data on clinical characteristics of the patients, risk factors, and prognostic factors are still scarce, especially studies outside China (Khot and Nadkar, 2020). Current analysis remains limited owing to the quality of primary data, although, early results indicate an association between smoking and COVID-19 severity (Grundty et al., 2020). In Malaysia, high smoking prevalence in both adults and adolescents creates a major burden on the healthcare system. Thus, there is a need to further strengthen the tobacco control policies and their implementation. Findings

Table 1
Clinical Staging of COVID-19 Infection.

Clinical staging	Features
I	Asymptomatic
II	Symptomatic, No pneumonia
III	Symptomatic, Pneumonia
IV	Symptomatic, Pneumonia, Requiring supplemental oxygen
V	Critically ill with multi-organ failure

*Based on Clinical Management of Confirmed COVID-19 Case in Adult and Paediatric Ministry of Health, Malaysia (updated August 30, 2021) (Ministry of Health, Malaysia 2021)

from this study will provide scientific evidence on the association of smoking and COVID-19 and also address the limitation of data availability. Therefore, this study aims to determine the association between smoking and the severity of disease in the patients infected with COVID-19 in Malaysia.

2. Methods

2.1. Study design

This is a multi-center observational study using secondary data from 18 COVID-19 designated hospitals in Malaysia. The data were collected retrospectively during the initial wave of the COVID-19 pandemic in Malaysia, which was from February 1, 2020, until May 30, 2020. Data used for this study have been verified and validated as reported in the study by Sim et al. (2020). The list of hospitals involved in this study is shown in the supplementary Table 1.

2.2. Inclusion and exclusion criteria

Patients included in this study were those aged 12 years and above, who had been diagnosed with COVID-19 by laboratory confirmation of reverse-transcriptase-polymerase chain reaction (RT-PCR) analysis using nasopharyngeal and/or oropharyngeal swabs, tracheal aspirates, sputum, or serum samples at designated National Public Health Laboratories, Institute for Medical Research, and accredited hospital laboratories. They were hospitalized in 18 designated COVID-19 hospitals in Malaysia and were followed up until they had completed the outcome, which was either discharged alive or dead.

2.3. Disease staging and clinical management

All COVID-19 cases admitted to the hospital were managed according to COVID-19 Management Guideline in Malaysia by the Ministry of Health. During this period, all cases were admitted for 14 days or until free of SARS-CoV-2 carriage on repeated nasopharyngeal/oropharyngeal swabs or death ensued. The clinical staging for patients presented with COVID-19 is shown in Table 1.

2.4. Study variables and outcome of interest

All patients with COVID-19 were grouped according to their smoking status either ever smoker or never smoker. Ever smokers were defined as patients who reported as active smokers and former smokers, whereas never smokers were defined as patients who reported as never to have smoked any cigarette throughout their entire life. Active smokers were defined as those who reported as currently using smoked tobacco products, such as manufactured cigarettes, whereas former smokers were defined as those who reported as currently non-smokers but had previously smoked daily. However, owing to the limitation in data collection, the duration of quitting for former smokers could not be determined.

Variables related to sociodemographic data, admission characteristics, clinical progression, laboratory and radiographic investigations, management, and clinical outcome were analyzed for associations with disease severity according to these two groups. Personal data included sex, age, history of smoking, and comorbidities such as chronic obstructive pulmonary disease (COPD), cancer, hypertension, and/or diabetes. Clinical data included initial symptoms, clinical presentation, vital signs, respiratory support, complications, and disease outcomes. The severity of COVID-19 infection was assessed by the presence of complications and outcomes of COVID-19 infection such as admission to the intensive care unit (ICU), the requirement of invasive ventilator support, and the outcome of whether patients survived or died.

2.5. Statistical analysis

Continuous variables with normal distribution were expressed as mean and standard deviation and analyzed using independent samples *t*-test, while those with skewed distribution were presented as median (Q1, Q3) and analyzed using Mann-Whitney *U* test. Categorical variables were presented as numbers (percentages) and analyzed using the chi-square test or Fisher's exact test. Logistic regressions were used to analyze the association between smoking status (independent variable) with disease severity upon discharge (dependent variable). Variables from disease severity that were complications and outcomes were selected to be included in the logistic regressions, based on clinical justification and statistical reasoning from univariate analyses. Missing data were treated with a listwise deletion in subsequent analyses. A two-sided $P < 0.05$ is considered statistically significant. R version 3.6.3 was used for all analyses.

3. Results

3.1. Sociodemographic, clinical histories, and disease staging

A total of 5,889 COVID-19 cases were admitted to hospitals all over Malaysia during the study period. The detailed characteristics of these patients were published in another study (Sim et al., 2020). Out of 5,889 cases, 529 (9.0%) patients were current smokers, 262 (4.4%) were former smokers, and 5,098 (86.5%) were non-smokers. For this study, the current and former smokers were grouped as ever smokers and non-smokers as never smokers. The median age of the patients with COVID-19 in ever smokers group was slightly older compared with never smokers (36 vs 34 years, $p < 0.001$).

As shown in Table 2, patients with COVID-19 in the ever smokers group had a significantly higher proportion of diabetes, cardiac disease, and chronic pulmonary disease compared with never smokers but the finding is vice versa for patients with a history of asthma. There was a significantly higher proportion of ever smokers with shortness of breath compared with never smokers. Other symptoms such as sore throat, nausea, vomiting, fever, and myalgia were significantly higher in never smokers.

At the time of presentation to the hospital, a higher proportion of ever smokers were classified as COVID-19 Stage III, Stage IV, and Stage V compared with never smokers. Further sub-analysis in Stage III to Stage V patients with COVID-19 demonstrated that the median age for ever smokers was significantly lower than that for never smokers (44 years old vs 52 years old, $p < 0.001$).

3.2. Physical examination at admission and investigations conducted on patients with COVID-19

For physical examination, higher blood pressure was observed in ever smokers while pulse rate and temperature were slightly

higher in the never smokers (Table 3). Ever smokers had significantly higher mean white blood cells count, neutrophil count, hemoglobin, hematocrit, and ALT level compared with never smokers. However, a higher proportion of never smokers had high C-reactive protein more than ≥ 5 mg/dl and lymphopenia. The mean lactate dehydrogenase (LDH) level was also higher in never smokers. Although not statistically significant, a higher percentage of ever smokers had abnormal chest x-ray findings at the time of presentation.

3.3. Complications and outcomes of COVID-19 infection

In Table 4, ever smokers had a significantly higher percentage of having complications of COVID-19 infection, which were acute liver injury, renal injury, acute respiratory distress syndrome (ARDS), deep vein thrombosis, and seizures. A higher proportion of ever smokers were admitted to the intensive care unit (ICU) and required oxygen support, but this was not statistically significant. There was no difference between types of ventilation received, worst diagnosis, and outcome by both groups.

Based on logistic regression analysis (Table 5), in terms of complications, ever smokers had higher odds of having a liver injury, acute renal injury, and acute respiratory distress syndrome. For disease outcome, there was no statistically significant difference between ever smokers and never smokers. Subgroup analysis was carried out between current, former, and non-smokers (Table 6). When compared with current smokers, former smokers had a significantly higher percentage of having liver and renal injury. In terms of disease outcomes, a higher percentage of former smokers were being admitted to ICU and required invasive ventilation compared with current smokers. Comparison between current and non-smokers, however, showed no significant differences between these two groups. The odds ratios are shown in Supplementary Table 2. Further analysis also found no significant association between smoking status with disease complications and outcomes when other variables, such as age, gender, and ethnicity, were controlled.

4. Discussion

To the best of our knowledge, this is the first study to determine the association between smoking and COVID-19 severity in laboratory-confirmed patients with COVID-19 admitted to nationwide hospitals in Malaysia. The COVID-19 severity was assessed in terms of complications and disease outcomes. The sample size for this study is much larger than other similar COVID-19 and smoking-related studies that reported sample sizes ranging from 41–1,099 (Zhou et al., 2020; Zhang et al., 2020; Huang et al., 2020; and Liu et al., 2020). Out of a total of 5,889 COVID-19 cases admitted to the hospitals, most (86.5 %) were non-smokers and the remaining (13.5 %) had a present or past history of smoking.

The prevalence of current smokers (9%) in patients with COVID-19 found in this study was lower compared with the national data, which was 21.3% (National Health and Morbidity Survey, 2019). However, the prevalence of current smokers in this study was higher compared with that in China as reported by Zhou et al. (2020). A review from Gonzalez-Rubio et al., 2020 based on the analysis of data from studies in China, United States, and Italy also showed a lower prevalence of smoking in COVID-19 hospitalized individuals compared with the countries' general prevalence of smoking. Based on this observation, the authors concluded that current smoking had a protective effect on the likelihood of hospitalization. However, this review raised serious concerns, as discussed by Berlin and Thomas, 2020, which highlighted poor data collection methods on smoking status, under-reporting

Table 2
Sociodemographic, clinical history, and disease staging of COVID-19 cases at presentation to hospital according to smoking status.

Variable	Total (n=5889)	Ever smoke (n=791)	Never smoke (n=5098)	p value
Age Group (n,%)				
< 30 years old	2486 (42.2%)	273 (34.5%)	2213 (43.4%)	< 0.001
31 to 50 years old	1919 (32.6%)	321 (40.6%)	1598 (31.3%)	
51 to 70 years old	1315 (22.3%)	167 (21.1%)	1148 (22.5%)	
Above 71 years old	169 (2.9%)	30 (3.8%)	139 (2.7%)	
Gender (n,%)				
Male	4221 (71.7%)	773 (97.7%)	3448 (67.6%)	< 0.001
Female	1668 (28.3%)	18 (2.3%)	1650 (32.4%)	
Ethnicity (n,%)				
Malay	3433 (58.4%)	434 (54.9%)	2999 (59.0%)	< 0.001
Chinese	391 (6.7%)	40 (5.1%)	351 (6.9%)	
Indian	135 (2.3%)	24 (3.0%)	111 (2.2%)	
Others	521 (8.9%)	96 (12.2%)	425 (8.4%)	
Non Malaysian	1396 (23.8%)	196 (24.8%)	1200 (23.6%)	
Co-morbidities (n,%)				
Hypertension	931 (15.8%)	132 (16.7%)	799 (15.7%)	0.467
Diabetes	578 (9.8%)	97 (12.3%)	481 (9.4%)	0.013
Asthma	196 (3.3%)	15 (1.9%)	181 (3.6%)	0.016
Cardiac disease	190 (3.2%)	41 (5.2%)	149 (2.9%)	< 0.001
Chronic kidney disease	92 (1.6%)	13 (1.6%)	79 (1.5%)	0.843
Chronic pulmonary disease	32 (0.5%)	9 (1.1%)	23 (0.5%)	0.015
Liver disease	12 (0.2%)	1 (0.1%)	11 (0.2%)	0.604
Symptoms at presentation				
<i>Respiratory symptoms</i>				
Cough	1897 (32.2%)	240 (30.3%)	1657 (32.5%)	0.226
Having sputum	779 (13.2%)	114 (14.4%)	665 (13.0%)	0.291
Sore throat	841 (14.3%)	80 (10.1%)	761 (14.9%)	< 0.001
Runny nose	608 (10.3%)	69 (8.7%)	539 (10.6%)	0.112
Shortness of breath	312 (5.3%)	55 (7.0%)	257 (5.0%)	0.026
<i>Gastrointestinal symptoms</i>				
Diarrhea	298 (5.1%)	38 (4.8%)	260 (5.1%)	0.724
Nausea and vomiting	108 (1.8%)	6 (0.8%)	102 (2.0%)	0.015
<i>Constitutional symptoms</i>				
Fever	1737(29.5%)	194 (24.5%)	1543 (30.3%)	< 0.001
Myalgia	238 (4.0%)	20 (2.5%)	218 (4.3%)	0.020
Arthralgia	124 (2.1%)	17 (2.1%)	107 (2.1%)	0.927
Fatigue	202 (3.4%)	27 (3.4%)	175 (3.4%)	0.978
Headache	189 (3.2%)	19 (2.4%)	170 (3.3%)	0.166
Admission case classification (n,%)				
Asymptomatic	2956 (50.2%)	412 (52.1%)	2544 (49.9%)	0.042
Symptomatic	1859 (31.6%)	219 (27.7%)	1640 (32.2%)	
Pneumonia without hypoxia	801 (13.6%)	112 (14.2%)	689 (13.5%)	
Pneumonia with hypoxia	210 (3.6%)	35 (4.4%)	175 (3.4%)	
Critically ill	63 (1.1%)	13 (1.6%)	50 (1.0%)	
Duration of admission (mean, SD)	14.8 (9.2)	14.5 (8.3)	14.8 (9.3)	0.953

Table 3
Physical examination upon admission and investigations conducted on patients with COVID-19.

Variable	Total(n=5889)	Ever smoke (n=791)	Never smoke (n=5098)	p value
Physical examination				
Blood pressure (mean, SD)				
Systolic	129.8 (17.6)	131.0 (17.5)	129.6 (17.6)	0.012
Diastolic	78.3 (11.8)	78.9 (11.5)	78.2 (11.8)	0.139
Pulse rate (mean, SD)	84.6 (13.8)	82.4 (14.1)	84.9 (13.7)	< 0.001
Respiratory rate (mean, SD)	19 (2.531)	19.193 (2.046)	19.184 (2.598)	0.533
Temperature (mean, SD)	36.8 (0.5)	36.7 (0.5)	36.8 (0.5)	0.018
Blood Investigation and Imaging				
Full blood count (mean, SD)				
White blood cells	7.8 (2.4)	8.1 (2.4)	7.7 (2.4)	< 0.001
Hemoglobin	14.4 (4.4)	14.9 (1.4)	14.3 (4.7)	< 0.001
Hematocrit	42.5 (8.9)	44.4 (5.8)	42.2 (9.3)	< 0.001
Platelet	270.0 (80.5)	264.5 (73.0)	270.9 (81.6)	0.147
Neutrophil count	4.7 (2.0)	4.9 (2.0)	4.6 (2.0)	0.002
Lymphocyte count	2.2 (0.9)	2.3 (0.9)	2.2 (0.9)	0.226
C-Reactive Protein (CRP) (mean, SD)	15.1 (41.1)	14.6 (43.6)	15.2 (40.6)	0.565
High CRP (≥5mg/dl) (n,%)	859 (27.7%)	104 (22.6%)	755 (28.6%)	0.008
Liver enzymes (mean, SD)				
ALT	35.5 (32.9)	38.8 (30.8)	35.0 (33.3)	< 0.001
AST	30.9 (26.0)	29.3 (15.6)	31.2 (27.3)	0.900
LDH (mean, SD)	246.0 (99.6)	235.4 (78.9)	247.8 (102.7)	0.002
Lymphopenia (<1 cell/uL) (n,%)	157 (4.5%)	11 (2.2%)	146 (4.9%)	0.008
Abnormal Chest X-ray (n,%)	1399 (31.0%)	222 (33.0%)	1177 (30.6%)	0.208

Table 4
Complications and outcomes of patients with COVID-19 according to smoking status.

Variable	Total (n=5889)	Ever smoke (n=791)	Never smoke (n=5098)	p value
Complications (n,%)				
Liver injury	393 (4.0)	66 (8.4)	327 (6.4)	0.043
Renal injury	236 (4.0)	45 (5.7)	191 (3.8)	0.010
Acute respiratory distress syndrome	136 (2.3)	28 (3.5)	108 (2.1)	0.013
Pleural effusion	27 (0.5)	5 (0.6)	22 (0.4)	0.437
Deep Vein Thrombosis	10 (0.2)	4 (0.5)	6 (0.1)	0.014
Seizure	7 (0.1)	3 (0.4)	4 (0.1)	0.022
Heart failure	19 (0.3)	5 (0.6)	14 (0.3)	0.099
Endocarditis	12 (0.2)	3 (0.4)	9 (0.2)	0.239
Cardiac arrhythmia	41 (0.7)	6 (0.8)	35 (0.7)	0.820
Cardiac arrest	38 (0.6)	8 (1.0)	30 (0.6)	0.167
Bacteremia	39 (0.7)	8 (1.0)	31 (0.6)	0.193
Admission to ICU (n,%)	193 (3.3)	34 (4.3)	159 (3.1)	0.083
Require oxygen (n,%)	474 (8.0)	71 (9.0)	403 (7.9)	0.303
Type of ventilation (n,%)				
Invasive	26 (3.3)	112 (2.2)	138 (2.3)	0.059
Non-invasive	49 (0.8)	6 (0.8)	43 (0.8)	0.806
Worst diagnosis outcome (n,%)				
No pneumonia	4211 (71.5)	545 (68.9)	3666 (71.9)	0.166
Pneumonia without hypoxia	1207 (20.5)	176 (22.3)	1031 (20.2)	
Pneumonia with hypoxia	303 (5.1)	40 (5.1)	263 (5.2)	
Critically ill	168 (2.9)	30 (3.8)	138 (2.7)	
Final outcome (n,%)				
Alive	5816 (98.9)	776 (98.1)	5040 (98.9)	0.073
Died	73 (1.2)	15 (1.9)	58 (1.1)	

Table 5
Logistic regression between smoking status, complications and outcomes of COVID-19 infection.

Variable	Smoking status Ever smoke (n,%)	Never smoke (n,%)	Odd Ratio(OR, 95% CI)	p-value
Complications				
Liver Injury				
Yes	66 (8.4)	327 (6.4)	1.33 (1.01-1.74)	0.043
No	719 (91.6)	4782 (93.6)		
Renal Injury				
Yes	45 (5.7)	191 (3.8)	1.55 (1.10- 2.14)	0.010
No	744 (94.3)	4835 (96.2)		
Acute Respiratory Distress Syndrome				
Yes	28 (3.5)	108 (2.1)	1.69 (1.09-2.55)	0.013
No	763 (96.5)	4984 (97.9)		
Disease Outcomes				
Admission to ICU				
Yes	34 (4.3)	159 (3.1)	1.40 (0.94-2.01)	0.084
No	757 (95.7)	4939 (96.9)		
Require invasive ventilation				
Yes	26 (3.3)	112 (2.2)	1.51 (0.96-2.30)	0.061
No	765 (96.7)	4986 (97.8)		
Died				
Yes	15 (1.9)	58 (1.1)	1.68 (0.91-2.90)	0.076
No	776 (98.1)	5040 (98.9)		

of smoking status, no biochemical verification of smoking status, especially in those claimed as non-smokers, and differences in the population characteristics that were being compared, suggesting a systematic error that compromised the conclusions. For our study, data were based on hospital record that was documented by the healthcare personnel, and smoking status was based on patient self-declaration upon admission to the hospital that most likely led to underreporting of smoking status in the COVID-19 cases in Malaysia.

In this study, current smokers and former smokers were grouped as ever smokers. This is due to the limitation in our data on the detailed history of quit smoking duration in former smokers. According to the Malaysian Clinical Practice Guidelines (CPG) Treatment of Tobacco Disorder 2016 (Ministry of Health, Malaysia 2016), a smoker is considered as a former smoker once he has successfully quit smoking, which is complete abstinence without

even a single puff of cigarette for at least six months from the last cigarette smoked. Therefore, the data on the history of smoking was incomplete and those patients who declared themselves as former smokers might not fulfill the definition of former smokers. The other important limitation is the duration of smoking in smokers, which was not assessed in this study. Patients who have been smoking for a longer duration are more likely to have a higher risk of complications than those who have been smoking for a shorter duration.

In all patients with COVID-19, ever smokers were found to be significantly ($p < 0.001$) much older (36 years old) compared with the non-smokers (34 years old). Although statistically significantly different, the median age of smokers is only two years older than never smokers, which may not have clinical significance. As reported in the Sim et al. (2020) study, the majority of affected individuals in Malaysia during this study period were of younger age

Table 6

Subgroup analysis between current, former and non-smokers with complications and disease outcomes.

Variable	Smoking status Current smoker(n,%)	Former smoker(n,%)	Non-smoker (n,%)	Current vs non-smoker(p-value)	Current vs formersmoker(p-value)
Complications					
Liver Injury					
Yes	36 (6.8)	30 (11.5)	327 (6.4)	0.733	0.025
No	493 (93.2)	231 (88.5)	4765 (93.6)		
Renal injury					
Yes	20 (3.8)	25 (9.6)	191 (3.8)	0.972	<0.001
No	509 (96.2)	236 (90.4)	4902 (96.2)		
Acute Respiratory Distress Syndrome					
Yes	15 (2.8)	13 (5.0)	108 (2.1)	0.287	0.125
No	514 (97.2)	248 (95.0)	4984 (97.9)		
Disease Outcomes					
Admission to ICU					
Yes	17 (3.2)	17 (6.5)	159 (3.1)	0.905	0.032
No	512 (98.7)	245 (93.5)	4939 (96.9)		
Require invasive ventilation					
Yes	12 (2.3)	14 (5.3)	112 (2.2)	0.915	0.022
No	517 (97.7)	248 (94.7)	4986 (97.8)		
Died					
Yes	7 (1.3)	8 (3.1)	58 (1.1)	0.704	0.093
No	522 (98.7)	254 (96.9)	5040 (98.9)		

group. In contrast, studies from other countries, such as China, Korea, and Singapore, reported a much older group of cases between 40 and 63 years. The difference in the age distribution could be related to the cluster effect from a 3-day religious gathering where most of the participants were young males.

Aging is an important factor that can affect the severity of diseases, especially if the primary organ is the lungs since pulmonary capacity and function decrease as the person ages (Sharma and Goodwin, 2006). In smokers, combinations of age-related lung function reduction and existing lung damage due to smoking were important determinants that lead to severe respiratory problems. This was supported by studies that found the risk of any infection and complications were higher in smokers (van Zyl Smit et al., 2010; Feng et al., 2011; Murin and Bilello, 2005) and elderly people (Gavazzi and Krause, 2002). Interestingly, this study found that in patients with COVID-19 who presented with Stage III and above, the median age for ever smokers was younger compared with never smokers. This further supports the fact that smokers have a higher risk of getting a severe infection owing to existing impairment in their lung function and capacity even though they are still young. Data from a population study in the United Kingdom also found a consistent association between smokers and the risk of developing symptomatic COVID-19 (Hopkinson et al., 2021). Another study from Bangladesh also reported a strong association between smoking and COVID-19 severity (Mohsin et al., 2021).

Based on the COVID-19 daily report by the Ministry of Health Malaysia in 2020, most patients with COVID-19 who died had at least one chronic non-communicable disease (NCD). This was later proven by the findings in the study by Sim et al. (2020) where underlying chronic diseases, such as chronic pulmonary disease or chronic kidney disease, had been identified as one of the important factors related to a more severe COVID-19 infection. In this study, a higher percentage of ever smokers had diabetes, cardiac disease, and chronic pulmonary disease compared with never smokers. This finding was alarming because it shows that smokers have multiple risk factors besides age and smoking status that can also cause them to have severe COVID-19 infection.

Upon presentation to the hospital, a significantly higher percentage of smokers complained of shortness of breath and had a more severe degree of COVID-19 infection. The presence of pneumonia was confirmed by abnormality findings on the chest x-ray, which was noted to be higher in smokers even though it was not statistically significant. This finding is consistent with the find-

ings from different studies conducted in China (Zhang et al., 2020; Guan et al., 2020).

In this study, the severity of the disease was evaluated by the presence of complications and disease outcomes. In terms of complications, the three most common complications in all patients with COVID-19 in Malaysia were acute respiratory distress syndrome (ARDS), acute liver injury, and kidney injury (Sim et al., 2020). In this study, the risks for these three complications were significantly higher in ever smokers compared with the never smokers. Further analysis was conducted between current and former smokers, those patients who reported themselves as former smokers had a higher risk of liver and renal injury compared with current smokers. These findings could be owing to the longer duration of smoking in former smokers than current smokers. Cigarette smoking is a known major risk factor for developing chronic diseases, such as chronic obstructive pulmonary disease, liver disease, and several malignancies (Charatchareonwittaya et al., 2020). The risk of death from these conditions increases with increasing exposure to cigarette smoking, as measured by the number of cigarettes smoked daily and the duration of smoking (Jacobs et al., 1999).

Ever smokers also have a higher risk of deep vein thrombosis and seizure. Tobacco smoke contains many chemicals that are harmful not only to the lung but also to other organs. At the same time, the chemicals in tobacco smoke also affect humoral-mediated immune responses in humans (Piao et al., 2009). All these factors make smokers more vulnerable to developing severe complications if they have any kind of infection. In terms of disease outcomes, this study found that a higher proportion of ever smokers were admitted to the intensive care unit (ICU), required invasive ventilatory support, and died compared with never smokers, although they were not statistically significant. In contrast, the study conducted by Kozak et al. (2020) found a statistically significant association between smoking and ICU admission and mortality amongst 226 patients in Toronto, Canada. Meta-analyses conducted by Zhao et al. (2020) using data from 7 studies (n=1,726 patients) also found a statistically significant association between smoking and severity of COVID-19 outcomes amongst patients (odds ratio, OR: 2.0, 95% CI 1.3 – 3.1). A more recent observational study with a large sample size supports the causal effect of smoking on the risk of severe COVID-19 (Clift et al., 2021).

In this study, there was no significant association found between smoking status with disease complications and outcomes

when other variables such as age, gender, and ethnicity were controlled. This insignificant association is most probably due to several limitations such as recall and documentation biases on smoking history and COVID-19 clinical histories. This is consistent with the Scientific Brief Report published by the World Health Organization in June 2020, where hospital-based studies had several limitations such as poor data quality and difficulty in collecting the history of smoking in an emergency context. On the other hand, during this initial pandemic wave in Malaysia, all patients diagnosed with COVID-19 were admitted to the hospital regardless of their severity as the country policy to curb the spread of this disease. In addition, the Mortality Rate and the Recovery Rate at that point of time were at 1.48% and 81.60%, respectively. These rates indicate that the clinical management of patients with COVID-19 in Malaysia is good and at par with other countries that were affected by the pandemic.

Despite the limitations that were mentioned earlier, this is the first study in Malaysia that investigated the association between smoking and COVID-19 infection using a large sample size. Although current analysis remains limited owing to the quality of data collected, early findings from this study will support the current policy for tobacco control and allow for better prevention and treatment of smoking cessation to reduce the burden of serious complications of COVID-19 infection in smokers.

5. Conclusions

The findings from this study further support the current evidence that suggests an association of smoking with COVID-19 complications and disease progression. As COVID-19 is still evolving, further research is warranted to determine the exact nature and magnitude of the association between smoking and COVID-19. Nevertheless, this pandemic brings the best opportunity for public health to continue highlighting the benefits of quitting smoking.

Ethics

The study was registered with the National Medical Research Register (NMRR-20-580-54339) and approved by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (KKM/NIHSEC/P20–706).

Competing interests

The authors declare that they have no competing interests.

Funding Source

No funding was required for this research.

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All authors contributed equally to this paper.

Acknowledgments

The authors would like to thank the Director-General of Health Malaysia for his permission to publish this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijid.2022.01.011](https://doi.org/10.1016/j.ijid.2022.01.011).

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