Original Article

The Relationship Between Smoking Status and Smoking Index Against COVID-19 Disease Course in Treated Patients at Dr. M Djamil General Hospital, Padang

Yulia Helexandra, Yessy S Sabri, Fenty Anggrainy

Department of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Andalas, dr. M. Djamil General Hospital, Padang

Corresponding Author:
Yulia Helenxandra | Department of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Andalas, dr. M. Djamil General Hospital, Padang | yhelexandra@gmail.com

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Abstract

Background: Smoking is a risk factor for the development and worsening of respiratory diseases, including COVID-19 infection. Smoking can increase the risk of the severity of COVID-19 by two times because in smokers there is an increase in the expression of the ACE-2 gene by 25% compared to non-smokers. The purpose of this study was to determine the relationship between smoking status and smoking index on the course of COVID-19 disease treated at Dr. M Djamil General Hospital.

Method: An observational analytic study with a retrospective cohort approach on COVID-19 patients who were treated at Dr. M. Djamil General Hospital. Data were taken from January to March 2021. The relationship between smoking status and smoking index on the course of COVID-19 was analyzed by Chi-Square.

Results: This study found the most age was above 50 years with a vulnerable age of 50-59 years (28.4%) and female gender (56.7%). Non-smoker status (64.2%) and moderate smoking index (51.4%) were the most commonly found in this study. Clinically non-progressive COVID-19 (53.7%) was the most common. This study found that the maximum length of stay for COVID-19 patients was less than 21 days (53.7%) and the outcome of patients recovered (62.2%). This study found a significant relationship between the smoking index on the clinical progress of COVID-19 patients and there was a significant relationship between smoking status and the outcome of COVID-19 patients. This study found that smoking status and the smoking index had no significant relationship with the length of stay of COVID-19 patients.

Conclusion: Smoking status is related to outcomes in COVID-19 patients and the smoking index is related to a progression in COVID-19 patients treated at Dr. M. Djamil General Hospital.

Keywords: COVID-19, smoking status, smoking index, progression, outcome.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a respiratory infection caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2). The Director-

General of the World Health Organization (WHO) officially, declared this disease a pandemic on March 11, 2020. Cases of COVID-19 as of July 19, 2020, have affected more than 200 countries with a total of 14 million cases with nearly 600 thousand deaths and a mortality rate of 4.3%. COVID-19 cases in Indonesia in March 2021 were around 1,403,722 cases, 38,049 cases died and 611,097 cases were declared cured. Data from the Health Office of West Sumatra Province as of March 11, 2021, there were 29,985 cases of COVID-19, 659 cases of which died and 28,297 cases were declared cured, while in the city of Padang there were 14,820 cases of COVID-19, 288 cases of which died and 14,188 cases were declared cured.[1–5]

Smoking is a risk factor for the development and worsening of various respiratory diseases, including COVID-19 infection. Patients with COVID-19 who have a smoking habit or history of smoking have a higher likelihood of developing more severe symptoms of COVID-19 disease than patients who do not smoke, therefore we must know information about smoking status and smoking index in patients whose condition will affect the severity of the disease, the need for mechanical ventilation, the need for hospitalization and mortality in the Intensive Care Unit (ICU). The meta-analytic study of Zhao et al. stating that smoking increases the risk of COVID-19 severity approximately twofold (OR=1.98; 95% CI=1.29–3.05).[6–9]

Research Liu et al. in a retrospective cohort study at three hospitals in Wuhan, China, reported that there was a significantly higher proportion of patients with a history of smoking with more severe COVID-19 disease progression than non-smoking COVID-19 patients (27% and 33% respectively; P=0.018). The cohort study Guan et al. in China found that 173 patients had severe symptoms, and 926 had mild symptoms. Of patients with severe symptoms, 16.9% were current smokers and 5.2% were ex-smokers, in contrast to patients with mild symptoms where 11.8% were current smokers and 1.3% were ex-smokers. Of the group of patients requiring mechanical ventilation, admitted to the ICU, or died, 25.5% were current smokers and 7.6% were ex-smokers.[10]

Research Zhang et al. demonstrated the clinical characteristics of 140 patients with COVID-19. The results showed that among patients with severe conditions (n=58), 3.4% were active smokers and 6.9% were ex-smokers, in contrast to non-severe patients (n=82) of whom 0% were active smokers and 3.7% former smokers, leading to an OR of 2.23; (95% CI=0.65–7.63; P=0.2). Research Liu et al. showed that among the population of 78 COVID-19 patients as the deteriorating group had a significantly higher proportion of patients with a history of smoking (27.3%) than the group showing improvement or stabilization (3.0%), with a statistically significant difference (P=0.018). Multivariate logistic regression showed that smoking history was a risk factor for disease progression (OR=14.28; 95% CI=1.58-25.00; P=0.018). A meta-analysis research conducted by Salah et al. showed

that there was a greater number of deaths in COVID-19 patients in smokers (29.4%) compared to non-smokers (17.0%).[11,12] This study was conducted to assess the relationship between smoking status and smoking index on the course of COVID-19 disease (clinical progression, length of stay, and the outcome) in patients treated at Dr. M Djamil General Hospital, as a COVID-19 referral hospital in West Sumatra.

METHOD

This study is an observational analytic study with a retrospective cohort design approach. The research was conducted at Dr. M Djamil General Hospital from January to September 2021 with secondary data from medical records of patients treated in the COVID-19 isolation room at Dr. M Djamil General Hospital.

This research has been approved by the research ethics committee of Dr. M Djamil General Hospital dated April 23, 2021. Inclusion criteria were COVID-19 patients aged more than 18 years who were treated at Dr. M Djamil General Hospital. The exclusion criteria were COVID-19 patients who were treated at Dr. M Djamil General Hospital who has the medical record data needed in an incomplete study consisting of smoking status and smoking index and COVID-19 patients who returned at their request.

Research data taken from medical records include age, gender, Body Mass Index (BMI), comorbidities, clinical severity degree, smoking status, smoking index and disease course. Data on the course of COVID-19 disease includes clinical progress (changes in clinical degree, changes in oxygen demand and changes in the treatment room from the usual COVID-19 isolation ward to the COVID-19 HCU or ICU isolation room), length of stay (less than 21 days and more than 21 days) and outcome (recovered, recovered with residual symptoms and died).

Data analysis was carried out descriptively and analytically. The analysis used includes univariate and bivariate analysis. The univariate analysis includes the distribution of the frequency and proportion of each independent and dependent variable in the study. The results of the analysis are presented in the form of tables and narratives. Bivariate analysis was used to find the relationship between independent (smoking status and smoking index) and dependent variables (clinical progress, length of stay and outcome) with statistical tests that were by the data scale using the Chi-square test. If value of $P<0.05$, then there is a relationship between the independent variable and the dependent variable. Analysis of the relationship between smoking status and smoking index with clinical progression (clinical worsening or not), length of stay, and the outcome will be carried out using a computer program.

RESULTS

This research was carried out from January to September 2021 and the research was carried out in the COVID-19 isolation room at Dr. M Djamil General

Hospital with 245 patients in the period January - March 2021. As much as 44 people were excluded from the study because they met the exclusion criteria so that 201 people were included in this study.

Most of the COVID-19 patients in this study were found in patients aged over 50 years with a total of 132 patients and most were found in the age group with a range of 50-59 years with a total of 57 patients (28.4%). More women were found in this study, 114 patients (56.7%). The nutritional status of COVID-19 patients treated based on BMI obtained the most BMI normoweight with 104 patients (51.7%), followed by the second most, namely overweight with 57 patients (28.4%). The most common comorbidities found in COVID-19 patients treated at Dr. M Djamil General Hospital are diabetes mellitus as many as 46 patients (22.9%) and hypertension as many as 42 patients (20.9%).

COVID-19 patients with non-smoker status were found at most, namely 129 patients (64.2%), then in former smokers as many as 42 patients (20.9%) and in smokers, there were 30 patients (14.9%). The most COVID-19 patients with moderate smoking index were 37 patients (51.4%), then 33 patients (45.8%) with severe degrees, and 2 patients (2.8%) with mild degrees.

The clinical degree of COVID-19 patients at the beginning of the patient treatment found to be the most moderate clinical degree, namely 126 people (62.7%), then at a critical clinical degree as many as 60 people (29.9%) and severe clinical degree found 15 patients (7,5%).

Table 1. Basic Characteristics of COVID-19 Patients

Characteristics	N	f (%)
Ages		
<50 years	69	34.3
50-59 years	57	28.4
60-69 years	43	21.4
≥70 years	32	15.9
Gender		
Female	114	56,7
BMI		
Underweight	15	7,5
Normal	104	51,7
Overweight	57	28,4
Obese	25	12,4
Comorbidities		
No Comorbid	57	28,3
Chronic Lung Disease	9	4,5
Cardiovascular Disease	16	8,0
Hypertension	42	20,9
Diabetes Mellitus	46	22,9
Kidney Disease	18	8,9
Liver Disease	5	2,5
Malignant Disease	8	4,0
Smoking Status		
Non-Smoker	129	64.2
Former Smoker	42	20.9
Smoker	30	14.9
Smoking Index		
Mild	2	2.8
Moderate	37	51.4
Severe	33	45.8
Clinical Degree		
Moderate	126	62.7
Severe	15	7.5
Critical	60	29.9
Clinical Progress		
No Progress	108	53.7
Progress	93	46.3
Length of Stay		
≤21 days	108	53.7
>21 days	93	46.3
Outcome		
Recover	125	62.2
Recover with Residual Symptoms	10	5.0
Died	66	32.8

Table 2. The Relationship between Smoking Status and Smoking Index on Clinical Progression of COVID-19 Patients

Characteristics	Progress		No Progress		P
	N	%	N	%	
Smoking Status					
Smoker	16	53,3	14	46,7	
Former Smoker	25	59,5	17	40,5	0,067
Non-Smoker	52	40,3	77	59,7	
Smoking Index					
Mild	0	0	2	100,0	
Moderate	24	64,9	13	35,1	0,028*
Severe	17	51,5	16	48,5	

Note= *P<0,05 statistically significant

Table 3. The Relationship between Smoking Status and Smoking Index based on Length of Treatment in COVID-19 Patients

Characteristics	>21 days		≤21 days		P
	N	%	N	%	
Smoking Status					
Smoker	15	50,0	15	50,0	
Former Smoker	22	52,4	20	47,6	0,543
Non-Smoker	56	43,4	73	56,6	
Smoking Index					
Mild	1	50,0	1	50,0	
Moderate	18	48,6	19	51,4	0,699
Severe	18	54,5	15	45,5	

Note= *P<0,05 significant

Table 4. Relationship between Smoking Status and Smoking Index based on Patient Outcomes in COVID-19 Patients

Characteristics	Died		Recover with Residual Symptoms		Recover		P
	N	%	N	%	N	%	
Smoking Status							
Smoker	13	43,3	2	6,7	15	50,0	
Former Smoker	16	38,1	5	11,9	21	50,0	0,029*
Non-Smoker	37	28,7	3	2,3	89	69,0	
Smoking Index							
Mild	0	0	0	0	2	100,0	
Modered	16	43,2	4	10,8	17	45,9	0,059
Severe	13	39,4	3	9,1	17	51,5	

Note= *P<0,05 significant

Clinical progression in COVID-19 patients treated at Dr. M Djamil General Hospital was the most in the non-progressive group which obtained as many as 108 patients (53.7%), while in the progressive group it was obtained as many as 93 people (46.3%). The length of stay of COVID-19 patients who were treated at Dr. M Djamil General Hospital was most commonly found for less than 21 days, namely 108 patients (53.7%) and with a length of stay of more than 21 days, 93 patients (46.3%). Outcomes of COVID-19 patients treated at Dr. M Djamil General

Hospital found the most was recovered group, as much as 125 patients (62.2%), while in the dead group there were 66 patients (32.8%), and in the recovered group with residual symptoms, 10 patients (5%).

The progression of COVID-19 disease (Table 2) was found in the smoker's group by 53.3% and in the ex-smoker group by 59.5%. The non-smoker group in COVID-19 patients who did not experience progression was found to be 59.7%. The relationship between smoking status and clinical progress of COVID-19 patients treated at Dr. M Djamil General Hospital conducted a Pearson chi-square statistical test and obtained P=0.067. It indicates that there is no relationship between smoking status and clinical progress of COVID-19 patients treated at Dr. M Djamil General Hospital.

The progression of COVID-19 disease in the moderate smoking index group was 64.9% and in the heavy smoking group, it was 51.5%. The degree of light smoking in COVID-19 patients who did not experience progression was 100%. The relationship between the smoking index and the clinical progress of COVID-19 patients treated at Dr. M Djamil General Hospital was analyzed using the Pearson chi-square test and obtained P=0.028 indicating that there is a relationship between the smoking index and the clinical progress of COVID-19 patients treated at Dr. M Djamil General Hospital.

The length of stay for COVID-19 patients was less than 21 days (Table 3), in the non-smoker group by 56.6% and in the smoker's group by 50%. The length of stay for COVID-19 patients more than 21 days was found in the former smoker's group by 52.4% and in the non-smoker group by 43.4%. The relationship between smoking status and length of stay in COVID-19 patients treated at Dr. M Djamil General Hospital conducted a Pearson chi-square analysis test and obtained P=0.543 indicating that there is no relationship between smoking status and length of stay for COVID-19 patients treated at Dr. M Djamil General Hospital.

The length of stay for COVID-19 patients of less than 21 days was found in the mild-grade group by 50% and in the moderate-grade group by 51.4%. The length of stay for COVID-19 patients more than 21 days was found in severe degrees of 54.5% and mild degrees of 50%. The relationship between the smoking index and the length of stay in COVID-19 patients treated at Dr. M Djamil General Hospital conducted a Pearson chi-square analysis test and obtained P=0.699 indicating that there is no relationship between the smoking index and the length of stay of COVID-19 patients treated at Dr. M Djamil General Hospital.

The outcomes of patients who died of COVID-19 were found to be greatest in the smoker's group by 43.3%, the outcomes of recovered patients with residual symptoms were found to be the most in the ex-smokers group by 11.9% and in the outcome of recovered patients, the highest rates were found in the non-smoker group by 69%. The results of the analysis using the Pearson chi-square test obtained

P=0.029 indicating that there is a relationship between smoking status and the outcome of COVID-19 patients treated at Dr. M Djamil General Hospital.

The outcomes of COVID-19 patients who died were found to be greatest in the moderate smoking index group by 43.2% and the heavy smoking index group by 39.4%. For the outcome of recovered patients with residual symptoms, the highest number was found in the moderate smoking index group of 20.8% and the heavy smoking group of 9.1% and on the outcome of the recovered patients, the highest number was found in the light smoking group of 100%. The results of the analysis using the Pearson chi-square test obtained P=0.059 indicating that there is no relationship between the smoking index and the outcome of COVID-19 patients treated at Dr. M Djamil General Hospital.

DISCUSSION

Based on the basic characteristics of COVID-19 patients treated at Dr. M Djamil General Hospital, which is shown in Table 1, it was found that the majority of the age groups in COVID-19 patients in this study were patients who were more than 50 years old with a total of 132 patients. The age group of more than 50 years was obtained the most with an age range of 50-59 years, namely 57 patients (28.4%). The results of this study are similar to the research of Surendra et al. In Jakarta, the study found that there were 1,836 patients aged more than 50 years in the 50-59 year age group as many as 941 patients (22%).[13] Based on the research by Zhang et al. conducted in Wuhan, China, the most patients suffering from COVID-19 were found at the age of over 50 years with the age group 50-69 years as many as 69 patients (49.3%). Most COVID-19 patients are in the age group above 50 years because older people are more susceptible to SARS-CoV-2 infection due to decreased function of T cells and B cells. Some comorbidities are often found in patients over the age of 50 years.[14]

There were more female patients infected with the SARS-CoV-2 virus in this study than male patients, namely 114 patients (56.7%). Different results were found in the study of Surendra et al. which stated that the most COVID-19 patients were found in men as many as 2,217 patients (52%).[13]

In the research of Zhang et al. found that the male group was found to be the most, namely 71 patients (50.7%).[14] Men were found to be more at risk with infection COVID-19 because there were several factors, including in men found more ACE-2 receptors than women and in men expressing more ACE-2 in the lungs and heart, in addition to the organs reproductive system, in which the testes have significantly more ACE-2 receptors than the ovaries. Differences in ACE-2 receptors may affect inflammation control, leading to the more persistent viral presence and deleterious inflammation in males.[14,15]

Differences in the immune system in men also affect and women usually produce a higher immune response when

compared to men. The difference is due to numbers of X of women cells. The X chromosome contains several important genes related to immunity and immune regulation that are extensively involved in shaping sex-specific innate and adaptive immune responses. The X chromosome in COVID-19 infection encodes a protein called Toll-like receptor 7 (TLR7). TLR7 helps control the innate immune response by recognizing single-stranded RNA of viral origin, such as coronavirus RNA that may be overexpressed in women and contribute to more rapid clearance of SARS-CoV-2.[16]

Sex hormones play a role in modulating the immune system and contribute to the variation seen in male and female immunological responses. The male hormone testosterone is immunosuppressive, while the female sex hormone estrogen tends to increase the immune response. Montopoli et al. argued that testosterone stimulates the expression of the TMPRSS2 gene, leading to increased male susceptibility to severe SARS-CoV-2 infection.[17,18]

The results of this study obtained the same results as the research of Chen et al. which shows that women in East Asia express higher ACE-2 receptors so they are more likely to be infected with SARS-CoV-2. Data on the distribution of COVID-19 patients in West Sumatra found the number of female COVID-19 patients (54.9%) in West Sumatra were higher than the male COVID-19 patients.[19]

For the variable of BMI group based on the baseline characteristics table, the normal BMI group was found to be the most (104 patients, 51.7%). The results of this study are by the research of Gao et al. in England, the highest BMI group was in the normal BMI group, which was 2,713,189 patients (39.3%).[20] A higher BMI level 25 in COVID-19 patients contributes for an increased risk of more severe pneumonia. The associated pathogenesis between obesity and severe COVID-19 may include immune dysregulation, comorbidities, and respiratory system disorders. Adiposity is associated with immune dysregulation, including increased inflammation and impaired host immune response.[21]

Fat cells, especially visceral adipocytes, can induce macrophages to release interleukin (IL)-1, IL-6, IL-8, IL-10, tumor necrosis factor-α, c-reactive protein, and resistin. The overproduction of these proinflammatory cytokines, as a cytokine storm, is also a mechanism of lung injury and multi-organ failure in COVID-19. The respiratory system also changes in obese people, namely changes in the respiratory mechanism, increased airway resistance, and decreased lung volume that can interfere with gas exchange.[21]

The comorbid group on the basic characteristics of this study was found to be the most in the no comorbid group, namely 57 patients (28.4%) then followed by the diabetes mellitus comorbid group as many as 46 patients (22.9%). Research Surendra et al. found in the no comorbid group as many as 2,849 patients (69%) then followed by hypertension comorbid as many as 795 patients (19%).[13]

Research Zhang et al. found in the no comorbid group of 90 patients (64.3%), in the hypertension comorbid group as many as 42 patients (30%).[14] Patients who have comorbidities are more susceptible to infection with the SARS-CoV-2 virus because they are in a prolonged pro-inflammatory state, impaired innate and adaptive immune function, and upregulation in patients.[22]

The smoking status group in this study was found more in the non-smoking group. Guan et al was found in non-smoker patients as many as 927 patients (85.4%), in ex-smokers as many as 21 patients (1.9%), and in smokers 137 patients (12.6%).[23] Research Cai et al. stated that smoking patients are very susceptible to COVID-19 infection because in smokers there is an increase in ACE-2 expression (by 25%) in the airway epithelium compared to non-smokers. This increase occurs because nicotine contained in cigarettes can activate peripheral nicotinic acetylcholine receptors (α7-nAChR) which will result in increased expression of the ACE-2 gene. The finding of increased ACE-2 expression in smokers suggests an increased risk for viral binding and the risk of SARS-CoV-2 entry in smokers.[6–9,14]

Furthermore, Cia et al. assessed the effect of smoking on ACE-2 expression in a single bronchial epithelial cell and stated that smoking causes remodeling of bronchial epithelial cells with loss of clara cells and excessive hyperplasia of goblet cells. This condition shows that smokers have a risk of complications of COVID-19 infection based on the ACE-2 expression profile that contributes to infection susceptibility, severity, and therapeutic outcome.[6–9,14]

CDC data showed, in 2019 in the United States, there were thirty-four million adults in the United States who smoked and more than 16 million had smoking-related illnesses. The ratio of male and female smokers is 15.3% and 12.7%.[24]Based on Basic Health Research data (2018), the proportion of the population who smokes consists of 62.9% being male and 4.8% female.[25,26] In this study, the non-smoker group was higher than the smokers, this result was obtained because the sex was mostly female where the female non-smoker group was 112 patients (55.7%) and female smokers were found to be 1 patient (0.49%). The results of this study are by CDC data in the United States and Basic Health Research data that the proportion of smokers is most commonly found in men compared to women.

The smoking index in this study was found to was found to be highest in the moderate degree group, namely, 37 patients (52.4%) and the severe degree group found 33 patients (45.8%). Research Katherine et al. reported that there were moderate grade groups of 67 patients (16.8%), severe grade 56 patients (16.4%), and mild grade 49 patients (14.4%).[27]

The clinical degree of COVID-19 being treated at Dr. M Djamil General Hospital found in the study was found to be the most moderate clinical degrees as many as 126 patients (62.7%). The critical

clinical degree in this study was found in 60 patients (29.9%). Research by Zunyou et al. conducted in China, found that there were 36,160 cases (81%), severe clinical degrees of COVID-19, and 6,168 cases (14%) and 2,087 cases (5%).[27] The clinical degree of COVID-19 patients in this study was found to be at most moderate clinical degrees because the study found the most patients who did not smoke.

Clinical progression in COVID-19 patients treated at Dr. M Djamil General Hospital found the most in this study was in the non-progressive group as many as 108 patients (53.7%) followed by the progressive group found as many as 93 patients (46.3%). Research Liu et al. in China, in 78 COVID-19 patients, there were 67 patients (85.8%) who did not experience progression and 11 patients (14.10%) who experienced progressivity.

Clinical progression in COVID-19 patients is influenced by several factors, namely age. Elderly individuals are physically weak and tend to have several comorbidities or comorbidities, which not only increasing the risk factors for pneumonia but also affecting their prognosis. The proportion of patients with a history of smoking was significantly higher in progression than those without a history of smoking.[12] This study found to non-progressive was the highest because patients who had a history of not smoking were found in this study.

Length of stay for COVID-19 patients treated at Dr. M Djamil General Hospital found in this study the most, namely in the group of the length of stay of fewer than 21 days as many as 108 patients (53.7%) and in the group of the length of stay of more than 21 days found as many as 93 patients (46.3%). Retrospective research Guo et al. conducted in China from January 20 to March 16, 2020, there were 36 patients (47.36%) who were hospitalized for less than 17 days and there were 39 patients (51.31%) who were hospitalized for more than 17 days.[28]

Research Guo et al. in patients hospitalized for more than 17 days was associated with female sex, fever and chronic kidney or liver disease, and elevated creatinine levels. In addition, bilateral pulmonary infiltrates were more often treated for more than 17 days. COVID-19 patients in China are more often male than female. Study of Guo et al. found that women had longer hospital stays than men, and in animal studies that significantly higher levels of ACE-2 were detected in older rats than in male rats.[28] This study was mostly found in hospitalizations of less than 21 days. It's because in this study most female patients usually produced a higher immune response than men. In addition, this study found the most moderate clinical degrees and non-smokers.

Outcomes for COVID-19 patients treated at Dr. M Djamil General Hospital found in this study was the most in the recovered group by 125 patients (62.2%) followed by the dead group with 66 patients (32.8%) and in the recovered group with residual symptoms 10 patients (5.0%) were found). Research Guan et al. conducted on 1,099 patients, there were

1,029 patients (93.6%) who were still being treated including 9 patients (0.8%) who were still recovering (there were still residual symptoms), 55 patients (1.4%) who had recovered and 15 patients (1.4%) died.[23]

Research Osibogun et al. conducted in Nigeria, the highest number of patients recovered was 78.98% and patients who died were 3.34%. The characteristics of recovered patients in Osibogun et al study were the most patients with moderate clinical degree (97.33%), women (97.29%), age 40-49 years (98.90%), and patients who had one comorbidity (91.53%).[29] This study obtained the most with cured outcomes because in this study the most women were found, the patient was a non-smoker and the clinical degree was moderate by the research of Osibogun et al.

This study found that the progression of COVID-19 disease in the smoker's group was 53.3% and in the ex-smokers group it was 59.5%. The non-smoker group in COVID-19 patients who did not experience progression was found to be 59.7% and this study shows that there is no significant relationship between smoking status and clinical progression of COVID-19 patients treated at Dr. M Djamil General Hospital with P=0.067.

This study found that the progression of COVID-19 disease in the moderate smoking group was 64.9% and in the heavy smoking group it was 51.5%. The degree of light smoking in COVID-19 patients who did not experience progression was 100%. The relationship between the smoking index and the clinical progress of COVID-19 patients treated at Dr. M Djamil General Hospital, in this study was significant P=0.028.

Smokers are more susceptible to have more severe infections due to poor mucociliary clearance and an exaggerated cellular response characterized by oxidative stress, increased permeability, excess mucus production, and the release of pro-inflammatory cytokines. Therefore, smokers are more likely to develop ARDS and get worse with respiratory disease because of the altered physiology.[12]

Cigarette smoke has been associated with increased expression of ACE-2 in type 2 pneumocytes and alveolar macrophages especially at the epithelial ends of the small airways compared to nonsmokers in COVID-19 patients. Nicotine in cigarettes can activate peripheral nicotinic acetylcholine receptors (α7-nAChR) which affect the homeostasis of the renin-angiotensin system (RAS) and contribute to the regulation of ACE/angiotensin (ANG)-II/ANG-II type 1 which contributes to lung disease. The nicotinic cholinergic system in smokers is also implicated in COVID-19 infection which can create a cytokine storm through the alpha7nicotinate (α7-nAChR) receptor that has the potential to modulate pro-inflammatory cytokine secretion.[12]

Research by Guan et al. which has a larger cohort study involving 1,099 COVID-19 patients in 30 provinces in China, found that 173 patients had severe symptoms, and 926 had mild symptoms. Of patients with severe symptoms, 16.9% were active smokers and 5.2% were ex-smokers, in

contrast to patients with mild symptoms where 11.8% were active smokers and 1.3% were ex-smokers. Of the group of patients requiring mechanical ventilation, admitted to the ICU, or died, 25.5% were current smokers and 7.6% were former smokers.[10]

Research by Zhang et al. demonstrated the clinical characteristics of 140 patients with COVID-19. The results showed that among patients with severe conditions (n=58), 3.4% were active smokers and 6.9% were ex-smokers, in contrast to non-severe patients (n=82) of whom 0% were active smokers and 3.7% former smokers, leading to an OR of 2.23; (95% CI=0.65–7.63; P=0.2). Research by Liu et al. showed that among the population of 78 COVID-19 patients as the deteriorating group had a significantly higher proportion of patients with a history of smoking (27.3%) than the group showing improvement or stabilization (3.0%), with a significant difference. statistically significant at the level of p=0.018. Multivariate logistic regression of patients in the study of Liu et al. showed a history of smoking as a risk factor for disease progression (OR=14.28; 95% CI=1.58-25.00; P=0.018).[11,12] The meta-analytic study of Zhao et al. Stating that smoking increases the risk of severity of COVID-19 approximately twofold (OR=1.98, 95% CI=1.29–3.05).[8,9]

The recovery time of COVID-19 patients is reflected by the length of stay which usually occurs on the 21st day after the patient is infected by the SARS-CoV-2 virus. Study by Surendra found that the length of stay for COVID-19 patients was 24 days in all cases and the estimated length of stay for patients who died was usually shorter than those who recovered, with a median of 4 to 21 days compared to 4 to 53 days.[14]

In a retrospective study, Guo et al. conducted in China, 36 patients (47.36%) were hospitalized for less than 17 days and 39 patients (51.31%) were hospitalized for more than 17 days. Research Guo et al. in patients hospitalized for more than 17 days was associated with female sex, fever and chronic kidney or liver disease, and elevated creatinine levels. In addition, bilateral pulmonary infiltrates were more frequently treated for more than 17 days.[28]

This study found that the length of stay of COVID-19 patients was less than 21 days in the non-smoker group by 56.6% and in the smoker's group by 50%. The length of stay for COVID-19 patients more than 21 days was found in the former smoker's group by 52.4% and in the non-smoker group by 43.4%. The relationship between smoking status and length of stay in COVID-19 patients treated at Dr. M Djamil General Hospital obtained P=0.543 indicating that there is no relationship between smoking status and length of stay of COVID-19 patients treated at Dr. M Djamil General Hospital.

This study found that the length of stay for COVID-19 patients was less than 21 days majority in the moderate degree group meanwhile the length of stay for more than 21 days was the majority in severe degrees. The relationship between the smoking index and the length of stay in

COVID-19 patients treated at Dr. M Djamil General Hospital obtained P=0.699 indicating that there is no relationship between the smoking index and the length of stay of COVID-19 patients treated at Dr. M Djamil General Hospital.

In the research of Guan et al. conducted on 1,099 patients, there were 1,029 patients (93.6%) who were still being treated including 9 patients (0.8%) who were still recovering (there were still residual symptoms), 55 patients (1.4%) who had recovered and 15 patients (1.4%) died.[23] COVID-19 patients who are accompanied by a history of smoking and smoking will cause a rapid worsening of the disease.[25,26] Meta-analysis research conducted by Salahet al. shows that there is a greater number of deaths in COVID-19 patients in smokers, namely 29.4% compared to non-smokers, namely 17.0%.[11,12]

This study shows that the outcome of COVID-19 patients who died was found to be the greatest in the smoker's group by 43.3%, the outcome of recovered patients with residual symptoms was found to be the most in the ex-smoker group of 11.9% and the outcome of recovered patients was found to be the most in the non-smoker group by 69%. This study showed a significant relationship between smoking status and the outcomes of COVID-19 patients treated at Dr. M Djamil General Hospital with P=0.029.

This study found that the outcome of COVID-19 patients who died was greatest in the moderate smoking index group by 43.2% and the heavy smoking index group by 39.4%, on the outcome of recovered patients with residual symptoms, the highest number was found in the moderate smoking index group of 20.8% and the heavy smoking group of 9.1% and on the outcome of the recovered patients the highest number was found in the light smoking group of 100%. This study showed that there was no significant relationship between the smoking index and the outcome of COVID-19 patients treated at Dr. M Djamil General Hospital with P=0.059.

This study found a significant relationship between smoking status and the outcome of COVID-19 patients and a significant relationship between the smoking index and clinical progress in COVID-19 patients treated at Dr. M Djamil General Hospital.

LIMITATIONS

There are some limitations to this study, namely, first, this study is a retrospective cohort study with data collection through medical records so that some of the data obtained still requires manual categorization. Second, the research sampling time is short, namely the period from January to March 2021. Third, this study only analyzed the relationship between smoking status and smoking index variables with clinical progression, length of stay, and the outcome in COVID-19 patients, but this study did not analyze other variables (ages, gender, BMI, and comorbidities) that may have a relationship

with clinical progression, length of stay, and the outcome in COVID-19 patients.

CONCLUSION

Characteristics of COVID-19 patients treated at Dr. M Djamil General Hospital are a woman, aged over 50 years with a maximum age group range of 50-59 years, non-smoker, moderate smoking index, clinical degree of COVID-19 is found to be the most moderate clinical degree in the group with moderate non-progressive with a length of stay of fewer than 21 days and the most common outcomes were recovered. There is a significant relationship between the smoking index on the clinical progress of COVID-19 patients but there is no significant relationship with smoking status. There is no significant relationship between smoking status and smoking index on the length of stay of COVID-19 patients treated at Dr. M Djamil General Hospital. There is a significant relationship between smoking status and the outcome of COVID-19 patients, but there is no significant relationship with the smoking index.

Further research is needed to see whether there is a relationship between other variables (ages, gender, BMI, and comorbidities) with clinical progression, length of stay, and the outcome in COVID-19 patients. This study can be used as a reference for management policies for COVID-19 patients who have a history of smoking so that clinical development of more severe COVID-19 disease does not occur and this research can be used as a reference for smoking cessation education in the community so that there is no development of more severe clinical degree of disease.

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