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Original Article

Association of Interleukin-2 (IL-2) Levels With Acid-Fast Bacillus (AFB) Sputum Conversion In Drug-Resistant Pulmonary Tuberculosis Patient

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Abstract

Background: Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb) which can be found on multiple organs, but mostly infect the lung. AFB smear is used to diagnose and evaluate therapy response, to show bacterial burden and the patient's infectious status. Combination of antituberculosis drugs for a long period of time could cause poor compliance and increased risk of resistance. Mtb infection induce immune response and release cytokines, one of which is interleukin-2 (IL-2) that regulate T lymphocyte cell. Higher IL-2 levels is found on patient with high bacterial burdern. This study aims to see the assosciation between IL-2 levels before and 30 days after DR-TB treatment, to see pre and post-treatment IL-2 levels with conversion of AFB smear, and correlation between pre-treatment IL-2 levels and AFB smear.

Method: This was a cohort prospective study at RSUD dr Saiful Anwar Malang. Thirty nine DR-TB patients underwent AFB smear before and 30 days after treatment, while IL-2 levels was also measured by Enzym-Linked Immunosorbent Assay (ELISA) technique.

Results: The levels of IL-2 before treatment was significantly higher compared to 30 days after treatment (P<0.001). There was no significant IL-2 levels difference between conversion and non-conversion group (P=0.23), and a weak, not-significant correlation between IL-2 levels and AFB smear (r=0.28; P=0.06).

Conclusion: The levels of IL-2 was significantly higher before than after treatment and it cannot be used to determine the positivity of acid-resistant bacilli smears in the sputum of patients with DR-TB. The limited timeframe and biomarker in this study raise the possibility to observe IL-2 as well as other biomarkers after intensive phase of TB treatment for future studies.

Keywords: drug resistance tuberculosis (DR-TB) , interleukin-2 (IL-2), AFB smear

INTRODUCTION

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. Despite several trials to implement a tuberculosis elimination strategy, Indonesia has high incidence of the case. World Health Organization (WHO) report on 2019 estimated tuberculosis death rate in Indonesia is 35 per 100,000 population, meaning that around 93,000 people died from tuberculosis (TB) in 2018. The number of tuberculosis cases has increased sharply since 2017 after efforts were done to track tuberculosis cases in hospitals. The number of tuberculosis case reports in 2018 was 565,869 cases, meanwhile, the number of TB case findings in 2019 Global TB Report was 570,289 cases.[1]

One of the burdens of tuberculosis is drug resistance. Rifampicin is an anti-tuberculosis drug that works by binding the RNA-beta polymerase subunit, thereby inhibiting the bacterial mRNA elongation. 96% of rifampicin resistance cases are caused by mutations in the "hot-spot region" by 81-bp spanning codons 507-533 in the rpoB gene.[2]

Drug-resistant tuberculosis (DR-TB) is still a problem frequently found in the world and also in Indonesia. Indonesia is included in high-burden countries for multidrug resistant tuberculosis (MDR-TB) cases. According to WHO, MDR-TB cases are about 3.3% of new cases. The proportion of MDR-TB mostly came from patients who had previously received anti-tuberculosis therapy, which counts to around 20%.[3]

In 2015, it was reported that there were 9.6 million new TB cases around the world, with 480,000 cases being MDR-TB with mortality rate of 190,000. Globally, in 2016, around 4.1% of new cases and 19% of previously treated cases were diagnosed with MDR-TB or rifampicin-resistant tuberculosis (RR-TB).[3]

The incidence of MDR-TB in 2015 was estimated to be around 600,000, with 82% (490,000) of cases being MDR-TB and the rest were rifampicin-resistant TB. The countries with leading MDR-TB cases were China, India, and Russia. Mortality caused by MDR-TB were around 240,000 cases. Meanwhile, the proportion for extensively drug resistant tuberculosis (XDR-TB) was around 6.2%. In Indonesia alone, there were 2.8% of new MDR-TB cases, with 16% of cases being patients who have been treated for TB. There were around 12 patients per 100,000 population who suffered from MDR-TB with the percentage of MDR-TB being 68%.[3,4] Based on the data from Prasetya, the proportion of new DR-TB patients at Saiful Anwar Hospital Malang reached 21 new patients each month.[5]

There are several cytokines which had a role in tuberculosis immunopathogenesis, i.e., interleukin-2 (IL-2), IL-4, and IL-10. Interleukin 2 is a cytokine that has been studied to be a recombinant for adjunctive immunological therapy against tuberculosis. Using this study, we had baseline data on IL-2 levels in new DR-TB cases and after 1 month of treatment. This is because the activation of IL-2 by T cells will activate immune response. Before performing as a

treatment, it is necessary to detect IL-2 levels in TB patients, especially in patients with drug resistance.[6]

There are previous studies assessing IL-2 levels in active tuberculosis patients. When it was compared between early diagnosis and after 2 months of antituberculosis drug therapy, IL-2 levels were found to be significantly higher in early detection. In addition, IL-2 levels on patients with TB were found to be higher than healthy patients.[6]

Conversion of sputum smear also determines whether the disease is infectious, the potential of transmission from TB patients to the community and resistance to antituberculosis drugs leads to poorer outcomes.[7,8] A study by Kim et al, showed that at 4 weeks of treatment, the sputum conversion rate was 52.7% in drug-sensitive-TB group and 45.7% in MDR and XDR-TB groups. Based on a study by Prasetya in 2019 at Saiful Anwar Hospital Malang, BTA sputum conversion time was obtained the most within the first month by 35.3%.[5]

This study will assess IL-2 levels in newly diagnosed TB patients with drug resistance, prior to and 1 month after DR-TB treatment.

METHOD

This is a cohort prospective study, conducted in March-July 2020. This study was conducted on pulmonary TB patients who were treated at MDR-TB Polyclinic at dr. Saiful Anwar Malang. The inclusion criteria in this study were patients diagnosed with rifampicin-resistant pulmonaryTB, aged 18-65 years, who were willing to participate in the study and signed an informed consent. Patients who had received anti-MDR-TB drugs for ≥1 month, patients with Human Immunodeficiency Virus (HIV) and pregnant women were not included in this study. The minimum sample size was 38. Samples were obtained by means of consecutive sampling that fulfilled the criterias. In this study, 39 subjects who met the inclusion and exclusion criteria were subjected to Acid Fast Bacillus (AFB) sputum smear and IL-2 levels measurement on day 0 and day 30 after receiving MDR-TB treatment (Shorter Regimen/Longer Regimen).

Data processing and analysis were carried out using IBM SPSS version 22.0 software. The data is tested for normality first to determine whether the data distribution is normal or not. The relationship between IL-2 levels before treatment and sputum smear result will be analyzed using Person correlation test if data with normal distribution or Spearman correlation test if data with abnormal distribution. The differences in IL-2 levels on day 0 and day 30 based on the conversion status of AFB sputum smear were analyzed using independent T-test if data with normal distribution or Mann-Whitney if data with abnormal distribution. Differences in IL-2 levels before and after treatment were analyzed using paired T-test if data with normal distribution or Wilcoxon if data with abnormal distribution.

The degree of confidence used is 95% or α=0.05

RESULTS

This research was conducted from March to July 2020, at the MDR-TB Polyclinic at dr. Saiful Anwar Malang. There were 39 subjects who met the inclusion and exclusion criteria and were willing to take part in the study by signing an informed consent.

The subjects of this study were rifampicin-resistant pulmonary TB patients aged 18-65 years with 44.85±12.85 years. Most of the research subjects were male which counted to 25 subjects and female which counted to 19 subjects. The research subjects had a mean body mass index (BMI) of 18.67±3.08. Most of the subjects (26 people) had previous history of pulmonary TB. Based on data on comorbid diseases, there were 13 subjects with DM and 3 with cardiovascular diseases as shown in Table 1.

Based on the clinical data recapitulation of DR-TB patients on treatment at dr. Saiful Anwar Malang, obtained results as shown in Table 2. Based on clinical symptoms, the majority of complaints were coughing for more than 2 weeks, as found in 26 subjects (66.7%). The main complaints of study subjects, ranged from the most to the least frequency, were prolonged cough, hemoptysis, shortness of breath, weakness and fever.

Table 1. Characteristic of the Study Subjects

Characteristics	N (%)	Mean±SD	CI 95%
Age		44,85±12,85	40,68-49,01
<20 years old	1 (2,6)		
20-29 years old	6 (15,4)		
30-39 years old	5 (12,8)		
40-49 years old	10 (25,6)		
50-59 years old	11 (28,2)		
60-69 years old	6 (15,4)		
Sex			
Male	20 (51,3)		
Female	19 (48,7)		
BMI		18,67±3,08	17,68-19,67
Underweight (<18,5)	18 (46,1)		
Normal (18,5-24,9)	20(51,30)		
Overweight (25-26,9)	1 (2,6)		
Comorbid			
DM	13 (33,3)		
Cardiovascular Disease	3 (7,7)		
No comorbid	26 (66,7)		
History of TB			
Yes	26 (66,7)		
No	13 (33,3)		

Based on laboratory findings for DR-TB patients on treatment at dr. Saiful Anwar Malang, chest X-rays were classified into minimal lesion, moderate lesion and far advance lesion.

Table 2. Clinical Characteristics of the Subjects

Clinical Characteristics	N	%
Chief Complaints		
Chronic cough	26	66,7
Bloody cough (Hemoptysis)	7	17,9
Shortness of breath	3	7,7
Weakness	2	5,1
Fever	1	2,6
TCM Result		
Detected very low	4	10,3
Detected low	4	10,3
Detected medium	22	56,4
Detected high	9	23
Pre-Treatment AFB smear		
Negative	11	28,2
Scant	2	5,2
1+	11	28,2
2+	5	12,8
3+	10	25,6
CXR		
Minimal lession	1	2,6
Moderate lession	13	33,3
Far advance lession	25	64,1
AFB Conversion		
Positive	1	2,6
Negative	38	97,4

The most common findings in this study were far advance lession, as found in 25 people (64.1%). Based on rapid molecular assays, the subjects mostly belonged to MTB detected medium group, as found in 22 people (56.4%). Based on other tests such as AFB smear, the most common findings were consecutively negative, 1+, and 3+. This showed that the number of AFB identified from the patient's sputum vary.

IL-2 levels measured pre-treatment and 30 days after treatment were not normally distributed, thus, data transformation was performed with $\log_{10}$ function. IL-2 levels were examined using ELISA method and measured in units of pg/ml. Paired T-test was performed to see whether there was a significant difference between IL-2 levels before and 30 days after treatment. Subjects underwent DR-TB therapy regimen and regularly took the drug for 1 month. In this study, the range of IL-2 was found between 2.119 – 37.982 pg/mL. Analysis with paired T-test can be seen in Table 3. Paired T-test showed a significant decrease in IL-2 values before and 30 days after treatment.

Table 3. Paired T test to compare IL-2 levels before and after treatment

Characteristics	Mean±SD (pg/ml)	P
IL-2 before treatment	0,94 (0,25)	<0,001
IL-2 after 1 month of treatment	0,72 (0,24)	

Table 4. Correlation between Il-2 levels before and 30 days after treatment based on AFB conversion status

Characteristics	Mean±SD (pg/ml)	P	CI 95%
Before treatment			
Non-conversion (n=1)	0,64	0,23	-0,31 (-0,82-0,20)
Conversion (n=38)	0,95 (0,25)		
After treatment			
Non-conversion (n=1)	0,46	0,28	-0,27 (-0,77-0,23)
Conversion (n=38)	0,73 (0,24)		

To see the correlation between IL-2 levels before and 30 days after treatment with BTA conversion, the independent T-test was performed. Comparison of IL-2 levels was carried out in groups with positive and negative BTA conversion. The value of group with a positive BTA result was 1 person, while the value of groups with a negative BTA result was 38 people. The correlation between IL-2 levels before and 30 days after treatment with BTA conversion can be seen in Table 4.

The difference between pre-treatment IL-2 levels in the conversion and non-conversion groups was 0.27 pg/ml. Meanwhile, the difference between IL-2 levels 30 days after treatment in the conversion and non-conversion groups was 0.31 pg/ml. There was no significant difference in IL-2 levels between the conversion and non-conversion groups before and after treatment.

The correlation between pre-treatment IL-2 values and AFB smear was analyzed using the Spearman test. This test was conducted to see whether there was a linear correlation between IL-2 value and AFB smear. The analysis result obtained the value of r=0.28 and P=0.064.

There was a weak correlation between IL-2 levels and AFB smear ($0.2<r<0.4$). The value of r showed a positive correlation, meaning that the higher IL-2 value was, the more BTA could be found. The value of $P>0.05$ that indicated that the correlation between two variables is not statistically significant.

DISCUSSION

The average the subjects age in this study was within the productive range. Based on 2017 WHO report and 2016 Indonesian Minister of Health Regulation, the productive age group is has the highest TB incidence. This is due to high mobility and wide social contacts out of the house in this group. Apart from contacting the disease, this group also plays a role in TB transmission.[9]

In this age range, various diseases such as diabetes mellitus and HIV also begin to arose, thus, increases the risk of TB infection. A study conducted in Shenzhen, China, showed a significant increase in TB incidence annually from 2011 to 2016 within the >45 years age group.[9] Similar results were found in a study conducted in Guangzhou from 2007 to 2012. The incidence of TB significantly rises in the 45-64 years age group. The high TB incidence in this population can be caused by dense living environments, poor sanitation, low public health awareness, and limited access to health facilities.[10]

The number of male and female subjects in this study was nearly the same, viz, 20 male subjects and 19 females. Data from WHO 2017 showed that nearly 6 million men suffer from TB with a death rate of 840,000, while there are 3.2 million cases in women with a death rate of nearly 500,000. This is in accordance to a study by Paudel which stated that DR-TB patients were dominated by male population. The high rate of DR-TB infection in males was associated with a history of dropping out of

treatment, in which with males are more prone to than females.[11] The higher ration of male TB patients, especially in developing countries, is caused by various socioeconomic factors. Men's role is more likely to be the backbone of the family, thus, having a higher likelihood of being accepted into a work sector that is not well organized. Low health awareness and working hours which limits the time used to go to health facilities also played an important role in the high number of TB cases in men.[12] The ratio of male and female subjects in this study was 1:1. This is probably due to the small number of samples and the use of consecutive sampling method, therefore making this number not accurately describing the actual ratio in the community.

Based on the results of the study, it was found that 66.7% of DR-TB patients in this study did not have comorbidities, while 33.3% had DM and 7.7% had cardiovascular disorders. This is in accordance with the research conducted by Prasetya in 2019 in Malang, in which was found that DR-TB patients with comorbidities are 43.8%, 42.6% of which being DM and 1.2% of which being HIV. Another study found that the prevalence of MD-TB in DM patients was 36% and TB patients with DM had a risk of becoming DR-TB patients 8.6 times greater than those without DM. DM can increase the risk of failure or relapse in TB treatment, and in TB patients with DM there was a delay in sputum conversion.[13]

Normal BMI range in Asian population is 18.5-23 kg/m^2. The average BMI in this study was 18.67 kg/m^2. Even though this value is still within the normal range, it is still within the lower limit, thus, it can be assumed that the nutritional status of the patient tends to be below average or poor. There is a strong correlation between pulmonary TB infection and low BMI. A study conducted in Korea on 304,202 subjects found that the risk of TB infection decreased as BMI increased. This protective effect can be explained as release of proinflammatory and tumor necrosis factor (TNF) markers in patients who have more visceral fat which tends to be higher. The presence of proinflammatory markers acts as an immune mediator that protects against TB infection.[14] Low BMI are also associated with TB reinfection and higher mortality rates in TB-HIV patients.[15]

About 66.7% of subjects in this study had a previous history of pulmonary TB. A research by Rifat et al. showed that 54% of MDR-TB patients had previously been infected with TB. Most MDR-TB patients underwent treatment more than once.[16] Unregulated TB treatment can lead to increase of *Mycobacterium tuberculosis* resistance pattern. In addition, poor health care in inadequate health facilities and transmission in the community also increases the incidence of MDR-TB. Similar results were also obtained in a research conducted in 2019 by Prasetya in Malang, in which was stated that 47.1% of diagnosed DR-TB patients were relapse cases where the patients had previous history of pulmonary TB and had underwent treatment.[5]

Clinical symptoms of TB were divided into respiratory complaints, include chronic cough, hemoptysis, shortness of breath, and non-respiratory complaints, for instance fever and weakness. The most frequently complained symptom in this study was prolonged cough (66.7%) while the least one was fever (2.6%). These results are in concordance with a study conducted by Tolossa et al. in Ethiopia in 2013. Tolossa et al. found that 72.4% patients had complained chronic cough as the main symptom.[17]

In Prasetya's study, the patients mostly complained with productive cough (wet cough) of more than 2 weeks, which were found in all subjects (100%).[5] Generally, the symptoms of DR-TB were the same as drug-sensitive-TB, in which the most common symptom was chronic cough. Another study conducted by Sirait et al also showed that the most common complaint (88%) was chronic cough.[18] Other symptoms that might be present are shortness of breath, chest pain, bloody cough or hemoptysis, and systemic symptoms i.e., fever, chills, night sweats, fatigue or malaise, and weight loss.[19]

About 71.8% of subjects in this study had positive AFB smear result (scanty, 1+, 2+, 3+). Systematic review and meta-analysis conducted by Hermosilla S et al using 162,574 subjects from 14 countries showed a positive smear result in 52% of adult TB patients.[20] Patients with positive smear had a higher risk of transmission than patients with negative smear result. The high results in this study, more than expected, can be due to the high burden and rate of infection in Indonesia. In addition, 33.3% of patients in this study had diabetes mellitus. Patients with diabetes mellitus had a higher probability of having a positive smear result than patients without diabetes mellitus (OR=5.0; 95% CI=2.4-20.7; P<0.01).[21]

AFB conversion in this study was assessed after the subjects underwent treatment for 30 days. 97.4% of patients had negative AFB conversion while 1 (2.6%) had not. However, the patient still showed a conversion from +3 to +1. This result is different from a study conducted in Lianyungang, China in 92 patients with MDR-TB. The median of duration for AFB conversion to negative was 1 month, however, only 60% of patients had AFB conversion at the end of treatment in the second month. Patients who experienced conversion within 2 months of treatment had a better outcome than patients who did not experience conversion (OR=7.19, CI 95%=2.60-19.84). The sensitivity and specificity of the conversion results to predict the outcome were 67.6% (CI 95%=50.2-82.0) and 76.4% (CI 95%=32.0-65.6). Patients responsive to ofloxacin are known to show a better response to therapy.[22]

Another study conducted in Ethiopia in 235 MDR TB patients showed a higher conversion rate. The median duration required for conversion was 54 days. The number of patients who successfully experience conversion to negative at the end of the second month of treatment was 89.2%. Patients with TB-HIV or low BMI experienced a longer conversion time.[23]

The high rate of AFB conversion within 1 month in this study could be due to the high effectiveness of the drug regimen, the absence of HIV as a comorbid in the patients, and the BMI of patients who were still within normal range.

Radiological chest X-ray in this study showed that the most common lesions were far advanced lung lesions, followed by moderate and minimal lesions. Several studies of DR-TB patients showed similar results, in which the X-ray showed cavitas, fibrosis, consolidation, calcification, atelectasis, and bullae.[24] Another study by Prasetya in 2019 found that the majority of chest X-ray examination of DR-TB patients showed lung TB with extensive lesions (90.6%). The sensitivity and specificity of chest X-ray in diagnosing TB were 86% and 83%.[5] A study by Sihombing et al on DR-TB patients showed infiltrate on 81 subjects (92.25%) cavity on 15 subjects (17.65%) and pleural effusion on 11 subjects (12.94%). Chest imaging on TB patients can provide an overview of various kinds of lesions.[25]

The IL-2 values in this study were measured twice, viz. before and 30 days after treatment. Pre-treatment IL-2 had a higher mean value than after treatment IL-2. There was a significant difference between IL-2 before and 30 days after treatment ($P<0.001$).The IL-2 is a cytokine produced by Th0, Th1 and some Cytotoxic T Lymphocytes (CTL). These cytokines stimulate the growth of B, T and NK cells, which subsequently stimulate the immune system through proliferation, maintain T lymphocytes and differentiate naïve T lymphocytes into effectors and memory cells. They are essential for cellular immunity and granuloma formation in MTB infection.[26] A study conducted by Hur et al. showed a significant increase in IL-2 on active TB patients compared to healthy patients.[27] Similar results were found in the study conducted by Wang et al. on 215 subjects. The IL-2 values were significantly higher in the group with active pulmonary TB than in the inactive TB and control groups.[28]

There are several studies that further assess the role of IL-2 as a diagnostic tool. The IL-2 performed well in identifying TB and non-TB patients, however it still failed to differentiate active and latent TB.[29] The results in this study support the role of IL-2 as a diagnostic tool. The significant reduction in IL-2 after 30 days of treatment also suggests its potential as a tool for evaluation of therapy in the future.

As previously explained, IL-2 plays a role in stimulating the immune system and protecting against TB infection. Patients with TB infection had higher IL-2 values than the normal group. Higher IL-2 values were also found at the start of treatment and significantly reduced as treatment progressed. In this study, the independent T-test was performed to assess the difference in mean IL-2 values prior to and 30 days after treatment in the positive and negative AFB conversion groups. There is only 1 subject (2.6%) who did not experience AFB conversion to negative after 30 days of treatment. Because there was only 1 subject included in the non-conversion category, the results of

comparation test between the conversion and non-conversion groups were less relevant. The log_{10} value of IL-2 prior to treatment was higher by 0.31 pg/ml (CI 95%=-0.82-0.20; P=0.23) in the conversion group than in the non-conversion group. The log_{10} IL-2 value 30 days after treatment was also higher by 0.27 pg/ml (95% CI=-0.77-0.23, P=0.28) in the conversion group than in the non-conversion group.

The results of this study differ from the results of research conducted by Luo et al. The aforestated research found that the group of patients who did not undergo conversion had significantly higher sIL-2R values than the conversion group. The sIL-2R is an IL-2 receptor found on the cell membrane. This receptor is released together with IL-2 by T cells. This suggests that sIL-2R is associated with the host immune status and severity in patients with active TB. The sIL-2R may be used as a marker to monitor TB patients on treatment.[30]

The difference in results in this study compared to previous studies is most likely because there is only 1 subject out of 39 total subjects who did not experience conversion. Reanalysis of a larger number of non-conversion groups was required to confirm the actual change of IL-2 values.

There was a weak and not-significant correlation between the IL-2 value and the AFB sputum smear ($0.2<r<0.4$; $P>0.05$). A positive R-value indicates that the higher the IL-2 value, the greater amount of AFB can be found in the smear. This result is similar to a study by Luo et al which showed no significant correlation between levels of IL-1β, sIL-2R, IL-6, and TNF-α in patients with lung TB, with the sputum smear classified as 1+, 2+, and 3+. Another study examined levels of IL-2, IL-7, IL-15, and IL-21 cytokines and also showed similar results. There were no significant differences in cytokine values between patients with bilateral and unilateral lung TB. There was also no significant cytokine levels difference in patients with and without cavities. Furthermore, there was no correlation between levels of IL-2, IL-7, IL-15, and IL-21 cytokines and the degree of AFB sputum smear in patients with lung TB. The absence of correlation between IL-2 values and the disease severity and bacterial load does not necessarily confirm their role in the course of TB disease. The IL-2 values are considered to have more influence on susceptibility or patient resistance to infection and do not reflect the pathogenesis of the disease too much.[31]

CONCLUSION

There was a significant decrease of IL-2 levels before treatment compared to 30 days after treatment, however there were significant differences in IL-2 levels before and 30 days after treatment between the conversion and non-conversion groups. There was a weak and not-significant correlation between IL-2 value and AFB sputum smear. A positive value of r indicates that the higher the IL-2 value, the greater the amount of AFB found in the smear results. The significant

reduction in IL-2 levels after 30 days of treatment also suggests its potential as a tool for evaluation and monitoring of therapy.

REFERENCES

1. World Health Organization. *Global Tuberculosis Report 2019*. World Health Organization; 2019.
2. Palomino JC, Martin A. Drug Resistance Mechanisms in Mycobacterium tuberculosis. *Antibiotics*. 2014;3(3):317.
3. World Health Organization (WHO). *Global Tuberculosis Report: Multidrug/Rifampicin-Resistant TB (MDR/RR-TB)*. World Health Organization (WHO); 2017.
4. Kementrian Kesehatan RI. Peraturan Menteri Kesehatan Republik Indonesia Nomor 67 Tahun 2016 tentang Penanggulangan Tuberkulosis. Published online 2016.
5. Prasetya FA. Faktor-faktor yang berpengaruh terhadap keberhasilan pengobatan panduan strandar jangka pendek pasien TBtb resisten obat (TB RO) di RSU dr Saiful Anwar Malang. Published online 2019.
6. AL-Khafaji JK, Al-Mosawi HMA, AL-Saeedi A-SAK. Serum level of IL-2, IgG and IgM in treated and untreated TB patients. *Adv Environ Biol*. 2015;9(27):85-89.
7. Liu Q, Lu P, Martinez L, et al. Factors affecting time to sputum culture conversion and treatment outcome of patients with multidrug-resistant tuberculosis in China. *BMC Infect Dis*. 2018;18(1):1-7.
8. Velayutham B, Nair D, Kannan T, et al. Factors associated with sputum culture conversion in multidrug-resistant pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2016;20(12):1671-1676.
9. Zhu M, Han G, Takiff HE, et al. Times series analysis of age-specific tuberculosis at a rapid developing region in China, 2011–2016. *Sci Rep*. 2018;8(1):1-7. doi:10.1038/s41598-018-27024-w
10. Li X, Li T, Tan S. Males, ages 45 years, businessperson, floating population, and rural residents may be considered high-risk groups for tuberculosis infection in Guangzhou, China: A review of 136,394 TB confirmed cases. *Rev Inst Med Trop Sao Paulo*. 2013;55(5):366-368.
11. Rumende CM. Risk Factors of Multidrug-Resistant Tuberculosis. *Int J Appl Sci Biotechnol*. 2017;5(4):548-554.
12. Nantha YS. A review of tuberculosis research in malaysia . *Med J Malaysia*. 2014;(69 Suppl A):88-102.
13. Viswanathan V, Vigneswari A, Selvan K, Satyavani K, Rajeswari R, Kapur A. Effect of diabetes on treatment outcome of smear-positive pulmonary tuberculosis--a report from South India. *J Diabetes Complications*. 2014;28(2):162-165.
14. Kim J, Kwak N, Lee HY, et al. Effect of drug resistance on negative conversion of sputum culture in

patients with pulmonary tuberculosis. *Int J Infect Dis*. 2016;42:64-68.
15. Naidoo K, Yende-Zuma N, Augustine S. A retrospective cohort study of body mass index and survival in HIV infected patients with and without TB co-infection. *Infect Dis Poverty*. 2018;7(1):1-6.
16. Rifat M, Hall J, Oldmeadow C, Husain A, Hinderaker SG, Milton AH. Factors related to previous tuberculosis treatment of patients with multidrug-resistant tuberculosis in Bangladesh. *BMJ Open*. 2015;5(9):e008273.
17. Tolossa D, Medhin G, Legesse M. Community knowledge, attitude, and practices towards tuberculosis in Shinile town, Somali regional state, eastern Ethiopia: a cross-sectional study. *BMC Public Health*. 2014;14(1).
18. Sirait N, Parwati I, Dewi NS, Suraya N. Validitas Metode Polymerase Chain Reaction GeneXpert MTB/RIF pada Bahan Pemeriksaan Sputum untuk Mendiagnosis Multidrug Resistant Tuberculosis. *Maj Kedokt Bandung*. 2013;45(4):234-240.
19. Kementrian Kesehatan RI. *Pengobatan Nasional Pelayanan Kedokteran Tatalaksana Tuberkulosis*. Kementerian Kesehatan RI; 2019.
20. Kunkel A, Abel zur Wiesch P, Nathavitharana RR, Marx FM, Jenkins HE, Cohen T. Smear positivity in paediatric and adult tuberculosis: Systematic review and meta-analysis. *BMC Infect Dis*. 2016;16(1):1-9.
21. Hermosilla S, You P, Aifah A, et al. Identifying risk factors associated with smear positivity of pulmonary tuberculosis in Kazakhstan. *PLoS One*. 2017;12(3).
22. Lv L, Li T, Xu K, et al. Sputum bacteriology conversion and treatment outcome of patients with multidrug-resistant tuberculosis. *Infect Drug Resist*. 2018;11:147.
23. Shibabaw A, Gelaw B, Wang SH, Tessema B. Time to sputum smear and culture conversions in multidrug resistant tuberculosis at University of Gondar Hospital, Northwest Ethiopia. *PLoS One*. 2018;13(6).
24. Icksan AG, Napitupulu MRS, Nawas MA, Nurwidya F. Chest X-Ray Findings Comparison between Multi-drug-resistant Tuberculosis and Drug-sensitive Tuberculosis. *J Nat Sci Biol Med*. 2018;9(1):42-46.
25. Sihombing H, Sembiring H, Amir Z, Sinaga BY. Pola Resistensi Primer pada Penderita TB Paru Kategori I di RSUP H. Adam Malik, Medan Primary Resistance in Category I of Pulmonary Tuberculosis Patients at Adam Malik Hospital, Medan. *J Respir Indo*. 2012;32:138-183.
26. Romero-Adrian TB, Leal-Montiel J, Fernández G, Valecillo A. Role of cytokines and other factors involved in the Mycobacterium tuberculosis infection. *World J Immunol 2015*. 2015;5(1):16-50.
27. Hur YG, Kang YA, Jang SH, et al. Adjunctive biomarkers for improving diagnosis of tuberculosis and monitoring therapeutic effects. *J Infect*. 2015;70(4):346-355.

28. Wang S, Diao N, Lu C, et al. Evaluation of the Diagnostic Potential of IP-10 and IL-2 as Biomarkers for the Diagnosis of Active and Latent Tuberculosis in a BCG-Vaccinated Population. *PLoS One*. 2012;7(12):e51338.
29. Sun Q, Wei W, Sha W. Potential Role for Mycobacterium tuberculosis Specific IL-2 and IFN-γ Responses in Discriminating between Latent Infection and Active Disease after Long-Term Stimulation. *PLoS One*. 2016;11(12).
30. Luo X, Wu F, Ma J, Xiao H, Cui H. Immunological recovery in patients with pulmonary tuberculosis after intensive phase treatment. *J Int Med Res*. 2018;46(9):3539-3551.
31. Kumar NP, Banurekha V V., Nair D, Babu S. Diminished plasma levels of common γ-chain cytokines in pulmonary tuberculosis and reversal following treatment. *PLoS One*. 2017;12(4):e0176495.

Original Article

Factors Related to Complaints of Lung Function Disorders In UPN Veteran Jakarta Employees

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Abstract

Background: One characteristic of lung dysfunction is obstruction of airflow in the respiratory tract. The prevalence of COPD as lung function disorder among men in Indonesia is 3.7% and 2.7% in DKI Jakarta. One of the causes of decreased lung function is smoking. A large portion of UPN Veteran Jakarta employees is smoker. This research was aimed to determine risk factors of lung dysfunction among employees in UPN Veteran Jakarta.

Method: A cross sectional study was conducted from April to May 2019 in UPN Veteran Jakarta. Total 102 samples of employees who work at UPN includes staff, lecturers, cooperative officers, office boys, and security guards were selected using purposive sampling. Measuring instruments used in this study were questionnaires, scales, microtoise and spirometer. Spirometer was used to measure lung function. Questionnaires to obtain data on gender, age, body mass index (BMI), employment status, education, allergies, history of lung disease, family history, Brinkman index, physical activity, vehicle emissions exposure and smoking environment. The data was analysed using the chi square test and logistic regression test

Results: The results of the logistic regression test showed risk factors of lung dysfunction were BMI (POR: 4.718; 95% CI 1.673-13.305), history of lung disease (POR: 3,424; 95% CI 0.836-14.028) and smoking environment (POR: 2.956; 95% CI 0.953-9.168).

Conclusion: The most influencing factors for lung dysfunction were BMI, history of lung disease, and smoking environment.

Keywords: risk factors, employees, lung dysfunction

INTRODUCTION

One of the lung function disorders is chronic obstructive pulmonary disease (COPD). It is a chronic lung disease characterized by obstruction of air flow in the airways which is progressive, non-reversible or partially reversible.[1] Disorders of the respiratory tract can be in the form of pulmonary function disorders that are obstructive, restrictive and mixed in the form of asthma, lung cancer, mediastinal tumors, tuberculosis, pneumonia and Chronic Obstructive Pulmonary Disease

(COPD).[2] The symptom is a cough for a duration of three months in a year which is experienced at least in two consecutive years and is not caused by other diseases. Emphysema occurs starting with the widening of the air cavities distal to the terminal bronchioles and damage to the walls of the alveoli.[3]

World Health Organization (WHO) in 2013 noted that COPD became the fifth disease with the highest prevalence worldwide, the death rate from this disease continues to increase every year. Chronic obstructive pulmonary disease along with asthma, acute lower respiratory tract infections, tuberculosis and lung cancer are the leading causes of death worldwide. The worldwide prevalence in the moderate to severe category mostly occurs at the age of more than 30 years at 6.3%.[4] Riskesdas showed that the prevalence of COPD in Indonesia in 2013 was 3.7% in men with the prevalence in West Java reaching 4%. While the prevalence of asthma at all ages in Indonesia reached 2.4% and the prevalence of asthma in West Java was around 2.8%.[5]

The main factors of COPD contributing as an irreversible lung function disorder are age, smoking habits, and air pollution. Currently, the number of young smokers, indoor air smokers and outside the workplace smokers are increased. Based on the results of the Indonesian Organization for Economic Co-operation and Development (OECD) economic survey Indonesia has a number of smokers which is high among men about 75% in all age categories but the lowest is among women about 3%.[6]

Research in America states that someone who has a history of asthma will increase the risk of losing lung function more quickly than individuals without a history of the disease.[7] Another study in London, England stated that the prevalence of asthma and bronchial hyperresponsiveness was higher in office boy workers than office workers. Lung function in janitors who have a history of asthma or asthmatics who have a smoking habit have a high risk, as well as office workers who have a history of asthma who have a smoking habit have a high risk of decreasing lung function. The results found that asthma in cleaning workers was accompanied by symptoms of productive cough, leading to chronic bronchitis, in a higher proportion than asthma in office workers.[8]

UPN Veteran Jakarta (UPNVJ) is a state government educational institution, in which employees support the activities of the academic community consisting of staff, lecturers, cooperative officers, office boys/girls and security guards. The working hours of employees are eight hours of work with one break from 12 PM until 1 PM. Employees who are often exposed to dust, motor vehicle fumes and cigarette smoke during working hours are office boys/girls and security guards.

Observations made before the primary study found that there were potential factors that could cause lung function abnormalities already existed in employees who worked in the UPN Veteran

Jakarta environment such as smoking behavior, exercise habits, history of disease (asthma and Acute Respiratory Infections or ARI), and pollution (motor vehicle fumes and smoking environment). However, measurement of lung function or identification of risk factors for lung disorders has not been carried out in employees who work in the UPN Veteran Jakarta environment.

Based on medical record data in the past year at the UPN Veterans Jakarta polyclinic, there were several respiratory complaints such as dry cough, cough, cough with phlegm, headache (cephalgia), influenza and asthma. The highest frequency of visits there are chief complaints of cough and cold. Regarding the follow-up to the decrease in lung function, no further diagnosis has been made for employees. Therefore, it is necessary to research the factors associated with decreased lung function in employees working in UPN Veteran Jakarta.

METHOD

This cross-sectional study was conducted from April to May 2019 with a sample of 102 employees working within the UPN Veterans Jakarta including staff, lecturers, cooperative officers, office boys/girls, and security guards. The sample was selected using purposive sampling with inclusion criteria having worked at UPNVJ for at least 1 year, willing to be a respondent, aged 20-70 years. Meanwhile, the exclusion criteria were if they were not willing to participate or did not fill out the questionnaire completely.

A modified questionnaire was used to obtain data on host factors (gender, age, body mass index (BMI), employment status, education, allergies, history of lung disease, family history), behavioral factors (smoking and physical activity) and environmental factors (frequency of emission of vehicle and smoking environment). Smoking behavior was assessed based on the Brinkman Index (IB). Pulmonary function abnormalities were determined based on the results of spirometry measurements. It is stated that there is an abnormality/decrease in lung function if the VEP_1 value is <80%.

Lung function is measured using portable spirometer. Subjects were asked not to smoke 30 minutes prior to measurement. The subject performs maneuvers with the maximum expiratory flow speed that can be achieved when forced expiration in a sitting position. Subjects were asked to inhale as much as possible, then exhale with maximum force as soon as the lips were pressed against the mouthpiece. Measurements were conducted 3 times and the highest results were taken.

The data that has been collected was analyzed using data analysis software. Chi Square test was used for the selection of candidate variables which were included in multivariate analysis. For multivariate analysis, logistic regression was used with Prevalence Odds Ratio (POR) as a risk measure.

This research has been approved by the ethics committee of the Jakarta Veterans National Development University with the number B/1921/5/2019/KEPK.

RESULTS

This study found a high proportion of employees experiencing decreased lung function as much as 64.71% (Table 1).

Table 1. Overview of Lung Function Abnormalities

FEP_1	N	%
<80%	66	64,71
>=80%	36	35,29

Based on Table 2 shows that the highest proportion is found in male gender (81.4%), age < 40 years (64.7%), normal BMI (56.9%), working as an office boy (41.2%), had high school education (68.6%), had no respiratory allergies (94.1%), had no history of lung disease (81.4%), and had no family history of lung disease (81.4%). The highest proportion was found in light smoking based on Brinkman Index (IB) (69.6%) and moderate physical activity (66.7%). Most respondents were exposed to motor vehicle emissions (63.7%) and were in a smoking environment (80.4%).

The Chi-square test showed insignificant results on the occurrence of lung function abnormalities for the variables of gender, age, employment status, education, allergies, history of lung disease, and family history with P>0.05. While BMI (P=0.002) there is a significant association with lung function abnormalities (Table 3).

Table 2. Demographics of Host Factors, Behavioral Factors and Environmental factor

Variable	N	%
Gender		
Female	19	18,6
Male	83	81,4
Age		
≥40 years	36	35,3
<40 years	66	64,7
BMI		
Obesity	7	6.9
Overweight	21	20.6
Thin	16	15,7
Normal	58	56.9
Occupation status		
Staff	25	24,5
Lecturer	7	6,9
Cooperative Officer	8	7,8
Office boy/ girl	42	41,2
Security	20	19,6
Education		
Junior high school	11	10,8
Senior high school	70	68,6
College	21	20,6
Allergic		
Yes	6	5,9
No	96	94,1
History of lung disease		
Yes	19	18,6
No	83	81,4
Family history of lung disease		
Yes	19	18,6
No	83	81,4
Smoking Behavior (Brinkman Index)		
Light Smoker (0-199)	71	69,6
Moderate Smoker (200 - 599)	26	25,5
Heavy Smoker (>600)	5	4,9
Physical Activity		
Enough	68	66,7
Not enough	34	33,3
Motor vehicle emission frequency		
At risk	65	63,7
No Risk	37	36,3
Smoker Environment		
At risk	82	80,4
No Risk	20	19,6

The proportion of heavy smokers who had lung function abnormalities was 74.2%. Meanwhile, the proportion of physical activity did not differ between groups. These two variables have no relationship to lung function abnormalities (Table 4).

The proportion of exposure to vehicle emissions at risk was higher than the group exposed to no risk. The proportion of respondents who are in a smoking environment is higher than those who do not have smokers in their environment. The two variables were not associated with lung function abnormalities (P>0.05) (Table 5).

Table 3. Relationship between Host Factors and Lung Function Abnormalities.

Variable	Lung Function Abnormalities				P	POR	CI 95%
	Yes		No				
	N	%	N	%			
Gender							
Female	13	68.4	6	31.6	0.787	0.881	0.300 - 2.589
Male	59	71.1	24	28.9			
Age							
≥40 years	26	72.2	10	27.8	0.824	1.13	0.460 - 2.777
<40 years	46	69.7	20	30.3			
BMI							
Abnormal	38	86.4	6	13.6	0.002*	4.471	1.633 - 12.240
Normal	34	58.6	24	41.4			
Occupational Status							
High	50	71.4	20	28.6	0.817	1.136	0.458 - 2.822
Low	22	68.8	10	31.3			
Occupation							
Moderate	57	70.4	24	29.6	1.000	0.95	0.329 - 2.742
High	15	71.4	6	28.6			
Allergic							
Yes	5	83.3	1	15.7	0.668	2.164	0.242 - 19.353
No	67	69.8	29	30.2			
History of lung disease							
Yes	16	84.2	3	15.8	0.175	2.571	0.690 - 9.586
No	56	67.5	27	32.5			
Family history of lung disease							
Yes	12	63.2	7	36.8	0.419	0.657	0.230 - 1.876
No	60	72.3	23	27.7			

Table 4. Relationship between Behavior Factor and Lung Function Abnormalities

Variable	Lung Function Abnormalities				P	POR	CI 95%
	Yes		No				
	N	%	N	%			
Smoking							
Heavy	23	74,2	8	25,8	0,64	1,29	0,500 - 3,334
Light	49	69	22	31			
Physical Activity							
Enough	24	70,6	10	29,4	1	1	0,405 - 2,468
Not enough	48	70,6	20	29,4			

Table 5. Relationship between Environmental Factor and Lung Function Abnormalities

Variable	Lung Function Abnormalities				P	POR	CI 95%
	Yes		No				
	N	%	N	%			
Motor vehicle emission frequency							
At risk	49	75,4	16	24,6	0,18	1,864	0,780 - 4,457
No Risk	23	62,2	14	37,8			
Smoker Environment							
At risk	61	74,4	21	25,6	0,105	2,377	0,865 - 6,531
No Risk	11	55	9	45			

Table 6. Factors Affecting Lung Function Abnormalities

Variable	B	P	POR	CI 95%	
				Lower	Upper
BMI	1,551	0,003	4,718	1,673	13,305
History of lung disease	1,231	0,087	3,424	0,836	14,028
Smoking environment	1,084	0,061	2,956	0,953	9,168
Constant	-0,712	0,205	0,491	-	-

Multivariate analysis was conducted to find the most dominant factors to lung function abnormalities. By performing a logistic regression test backwards on 12 variables, it was found that 3 variables that most influence lung function abnormalities.

Based on the final model with column B in Table 6 above, get a formula to determine the magnitude of the risk of respondents who have complaints of Chronic Obstructive Pulmonary Disease (COPD). Obtain the formula for the risk of COPD complaints:

Y = -0,712 + 1,551(IMT) + 1,231(RPP) + 1,084(LP)

Note: BMI = Body Mass Index; RPP = History of Lung Disease; LP = Smoker's Neighborhood

DISCUSSION

This study shows that subjects with pulmonary function disorders are greater than those without functional disorders. This can be explained due to the average subject is men aged less than 40 years who have smoking behavior and the smoking environment is less prevalent. This group is vulnerable to developing COPD in the future. Most subjects worked as office boy/girl (41.2%). This is in accordance with research conducted by Zock et al. The subjects in this study were female office workers by 67% and female cleaning workers (83.6%).[8] Most of the subjects were high school graduates occupying position as security guards and office boys/girls. Most subjects do not have allergies related to lung disease, history of lung disease and genetics of lung disease because on average the respondents are healthy and productive people, however, they still have the risk of developing lung function disorders.

Based on the Chancellor of UPN Veterans Jakarta Regulation No. 11 (2019), it is stated that UPNVJ is a smoke-free area[10] however, the smoking behavior of the subject is still quite highwith light smokers as high as 69.6%. This can have an impact on health, especially COPD complaints because the main cause of COPD leads to the prevalence of tobacco

smoking.[10] Subjects had sufficient activity of 66.7%, because some of the subjects admitted that they always followed the routine gymnastics program scheduled every Friday on campus.

Many respondents in this study are bikers because the campus is located on a road with high level of congestion during rush hours from work and after work. Those subjects frequently did not wear mask while riding a motorcycle. This can cause the subject to be exposed to the risk of the frequency of motor vehicle emissions. Subjects who are at risk of being exposed to the frequency of motor vehicle emissions are 63.7%.

Although there is already a Regulation of the Chancellor of the UPN Veterans Jakarta No. 11 of 2019 regarding the smoking ban, this has not been implemented by the subject in the campus environment. Subjects smoked while eating together in an environment near campus. There are some subjects who do not smoke, and they are in that environment, so they are exposed to secondhand smoke. Passive smoking behavior among employees is still quite high at 80.4%.

This study shows that the male sex tends to have lung function abnormalities by 71.1% with P=0.787. The results of P>0.005 can be concluded that there is no significant relationship between gender and lung function abnormalities. Riskesdas in 2013 stated that the prevalence of male COPD is higher than the prevalence of female COPD.[11] In the age group <40 years, 46 respondents (69.7%) had pulmonary function disorders with a P=0.824, with this result, P>0.005, that there was no significant relationship between age and lung function disorders. World Health Organization in 2013 stated that the prevalence of COPD in people aged 30 years and over was 6.3% worldwide.[4] Body mass index (BMI) obtained P=0.002, meaning that there was a significant relationship between BMI and pulmonary function abnormalities. According to research by Ederina et al, COPD sufferers tend to experience malnutrition, underweight and drastic weight loss. Body weight can affect the maximum volume of air that can be accommodated by the lungs, because the lower the body weight or normal weight, the better the air that can be accommodated by the lungs.[12]

Analysis of the relationship between work status variables and pulmonary function disorders obtained P=0.817, meaning that there was no significant relationship between occupational status and pulmonary function disorders. This is in line with Prazasta's research that there is no relationship between work status, whether working or not working with COPD.[13] Socio-economy may be a risk factor for COPD, but there are other linkages such as poor ventilation, poor nutrition and smoking culture.[14]

Analysis of the relationship between education and lung function disorders with P=1.000, meaning that there is no relationship between the last education factor and lung function disorders. This is in line with research conducted in Yogyakarta that there is no significant relationship between education and

patients with chronic obstructive pulmonary disease (COPD) at the Yogyakarta pulmonary disease treatment center with P=0.754.[15] Based on the results of Riskesdas (2013) the prevalence of COPD tends to be higher in people with low education levels and the lowest ownership quintile index.[11]

The relationship between respiratory allergy-related factors and lung function abnormalities obtained P=0.668, meaning that there is no significant relationship between respiratory-related allergic factors and lung function abnormalities. Allergies mentioned in questionnaire are allergies related to dust or animal dander. According to from Suma'mur dust of a certain size when inhaled into the lungs will be retained and buried in the upper respiratory tract and settles in the bronchioles until the alveoli can cause a decrease in lung function. This variable is not in line with the theory because very few respondents have allergies related to breathing (dust and star feathers) and not all people who have allergies related to breathing have lung function abnormalities.[16]

The relationship between the history of lung disease and lung function abnormalities obtained P=0.175, meaning that there was no significant relationship between the history of lung disease and lung function abnormalities. This is also not in line with Budiono's thesis which states that there is a relationship between a history of lung disease and impaired lung function (P=0.015) with respondents who have a history of lung disease 2.1 times more at risk of developing pulmonary disorders.[17] Research in America states that someone who has a history of lung disease will have a greater risk of losing lung function significantly.[7]

Analysis of the relationship between genetics and lung function disorders obtained P=0.419, meaning that there is no significant relationship between genetic/hereditary factors and lung function disorders. The main genetic factor is the lack of alpha 1 antitrypsin, namely serine protease inhibitors or substances that can inhibit the breakdown of peptide bonds between amino acids.[14]

The relationship between smoking behavior and lung function abnormalities obtained P=0.645, it can be concluded that there is no relationship between smoking behavior factors and lung function disorders. This is not in line with the research of Tana et al. which found that there is a significant relationship between smoking and lung function abnormalities with P=0.0001.[3]

Analysis of physical activity with pulmonary function abnormalities in UPN Veteran Jakarta employees found that respondents with moderate physical activity had lung function disorders of 70.6%, while respondents who lacked physical activity had 70.6% of lung function disorders. Exercise can increase the vital capacity of the lungs even if only slightly, but if the vital capacity of the lungs increases it will cause the air entering or leaving the lungs to decrease.[18]

The results of the analysis of the relationship between the frequency of motor vehicle emissions with lung function

disorders obtained P=0.180, meaning that there is no relationship between the frequency of motor vehicle emissions and lung function disorders. PPE can decrease the risk of motor vehicle emissions. Air pollution can cause disruption of body functions, one of which is COPD. Substances that affect the most are sulfur oxides, nitrogen dioxide and ozone.[14]

Analysis of the relationship between environmental factor and lung function abnormalities obtain P=0.105, it can be concluded that there is no relationship between smoking environmental factors and lung function disorders. Respondents who are at risk of smoking or passive smoking are 2.3 times more likely to have lung function abnormalities than those who are not at risk of smoking. Secondhand smoke increases the risk of respiratory symptoms and chronic obstructive pulmonary disease (COPD) and inhaling air containing cigarette smoke can affect fetal growth and even infertility.[19]

The most influential variables on pulmonary function abnormalities in UPN Veteran Jakarta employees are Body Mass Index (BMI), history of lung disease and smoking environment. The results of the multivariate analysis showed that an abnormal body mass index statistically affected the risk for lung function abnormalities. The results of this study support the previous research (thesis) conducted by Budiono on car painting employees. Meanwhile, 25.7% had impaired function in normal nutritional status. Patients with chronic obstructive pulmonary disease experience malnutrition due to loss of lung muscle mass and decreased ventilation capacity. If protein intake is lacking, the body will break down respiratory proteins.[17]

The results of the study at the Arifin Achmad Hospital Pekanbaru stated that COPD patients tended to be malnourished, underweight from BMI, weight loss and 19-60% of COPD patients were declared malnourished.[12] Body weight affects the vital capacity of the lungs, because the higher the body weight or body mass, the worse the lung capacity. This is because overweight and obese people have a lot of saturated fat that can clog the respiratory tract and obese and obese people rarely exercise or do physical activity.[20]

The results of multivariate analysis in this study showed that someone who had a history of lung disease was 3.4 times more likely to have lung function disorders than someone who had no history of lung disease. Examples of history of illness suffered by a small number of employees are asthma 3.9%, ARI 4.9%, pulmonary TB 5.9% and pneumonia 3.9%.

This study is in line with previous research conducted by Budiono which stated that subjects with a history of lung disease were 62.5% and subjects who did not have a history of lung disease were 42%. Decreased lung function in a person as a result of abnormal lung growth during childhood or adolescence, this is related to increasing the risk of COPD complaints in that person.[17] Research in America states that if someone who has a history of lung disease will have a greater risk of losing

lung function than people who do not have a history of lung disease.[7]

The results of the multivariate analysis obtained on this variable indicate that someone who has a risk of smoking environment within the scope of colleagues or family is 2.9 times more at risk of having lung function disorders than someone who is not at risk of having a smoking environment within the scope of work friends or family. The picture of cigarettes causing damage to the respiratory tract is a depiction of the way harmful irritants contained in cigarettes enter the respiratory tract. These irritants can burn the lung cilia, which can lead to infection.

In other words, smoking can cause airway constriction thereby increasing the risk of airway abnormalities and the incidence of COPD.[21] The effects of passive smoking are bad odors, psychological effects, stroke, watery eyes (blindness), lung cancer, COPD, asthma, arterial blockages, heart attacks, angina, low baby weight, miscarriage, and complications during pregnancy give birth.[14]

Based on the formula obtained by someone who has 3.1 times more risk if that person has an abnormal BMI, has a history of lung disease and is at risk for smoking environment.

CONCLUSION

The prevalence of pulmonary function disorders in UPN Veteran Jakarta employees in 2019 was 70.6% who experienced COPD complaints. The results of the logistic regression test get the formula Y = -0.712 + 1.551 (BMI) + 1.231 (RPP) + 1.084 (LP), meaning that if a person has an abnormal BMI, there is a history of lung disease and environmental risk, smokers have 3.1 times more risk of lung sound abnormalities.

REFERENCES

1. PDPI. *Penyakit Paru Obstruktif Kronik (PPOK) Pedoman Diagnosis & Penatalaknsanaan Di Indonesia*. Jakarta: PDPI; 2003.
2. Sholihah M, Tualeka AR. Studi Faal Paru dan Kebiasaan Merokok pada Perusahaan Konstruksi di Surabaya. *Indones J Occup Saf Heal*. 2015;4(1):1-10.
3. Tana L, Delima D, Sihombing M, Muljati SMS, Ghani L. Sensitifitas dan Spesifisitas Pertanyaan Gejala Saluran Pernapasan dan Faktor risiko untuk Kejadian Penyakit Paru Obstruktif Kronik (PPOK). *Bul Penelit Kesehat*. 2016;44(4):287-296.
4. WHO. *World Health Statistics*. Geneva: WHO; 2013.
5. Kementerian Kesehatan RI. *Hasil Utama Riskesdas 2018*. Jakarta; 2018.
6. OECD. *Survei Ekonomi OECD Indonesia 2018: Ikhtisar*. Jakarta: OECD; 2018.
7. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet*. 2007;370(9589):765-773.
8. Zock JP, Kogevinas M, Sunyer J, et al. Asthma characteristics in cleaning workers, workers in other risk jobs and

office workers. *Eur Respir J*. 2002;20(3):679-685.
9. Rektor UPN "Veteran" Jakarta. Peraturan Rektor Universitas Pembangunan Nasional "Veteran" Jakarta Nomor 11 Tahun 2019 Tentang Kawasan Dilarang Merokok Di Lingkungan Kampus Universitas Pembangunan Nasional "Veteran" Jakarta. 2019.
10. Global Initiative for Chronic Obstructive Lung Disease. *Global Initiative for Chronic Obstructive Lung Disease: Pocket Guide to COPD Diagnosis, Management and Prevention - a Guide for Health Care Professionals*. Global Initiative for Chronic Obstructive Lung Disease; 2017.
11. Kementrian Kesehatan RI. *Riset Kesehatan Dasar Kementerian RI 2013*. Jakarta: Kementrian Kesehatan RI; 2013. doi:1 Desember 2013
12. Enderina G, Adrianison, Christianto E. Gambaran Status Gizi Pada Pasien Penyakit Paru Obstruktif Kronik (Ppok) Di Rawat Inap RSUD Arifin Achmad Pekanbaru. *J Online Mhs Fak Kedokt Univ Riau*. 2016;3(2):1-9.
13. Prazasta RP. Penilaian Tingkat Risiko Dan Faktor-Faktor Yang Berhubungan Dengan Penyakit Paru Obstruktif Kronik Pada Masyarakat Binaan KPKM Buaran FKIK UIN Syarif Hidayahtullah Tahun 2015. *UIN Syarif Hidayatullah*. 2015.
14. Kementrian Kesehatan RI. Keputusan Menteri Kesehatan RI Nomorr 1022/MENKES/SK/XI/2008 tentang Pedoman Pengendalian Penyakit Paru Obstruktif Kronik. 2008.
15. Patriani AA, Paramastri I, Priyanto MA. Pemberdayaan Keluarga dalam Rehabilitasi Medik Paru pada Penderita Penyakit Paru Obstruksi Kronik di Balai Pengobatan Penyakit Paru-Paru Yogyakarta. *Ber Kedokt Masy*. 2010;26(2):55-62.
16. Suma'mur. *Hygiene Perusahaan Dan Kesehatan Kerja*. Jakarta: Seagung Seto; 2009.
17. Budiono I. *Faktor Risiko Gangguan Fungsi Paru Pada Pekerja Pengecatan Mobil (Studi Pada Bengkel Pengecatan Mobil Di Kota Semarang)*. Semarang: Universitas Diponegoro; 2007.
18. Fathurrahman C, Jayanti S, Ekawati. Faktor-Faktor Yang Berhubungan Dengan Gangguan Fungsi Paru Pada Pekerja Yang Terpapar Potassium Permanganate Dan Phosphoric Acid Di Industri Garmen. *J Kesehat Masy*. 2014;2(1):42-49.
19. Oemiati, Ratih. Kajian Epidemiologis Penyakit Paru Obstruktif Kronik (PPOK). *Media Heal Res Dev*. 2013;23(2):82-88.
20. Habibah E, Junaidi Junaidi, Hermawan I. Hubungan Berat Badan dan Kapasitas Vital Terhadap VO2Max pada Anggota Tubuh Ekstrakulikuler Futsal SMAN 1 Cibungbulang. *J Segar*. 2017;5(2):62-69.
21. Susanti PFE. Influence Of Smoking On Chronic Obstructive Pulmonary Disease (COPD). *Med J Lampung Univ*. 2015;4(5):67-75.

Original Article

The Effect of Ginseng Extract Supplementation on Procalcitonin Level, Neutrophil, and Length of Stay In Patients With Community Acquired Pneumonia

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Abstract

Background: Pneumonia is an acute inflammation of the lung parenchyma caused by microorganisms (bacteria, viruses, fungi, parasites) and causes of high morbidity and mortality. Ginsenoside in ginseng have anti-inflammatory effects, potentially as adjunctive therapy in community-acquired pneumonia (CAP) patients. As much as 43% of patients at dr. Moewardi Hospital in 2016 were hospitalized have passed away. The aim of this study was to determine the effect of ginseng extract on levels of procalcitonin, neutrophils, and length of stay of community-acquired pneumonia patients.

Method: The quasi-experimental clinical trial with the pretest posttest design approach was conducted on 26 community acquired pneumonia patients who were hospitalized in Dr. Moewardi Hospital Surakarta from October until November 2019 using consecutive sampling. The control group (n=13) received standard antibiotics while the treatment group (n=13) received additional ginseng extract 2x100 mg/day for 14 days. Procalcitonin was measured at admission, third and fourteenth day; neutrophils are measured at admission and third day; length of stay is based on the number of days of treatment in hospital.

Results: There was a significant difference (P=0.001) towards decreased of serum procalcitonin levels between treatment group (-0.63±0.06) compared to control group (-0.38±0.07). There was a significant difference (P<0.001) towards decreased of neutrophil levels between treatment group (-6.68±1.34) compared to control group (-3.51±0.88). There was a significant difference (P=0.001) towards decreased of length of stay between treatment group (5.69±0.95) compared to control group (7.15±0.99).

Conclusion: Ginseng extract containing ginsenoside as its main ingredient, can act as an anti-inflammatory which can be used as adjunctive therapy in community-acquired pneumonia patients who are hospitalized to accelerate clinical improvement and shorten the length of stay.

Keywords: pneumonia, ginseng, procalcitonin, neutrophil, length of stay.

INTRODUCTION

Respiratory tract infections are still a public health problem. They are one of the leading causes of death globally despite advances in diagnostics, antibiotic therapy, and even intensive care.[1] The World Health Organization (WHO) report states that the highest cause of death from infectious diseases in the world is acute respiratory infections, including Pneumonia. Pneumonia is defined as an acute inflammation of the lungs caused by microorganisms (bacteria, viruses, fungi, parasites).[2]

The incidence of community acquired pneumonia (CAP) varies considerably according to age, comorbidities, geographic location, study methods, case definition and study population. A recent study of Asian countries reported that CAP is responsible for 420.5 episodes per 10.000 discharges in Indonesia. Mortality rate in hospitalized patients is 6–20%, but it varies widely according to treatment setting and severity disease, while mortality in primary care and ambulatory patients is less than 1% in most of the population, rising in patients over 65 years. One-nineth of patients hospitalized with CAP will need intensive care unit (ICU) admission and mortality in these patients reaching 50%.[3]

Widmer et al. in Switzerland in 2008 conducted a prospective study of 875 pneumonia patients to determine the factors that influence the length of hospitalization. The size of stay of the patient is influenced by age, the clinical condition of the patient, the need for home care, comorbidities, multi-lobar lung disorders, disease complications, and the severity of Pneumonia characterized by high levels of procalcitonin (PCT), C-reactive protein (CRP), patient risk class based on Pneumonia. Severity Index (PSI), and the need for intensive care.[4]

Antibiotics play an essential role in controlling disease, but irrational use and the presence of mutations in microorganisms cause the elimination of microorganisms to be non-optimal. The use of herbal medicines is increasing and is considered an additional therapy in the treatment of infectious diseases, assuming that they are widely available, more economical, and have minimal side effects so that they are safer to use. The pharmacological effects of natural products, especially their anti-inflammatory and antimicrobial effects, have become an attractive new treatment strategy. Combining natural products with antibiotics can provide a synergistic effect on antibiotics and minimize toxicity.[5–8]

Ginseng is one of the most studied herbal plants, especially in Asia. Ginseng grows well in environments with cool air and dry climates. Ginsenoside is the main active component of ginseng. Ginseng has antimicrobial, anti-inflammatory, and antioxidant properties. Choi et al. in 2012 showed that the aqueous extract of KRG provided anti-bacterial activity against Listeria monocytogenes with an MIC50 of 1.0 mg/mL. Lee et al. used 0.2% ginseng extract to induce cell morphological damage and loss of structural integrity of the bacterial cell wall.[9,10] And TNF- through

inhibition of the mitogen-activated protein kinases (MAPK) pathway and nuclear factor kappa – light chain enhancer of activated B cells (NF–κB).[11,12]

This study aims to determine the effect of giving ginseng as an anti-inflammatory in pneumonia patients. Researchers hope to prove the role of ginseng as an adjunct therapy in improving symptoms and shortening patients' length of stay. Markers of decreased inflammatory reactions will be measured by reducing procalcitonin and neutrophils in the blood.

METHOD

Community acquired pneumonia is an acute inflammation of the lung parenchyma that is acquired in the community. Community acquired pneumonia is associated with high and variable mortality rates among hospitalized patients. The ability to assess prognosis of people with CAP is very important. Accurate assessment of prognosis may help physicians make clinical decisions about hospitalization and management. The clinical prediction rule for CAP patients called the pneumonia severity index (PSI). The PSI is a clinical prediction rule that can be used to predict the need for hospitalization, calculate the probability of morbidity and mortality among patients with CAP.[2]

Empirical therapy for CAP patients is a respiratory fluoroquinolone such as Levofloxacin or Moxifloxacin, or β-lactam plus a macrolide. Discharge criteria for patients with community acquired pneumonia is if clinically stable. Clinically stable criteria are able to eat and drink, temperature ≤37.8°C, respiratory rate ≤24/min, pulse rate ≤100/min, oxygenation saturation ≥90% or PO_2 ≥60mmHg, white blood cell count $<12\times10^9$/L, dan the comorbidities are stable.[2]

This research is a clinical trial using the Quasi Experimental method and a pre-test and post-test design. The research was conducted at Dr. Hospital Moewardi Surakarta in October 2019. The study population was community pneumonia patients undergoing treatment at RSUD Dr. Moewardi Surakarta in October 2019. Sampling was done by the consecutive selection, namely selecting topics based on predetermined characteristics.

The inclusion criteria for this study were community pneumonia patients aged more than 18 years, hospitalized in an ordinary room, willing to participate in the survey, PORT value 51–130. Exclusion criteria were nosocomial Pneumonia had comorbid or immunocompromised conditions (HIV, chronic kidney failure, pregnancy), heart disease patients on warfarin therapy. The drop out criteria included patients who died during follow-up, resigned, severe side effects during the study, and patients lost to follow-up (not control at post-test).

Data analysis was performed with SPSS 21 for Windows. Statistical test to determine the distribution or distribution of data using Shapiro Wilk and Kolmogorov Smirnov. Test the difference between the control and treatment groups with an independent T-test or

Mann Whitney test. Different tests before and after treatment using pair T-test or Wilcoxon test.

RESULTS

This research was conducted on community pneumonia patients hospitalized at Dr. Moewardi. The total number of samples that met the inclusion criteria and were willing to participate in the study were 30 patients, 4 patients entered the discontinuous criteria, so the number of samples at the end of the study was 26 patients. The research sample was divided into 2 groups: the control group and the treatment group. The control group was only given standard therapy with antibiotics, while the treatment group was given standard treatment plus ginseng extract. Each group consisted of 13 community pneumonia patients.

The essential characteristics of the study subjects are shown in Table 1. The vital parts of the patients included gender, age, body mass index (BMI), smoking history, previous treatment history, Pneumonia Severity Index (PSI) score and bacterial culture.

Table 1. The Characteristics of Study Subjects

Characteristics	Group		P
	Control	Treatment	
Gender[2]			1,000
Male	9 (69,2%)	10 (76,9%)	
Female	4 (30,8%)	3 (23,1%)	
Age[1]	57,08±8,72	59,38±11,00	0,559
BMI[1]	18,37±2,64	19,14±2,64	0,467
Smoking history[2]			1,000
Smokers	6 (46,1%)	5 (38,4%)	
Ex-smokers	3 (23,1%)	4 (30,8%)	
Non-smokers	4 (30,8%)	4 (30,8%)	
Previous treatment history (90 days) [2]			1,000
Yes	11 (84,6%)	8 (61,5%)	
No	2 (15,4%)	5 (38,5%)	
PSI Score (Pneumonia Severity Index)			0,654
II	4 (30,8%)	6 (46,2%)	
III	4 (30,8%)	4 (30,8%)	
IV	5 (38,5%)	3 (23,1%)	
Bacterial cultur[1]			0,540
Klebsiella pneumoniae	5 (38,4%)	4 (30,8%)	
Pseudomonas aeruginosa	1 (7,7%)	3 (23,1%)	
Enterobacter cloacae	1 (7,7%)	1 (7,7%)	
Staphylococcus haemolyticus	3 (23,1%)	2 (15,3%)	
Staphylococcus aureus	1 (7,7%)	0 (0,0%)	
Escherichia coli	1 (7,7%)	0 (0,0%)	
No growth	1 (7,7%)	3 (23,1%)	

Notes: [1]Different test is done by T-test; [2]Different tests were performed using chi-square/fhiser exact test; PSI scores (ordinal data) were performed using the Mann Whitney test.

Gender characteristics of the 30 research subjects, 19 subjects (63%) were male, with the mean age of the control and treatment groups being 57.08±8.72 years and 59.38±11.00 years. The average body mass index in the control and treatment groups was 18.37±2.64 and 19.14±2.64. The characteristics of smoking status in the control group were 6 patients (46.2%) still smoking, 3 patients (23.1%) ex-smokers, and 4 patients (30.8%) not smoking. Subjects who still smoked in the treatment group were 5 patients (38.4%), 4 patients (30.8%) used to smoke, and 4 patients (30.8%) who did not smoke.

Characteristics of previous treatment history in the control group showed that 11 patients (84.6%) had been treated previously, and 2 patients (15.4%) had no previous treatment history. In the treatment group, 8 patients (61.5%) had been treated previously, and 5 patients (38.5%) had no previous treatment history. Most of the bacteria that caused pneumonia in the control and treatment groups were Klebsiella pneumonia, namely 5 patients (38.5%) in the control group and 4 patients (30.8%) in the treatment group.

The basic characteristics of the research subjects based on the results of the homogeneity analysis showed that almost all qualitative/categorical and quantitative/numerical variables had values that were not significantly different between the control and treatment groups. This indicates that the samples in both groups are homogeneous and meet the experimental feasibility rules.

Table 2 shows the effect of giving ginseng extract on neutrophil levels. The decrease in neutrophil levels in the control group was 3.51±0.88; while in the treatment group, it was 6.68±1.34. Decreased serum neutrophil levels in the treatment and control groups obtained P<0.001, meaning that the control and treatment groups experienced a significant decrease in serum neutrophil levels. However, the reduction of neutrophil levels was greater in the treatment group. It was statistically significant (P<0.001) so that the administration of ginseng extract effectively accelerated the decrease in serum neutrophil levels.

Table 3 shows the effect of giving ginseng extract on procalcitonin levels. The decrease in PCT levels on the third day compared to the initial PCT in the control and treatment groups was 0.38±0.07 and 0.63±0.06, respectively. The decrease in PCT levels on the fourteenth day compared to the initial PCT in the control and treatment groups was 1.36±0.53 and 1.43±0.56, respectively.

Different tests before and after treatment in the control group obtained P=0.001. In contrast, the treatment group got value of P=0.001, which means that both the control and treatment groups experienced a significant decrease in PCT levels.

The decrease in PCT on the third day in the treatment group was greater than in the control group. The administration of ginseng extracts effectively accelerated the decrease in PCT levels.

Table 2. Different test of serum neutrophil levels between the control group and the treatment group

Group	Neutrofil (%)			
	Day-0	Day- 3	P	Difference
Treatment	86,48±5,76	79,81±4,98	<0,001 [b]	-6,68±1,34
Control	84,21±3,89	80,71±3,81	<0,001 [b]	-3,51±0,88
P	0,250[a]	0,610 [a]	-	-

Notes: [a]different test with independent t test; [b] Test different premises Pair t test.

Table 3. Different test of Procalcitonin levels between the control group and the treatment group

Group	*Procalcitonin* (PCT)					
	Day-0	Day-3	Day-14	P	Δ day 3 – 0	Δ day 14 – 0
Control	1,45±0,55	1,07±0,53	0,08±0,03	<0,001[c]	-0,38±0,07	-1,36±0,53
Treatment	1,49±0,57	0,86±0,54	0,06±0,02	0,001[d]	-0,63±0,06	-1,43±0,56
P	0,852[a]	0,200[b]	0,007[b]	-	-	-

Notes: [a]different test is carried out with the Independent t test; [b] Differential test was performed with Mann Whitney; [c]Test the difference is done by Pair t test; [d]A different test was carried out with the Wilcoxon test.

The decrease in PCT levels on the fourteenth day in the control group was not much different from the treatment group and not statistically significant.

Table 4. Test for different lengths of stay in the control group and the treatment group

Variable	Group		P
	Control (n=13)	Treatment (n=13)	
Length of Hospitalization (days)	7,15±0,99	5,69±0,95	0,001

Note: Different test using Independent t test.

Table 4 shows the effect of giving ginseng extract on the length of stay of community pneumonia patients. Patients' average length of stay in the treatment group was 5.69±0.95 days, shorter than the control group, which was 7.15±0.99 days.

The different tests of the control and treatment groups showed P=0.001, which means that there was a significant difference in length of stay between the control group and the treatment group. These results indicate that administration of ginseng extract effectively shortens the length of stay of community pneumonia patients.

DISCUSSION

Pneumonia is an acute inflammation of the lung parenchyma caused by microorganisms (bacteria, viruses, fungi, parasites). Community pneumonia is pneumonia acquired in the community or outside of a hospital. Community pneumonia is one of the most common acute infections requiring hospitalization and a cause of high morbidity and mortality worldwide.[2]

The diagnosis of pneumonia was made based on anamnesis (history of cough, shortness of breath, fever), physical examination (fever, tachycardia), and confirmed by chest X-ray and laboratory. The use of validated scoring systems and biomarkers such as procalcitonin helps determine the severity of pneumonia and guides outpatient or inpatient decisions. Proper administration of antibiotics is essential to prevent the worsening of pneumonia patients and shorten the length of treatment. Antibiotic treatment is not always effective in sterilizing the entire respiratory system, so the use of additional drugs for pneumonia has been widely

developed, especially in patients with a history of recurrent infectious diseases and patients with comorbidities.[13–15]

Ginseng is an herbal plant commonly found in Asia with the main content of ginsenoside. Ginsenoside has an anti-inflammatory effect by inhibiting the interaction of LPS with TLR4 on macrophages, inhibiting TNF- production due to LPS stimulation, inhibiting NF-B signaling activation, and inhibiting IL-8 production. Ginsenoside can also suppress TLR2 expression, thereby inhibiting the production of IL-2 and IFN-γ. Giving ginseng extract to the treatment group is expected to reduce serum neutrophil levels procalcitonin and shorten the length of hospitalization.[9,16,17]

Giving ginseng extract on serum neutrophil levels was seen from the decrease in serum neutrophil levels on the third day compared to the initial arrival, both in the control and treatment groups. The reduction in serum neutrophils in the treatment group was greater than the control group and was statistically significant ($P<0.001$). This study showed that standard therapy plus administration of ginseng extract could reduce serum neutrophil levels in community pneumonia patients, with a significant difference compared to the control group.

The interaction of specific microbial adhesins with cellular receptors causes the activation of the transcription factor NF-B, producing various pro-inflammatory cytokines or chemokines (IL-1β, IL-6, IL-8, IL-17, IL-18, and TNF-α). Pro-inflammatory cytokines activate the vascular endothelium, making chemoattractant that allow trans-endothelial migration of neutrophils and acute-phase reactants. Standard therapy, namely antibiotics, caused the decrease in serum neutrophil levels in the control group. Giving antibiotics can affect a person's immune system. Antibiotics can reduce the release of cytokines, thereby reducing the migration of neutrophils to the site of infection, inhibiting the synthesis of pro-inflammatory cytokines and chemokines, and facilitating the release of anti-inflammatory cytokines.[14,18–20]

Another way antibiotics reduce the number of neutrophils is to decrease granulopoiesis and induce antibodies against the formation of haptens in neutrophils. The decrease in serum neutrophil levels in the treatment group given standard therapy plus ginseng extract resulted in a more significant reduction in serum neutrophil levels than the control group, presumably due to a synergistic effect between the two. The bactericidal activity of ginsenoside disrupts the potential membrane integrity of bacterial cells, inhibiting DNA mutagenesis, anti-quorum sensing, anti-adhesive activity, inhibiting pathogen-induced hemagglutination, and modulating the immune system.[14,18–20]

This study showed that Klebsiella pneumonia was the dominant pathogen of CAP cases in Dr Moewardi Hospital. This can be caused by infection with Klebsiella pneumonia which is endemic in Surakarta. Other risk factors that may be responsible for the high bacteremia of Klebsiella

pneumonia are older age, underlying chronic lung disease, patients with severe clinical conditions, immunocompromised patients, and previous medical history.[21]

Luan et al's research at Shijitan Hospital, Beijing in 2017 found that Klebsiella pneumonia was the main cause of adult CAP cases (27.4%). The results of the pathogenic bacterial profile at Dr M. Djamil Hospital, Padang in 2016 by Narlis et al, found that 55.23% of CAP patients were caused by Klebsiella pneumonia. Assefa et al obtained sputum cultures of CAP patients in Gondar, Ethiopia as much as 31% caused by Klebsiella pneumonia. In contrast to the results of the study above, Costa et al found that 45.7% of CAP patients admitted to the Northern Portugal University Hospital were caused by Streptococcus pneumoniae. Sputum culture results of CAP patients at the referral hospital in Hiwot, Northwest Ethiopia 35.9% were caused by Streptococcus pneumoniae.[21–25]

The results of this study are like those of a 2008 study conducted by Song et al. in Denmark, who reported fewer macroscopic lung abnormalities (P=0.0003) and a lower percentage of PMN from bronchial lavage (P=0.0006) in *P. aeruginosa* - infected rats. And given an injection of ginseng extract, 2mg/kgBW for 2 weeks compared to the control group. Research by Nguyen et al. in 2015 in Korea on mice infected with S. pneumoniae and given ginseng extract 100mg/kgBW for 15 days found a decrease in TNF-α, IL-1β levels, decreased TLR-4 receptors, and neutrophil infiltration 48 hours after infection.[20]

Serum procalcitonin (PCT) levels on the third and fourteenth days compared to the initial presentation decreased in the control and treatment groups. The decrease in serum PCT on the third day in the treatment group was greater than in the control group and was statistically significant (P<0.001). In contrast, the decrease in serum PCT on the fourteenth day in the treatment and control groups was not significantly different. The difference in decline was not statistically significant (P=0.758).

From these results, it can be concluded that administration of ginseng extract as an adjunct therapy in addition to standard treatment was able to reduce PCT levels and was statistically significant compared to standard treatment. Empirical antibiotic therapy for community pneumonia patients at RSUD Dr. Moewardi was adjusted to the bacterial pattern of the hospital, where fluoroquinolone antibiotics (Levofloxacin, Ciprofloxacin) or -lactams (Ampicillin, Cefoperazone) plus macrolides (Clindamycin, Azithromycin) were shown to be effective in reducing serum PCT levels in pneumonia patients.

Procalcitonin is a pro-peptide precursor to calcitonin. Procalcitonin is regulated in response to microbial toxins and bacterial-specific pro-inflammatory mediators such as IL-1β, IL-6, and TNF- and PCT levels decrease as pro-inflammatory mediators decrease during recovery. The average physiologic level of PCT in serum is less than 0.1 ng/ml, increasing hundreds of times in systemic bacterial infections. Procalcitonin is not a

marker in the very early phase of disease because levels only increase between 2 and 6 hours after infection, peak in 6 to 24 hours, decrease slowly over 48-72 hours, and persist for several days in the blood in the presence of systemic infection. PCT levels generally fall below 1 ng/ml (or 1 g/l) within 48 hours without infection, indicating the importance of repeat PCT measurements. Serial measurements of PCT over time are informative, and absolute trendlines are more valuable than percentage declines from baseline.[26,27]

The results of this study showed that the decrease in PCT levels on the third day in the treatment group was much greater than the control group. Giving antibiotics can reduce the release of pro-inflammatory cytokines so that PCT levels in the blood will decrease. Giving standard therapy plus ginseng extract was able to reduce procalcitonin levels more than the group that only received standard therapy. This could be due to the synergistic effect between antibiotics and ginseng extract, thereby accelerating the decrease in serum PCT levels.[7,10,28]

Giving ginseng extract was able to inhibit the activity of NF-kB so that it would inhibit the production of pro-inflammatory cytokines. Panax ginseng can increase the phagocytic activity of macrophages and NK cells. Activation of the immune system can be through the formation of TLR complexes, thereby inhibiting the production of pro-inflammatory cytokines and preventing sepsis. The decrease in PCT levels on the fourteenth day in the treatment group and the control group did not differ much, this could be related to the PCT half-life in the blood so that PCT levels had decreased along with the decrease in systemic infection after therapy.[7,10,28]

The results of this study are similar to a study conducted by Hong et al in 2011 which showed that administration of a low concentration of 0.25% ginseng extract could reduce biofilm formation in vitro, increase motility and reduce clustering of Pseudomonas aeruginosa. Staphylococcus aureus significantly reduced bacterial colony formation in the bloodstream, spleen and kidney, which may correlate with bactericidal activation of macrophages. Ginseng pre-treatment can reduce levels of IL-1β, IL-6, IL-12, IL-18, TNF-α, and IFN-γ.[9,10]

A 2008 study by Sung et al. in Korea compared the administration of standard antibiotics with a combination of antibiotics and saponins from ginseng extract against MRSA bacterial cultures. The combination of ginseng extract with kanamycin against MRSA bacteria showed a synergistic or additive effect with a fractional inhibitory concentration (FIC) index value of 0.375–0.75 while the combination of ginsenosides and cefotaxime had an additive effect on MRSA with an FIC index value of 0.625.[29–31]

Ahn et al.'s 2005 study in Korea on 12 rats injected with S. aureus intraperitoneally. Administration of ginseng extract was able to increase survival and reduce the burden of bacteria in the blood during sepsis in mice infected with S. aureus. The combination of ginseng extract and vancomycin gave a higher survival rate

than the administration of each treatment.[20,28]

The results showed that the length of stay for community pneumonia patients in the treatment group was shorter than the control group and was statistically significant with P<0.001. The hope of giving ginseng extract to community pneumonia patients is that it can help reduce symptoms, accelerate clinical improvement, thereby shortening the length of stay of patients.

In this study, there was a significant difference in length of stay between the control and treatment groups, this could be due to the administration of antibiotics plus ginseng extract that could modulate the immune system, inhibit NF-B activity, and decrease the production of pro-inflammatory cytokines. This reduction in systemic inflammatory reactions will accelerate the patient's clinical improvement so that it will shorten the length of stay for pneumonia patients.

Similar results were obtained from a study conducted by Scaglione et al on 75 chronic bronchitis patients. All patients received 875 mg of amoxicillin and 125 mg of clavulanic acid twice daily for 9 days. Patients were divided into two groups, the first group received only antibiotic therapy and the second group was added with 100 mg of standardized ginseng extract (G115®) twice a day. The results showed that the elimination of bacteria and clinical improvement in the second group was faster than the first group, with an average time of 5.9 days and 6.7 days. Patients are considered cured and can be discharged after reducing or even disappearing symptoms of infection, such as coughing, shortness of breath, wheezing, fever, vital signs within normal limits and good oral intake.[12]

There has been no previous study on the effect of ginseng extract on PCT levels, serum neutrophils, and length of stay at the same time, so the results cannot be compared with other studies. Previous studies regarding the administration of ginseng extract have been conducted on patients with chronic bronchitis, cystic fibrosis patients, and patients infected with the influenza virus. The results showed a decrease in inflammatory cytokines, increased phagocytosis and clearance of microorganisms thereby accelerating the clinical improvement of patients.[9,12]

CONCLUSION

The administration of ginseng extract at a dose of 2x100 mg/day can be given as an adjunctive therapy in hospitalized community pneumonia patients to accelerate clinical improvement and shorten the length of stay of patients.

REFERENCES

1. Villena J, Laiño J, Suvorov A, Melnikov V, Alvarez S. Immunobiotic and recombinant lactic acid bacteria: soldiers in the fight against Streptococcus pneumoniae. *Recent Trends Immunol*. 2022.
2. Perhimpunan Dokter Paru Indonesia. *Pneumonia Komunitas: Pedoman Diagnosis Dan Penatalaksanaan Di*

Indonesia. 2nd ed. Jakarta: Badan Penerbit FKUI; 2014.

3. Ferreira-Coimbra J, Sarda C, Rello J. Burden of Community-Acquired Pneumonia and Unmet Clinical Needs. *Adv Ther*. 2020;37(4):1302-1318.
4. Suter-Widmer I, Christ-Crain M, Zimmerli W, et al. Predictors for length of hospital stay in patients with community-acquired pneumonia: results from a Swiss multicenter study. *BMC Pulm Med*. 2012;12.
5. Aydin H, Bagcigil AF. Antibacterial activity of Korean ginseng tea. *Med Wet*. 2007;63(2):190-191.
6. Kang OJ, Kim JS. Comparison of Ginsenoside Contents in Different Parts of Korean Ginseng (Panax ginseng C.A. Meyer). *Prev Nutr food Sci*. 2016;21(4):389-392.
7. Kim YR, Yang CS. Protective roles of ginseng against bacterial infection. *Microb cell (Graz, Austria)*. 2018;5(11):472-481.
8. Riaz M, Rahman NU, Zia-Ul-Haq M, Jaffar HZE, Manea R. Ginseng: A dietary supplement as immune-modulator in various diseases. *Trends Food Sci Technol*. 2019;83:12-30.
9. Wu H, Høiby N, Yang L, Givskov M, Song Z. Effects of radix ginseng on microbial infections: a narrative review. *J Tradit Chinese Med = Chung i tsa chih ying wen pan*. 2014;34(2):227-233.
10. Liou CJ, Huang WC, Tseng J. Long-term oral administration of ginseng extract modulates humoral immune response and spleen cell functions. *Am J Chin Med*. 2005;33(4):651-661.
11. Kee JY, Jeon YD, Kim DS, et al. Korean Red Ginseng improves atopic dermatitis-like skin lesions by suppressing expression of proinflammatory cytokines and chemokines in vivo and in vitro. *J Ginseng Res*. 2017;41(2):134-143.
12. Scaglione F, Weiser K, Alessandria M. Effects of the Standardised Ginseng Extract G115® in Patients with Chronic Bronchitis. *Clin Drug Investig 2001 211*. 2012;21(1):41-45.
13. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet (London, England)*. 2015;386(9998):1097-1108.
14. Feldman C, Anderson R. Community-Acquired Pneumonia: Pathogenesis of Acute Cardiac Events and Potential Adjunctive Therapies. *Chest*. 2015;148(2):523-532.
15. Christ-Crain M, Opal SM. Clinical review: The role of biomarkers in the diagnosis and management of community-acquired pneumonia. *Crit Care*. 2010;14(1):1-11.
16. Park SY, Kim H Bin, Kim JH, et al. Immunostimulatory Effect of Fermented Red Ginseng in the Mouse Model. *Prev Nutr Food Sci*. 2014;19(1):10.
17. Song Y, Zhao F, Zhang L, Du Y, Wang T, Fu F. Ginsenoside Rg1 exerts synergistic anti-inflammatory effects with low doses of glucocorticoids in vitro. *Fitoterapia*. 2013;91:173-179.
18. Lorenzo MJ, Moret I, Sarria B, et al. Lung inflammatory pattern and

antibiotic treatment in pneumonia. *Respir Res*. 2015;16(1).
19. Shuman M, Demler TL, Trigoboff E, Opler LA. Hematologic impact of antibiotic administration on patients taking clozapine. *Innov Clin Neurosci*. 2012;9(11-12):18-30.
20. Song Z, Kharazmi A, Wu H, et al. Effects of ginseng treatment on neutrophil chemiluminescence and immunoglobulin G subclasses in a rat model of chronic Pseudomonas aeruginosa pneumonia. *Clin Diagn Lab Immunol*. 1998;5(6):882-887.
21. Luan Y, Sun Y, Duan S, Zhao P, Bao Z. Pathogenic bacterial profile and drug resistance analysis of community-acquired pneumonia in older outpatients with fever. *J Int Med Res*. 2018;46(11):4596-4604.
22. Narlis N, Nasrul E, Efrida E. Pola Kuman dan Uji Kepekaan pada Pasien Community Acquired Pneumonia di RSUP Dr. M. Djamil Padang Tahun 2016. *J Kesehat Andalas*. 2019;8(3):553-557.
23. Assefa M, Tigabu A, Belachew T, Tessema B. Bacterial profile, antimicrobial susceptibility patterns, and associated factors of community-acquired pneumonia among adult patients in Gondar, Northwest Ethiopia: A cross-sectional study. *PLoS One*. 2022;17(2):e0262956.
24. Costa MI, Cipriano A, Santos F V., et al. Clinical profile and microbiological aetiology diagnosis in adult patients hospitalized with community-acquired pneumonia. *Pulmonology*. 2022;28(5):358-367.
25. Temesgen D, Bereded F, Derbie A, Biadglegne F. Bacteriology of community acquired pneumonia in adult patients at Felege Hiwot Referral Hospital, Northwest Ethiopia: A cross-sectional study. *Antimicrob Resist Infect Control*. 2019;8(1):1-8.
26. Vijayan AL, Ravindran S, Saikant R, Lakshmi S, Kartik R, Manoj G. Procalcitonin: A promising diagnostic marker for sepsis and antibiotic therapy. *J Intensive Care*. 2017;5(1):1-7.
27. Pereira JM, Paiva JA, Rello J. Assessing severity of patients with community-acquired pneumonia. *Semin Respir Crit Care Med*. 2012;33(3):272-283.
28. Ahn JY, Song JY, Yun YS, Jeong G, Choi IS. Protection of Staphylococcus aureus-infected septic mice by suppression of early acute inflammation and enhanced antimicrobial activity by ginsan. *FEMS Immunol Med Microbiol*. 2006;46(2):187-197.
29. Nguyen CT, Luong TT, Lee SY, et al. Panax ginseng aqueous extract prevents pneumococcal sepsis in vivo by potentiating cell survival and diminishing inflammation. *Phytomedicine*. 2015;22(11):1055-1061.
30. Wu H, Lee B, Yang L, et al. Effects of ginseng on Pseudomonas aeruginosa motility and biofilm formation. *FEMS Immunol Med Microbiol*. 2011;62(1):49-56.

31. Sung WS, Lee DG. The combination effect of Korean red ginseng saponins with kanamycin and cefotaxime against methicillin-resistant Staphylococcus aureus. *Biol Pharm Bull*. 2008;31(8):1614-1617.

Original Article

Association Between Comorbidities and Outcome of COVID-19 Patients at dr. M. Djamil General Hospital Padang

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Abstract

Background: COVID-19 has spread rapidly throughout the world with high morbidity and mortality estimated up to 20%. This number will increase with the presence of comorbidities. Comorbidities were associated with complex clinical management and impacted on COVID-19 disease outcomes. This study aims to determine the association between comorbidities and the outcome of COVID-19 patients at Dr. M. Djamil Hospital.

Method: We conducted an observational study with a retrospective cohort design on COVID-19 patients treated at Dr. M. Djamil Hospital. Data were taken from medical records from January to March 2021. Association between comorbidities and the outcome of COVID-19 patients was analyzed by Chi-Square or Fisher Exact Test.

Results: The majority patientss were female (56.4%) and ages above 50 years old (64.3%) were the majority of patients. The most common was hypertension (36.56%). The longest length of stay of COVID-19 patients was more than 21 days (52.9%). The outcomes of COVID-19 patients were recovered (59.5%), recovered with sequelae (5.7%), and died (34.8%). Diabetes mellitus affected the end of treatment outcome. There was no relationship of type of comorbidity with length of stay. The more co-morbidities a patient suffers, the condition when infected with COVID-19 will get worse.

Conclusion: The number of comorbidities affects the outcome of COVID-19 patients. Diabetes mellitus is most common that affects the end of treatment outcome for COVID-19 patients at Dr. M. Djamil Hospital.

Keywords: comorbidities, COVID-19, end of treatment outcome, length of stay, outcome COVID-19

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) or known as COVID-19 is a new type of outbreak and currently a global pandemic.[1,2] Reports of COVID-19 cases in Indonesia at the end of February 2021 showed new cases were decreased by 8.5% with the death rate increasing by 74.8%. The number of confirmed cases recorded on March 11, 2021, was around 1,403,722 cases, 38,049

death cases and 611,097 were declared cured.[3]

Based on the data from the West Sumatra Provincial Health Office as of March 11, 2021 as much as 29,985 people tested positive for COVID-19, 659 of them died and 28,297 were declared cured, while in the COVID-19 case in Padang City 14,820 people tested positive for COVID-19, 288 of them died and 14,188 were declared cured.[4,5]

The COVID-19 pandemic has spread rapidly throughout the world with high morbidity and mortality estimated at up to 20%.[6] The morbidity and mortality will increase in the presence of comorbidities. SARS-CoV-2 has the ACE-2 receptor which is found on the surface of the host cell and is used to enter the cell. Comorbidity is associated with increased expression of the ACE-2 receptor and higher release of proprotein convertase, thereby increasing the amount of virus that enters the host cell. Meta-analysis studies report that hypertension, diabetes mellitus, chronic respiratory disease, cardiovascular disease, and obesity may be risk factors for worse outcomes.[7–9]

Research conducted by Khedr et al showed that the most frequent comorbid in the group studied was cardiovascular disease (69%) followed by diabetes mellitus (54.2%). Clinical improvement was noted in nearly 68% of hospitalized COVID-19 cases (improved and discharged from the hospital) with a significantly lower frequency of cure in comorbid patients (59% vs. 81%) and a significantly higher mortality rate in cases with comorbidities.[8,9] Comorbidities will affect the length of stay of COVID-19 patients, a study conducted by Thiruvengadam et al stated that patients with two or more comorbidities had a longer length of stay compared to patients without comorbidities. The study conducted by Guan et al found that COVID-19 patients with any comorbidity will produce a worse outcome than those without comorbidities and the number of comorbid also correlates with a worse outcome.[10,11]

METHOD

An observational analytic study with a retrospective cohort design was conducted in the COVID-19 isolation room at Dr. M. Djamil General Hospital Padang. The time of this study was carried out from January to September 2021. The study population was all COVID-19 patients who were treated in the COVID-19 isolation room of Dr. M. Djamil General Hospital Padang from January 1, 2021 to March 31, 2021.

The inclusion criteria for patients sampling were COVID-19 patients with positive nasopharingeal swab for SARS-CoV-2 who were treated in the COVID-19 isolation room, Dr. M Djamil General Hospital Padang for the period January 1 to March 31, 2021, and has complete medical record data, aged >18 years. Meanwhile, the exclusion criteria are patients who go home at their request while still being treated for COVID-19 and patients with mild clinical degrees.

This research has been approved by the Research Ethics Committee of Dr. M.

Djamil General Hospital Padang on April 23, 2021 with No. 146/KEPK/2021.

Data analysis was carried out descriptively and analytically. Bivariate analysis was used to find association between independent and dependent variables with a statistical test that was by the data scale, namely the test Chi-square. If the value of P<0.05, then there is an association between the independent variable and the dependent variable. This analysis uses the statistical test Chi-square or Fisher's Exact Test if the data obtained does not meet the requirements for the test Chi-square.

RESULTS

In total 227 confirmed COVID-19 patients in this study, the characteristics of the research subjects are presented in Table 1. The highest age group was found to be over 50 years old as many as 146 people (64.3%). According to gender, the majority were women as many as 128 people (56.4%). As much as 91 people (40.1%) had 1 comorbid and based on the presence of comorbidities in confirmed COVID-19 patients, hypertension was the most common, as many as 83 people (36.56%).

From the data, it was found that 120 people (52.9%) of confirmed COVID-19 patients had length of stay for 21 days. The outcomes of patients who recovered, recovered with sequelae, and died were 135 people (59.5%), 13 people (5.7%), and 79 people (34.8%) respectively.

Table 1. Characteristics of COVID-19 Patients (N=227)

Patient Characteristics	N	%
Ages		
<50 years	81	35.7%
50-59 years	63	27.8%
60-69 years	50	22.0%
≥70 years	33	14.5%
Gender		
Female	128	56.4%
Number of Comorbidities		
No Comorbid	49	21.5%
1 Comorbid	91	40.1%
>1 Comorbid	87	38.4%
Comorbid Types		
Cardiovascular Disease	38	16.8%
CAD	24	10.6%
HHD	5	2.2%
CHF	9	4.0%
Hypertension	83	36.6%
Mild	35	15.4%
Moderate	46	20.3%
Severe	0	0%
Hypertensive Crisis	2	0.9%
Diabetes Mellitus	75	33.0%
Controlled	13	5.7%
Uncontrolled	62	27.3%
Chronic Lung Disease	10	4.4%
Pulmonary Tuberculosis	7	3.1%
Asthma	2	0.9%
COPD	1	0.4%
Chronic Kidney Disease	28	12.3%
Stadium 1	1	0.4%
Stadium 2	2	0.9%
Stadium 3	1	0.4%
Stadium 4	0	0%
Stadium 5	24	10.6%
Cerebrovascular Disease	4	1.8%
Stroke	4	1.8%
Chronic Liver Disease	4	1.8%
Immunodeficiency	2	0.9%
HIV	2	0.9%
Obesity	14	6.2%
Mild (stage 1)	0	0%
Moderate (stage 2)	0	0%
Severe (stage 3)	14	6.2%
Malignancy	14	6.2%
Length of Stay		
<21 Days	107	47.1%
≥21 Days	120	52.9%
Patient Outcomes		
Recovered	135	59.5%
Recovered with Sequelae	13	5.7%
Died	79	34.8%

Note: CAD=Coronary Artery Diseasel; HHD=Hypertensive Heart Disease; CHF=Congestive Heart Failure; COPD=Chronic Obstetric Pulmonary Disease; HIV=Human immunodeficiency virus

Table 2. Association between Comorbid Types and Length of Stay of COVID-19 Patients

Comorbid Types	Length of Stay		P
	≥21 Days n (%)	<21 Days n (%)	
Cardiovascular Disease			
None	94 (49.7)	95 (50.3)	0.070
CAD	16 (66.7)	8 (33.3)	
HHD	5 (100.0)	0 (0.0)	
CHF	5 (55.6)	4 (44.4)	
Hypertension			
None	71 (49.3)	73 (50.7)	0.536
Mild	20 (57.1)	15 (42.9)	
Moderate	28 (60.9)	18 (39.1)	
Hypertensive Crisis	1 (50.0)	1 (50.0)	
Diabetes mellitus			
None	70 (46.0)	82 (54.0)	0.074
Controlled	5 (38.5)	8 (61.5)	
Uncontrolled	40 (64.5)	22 (35.5)	
Chronic Lung Disease			
None	113 (52.1)	104 (47.9)	0.589
Pulmonary Tuberculosis	5 (71.4)	2 (28.6)	
Asthma	1 (50.0)	1 (50.0)	
COPD	1 (50.0)	0 (0.0)	
Chronic Kidney Disease			
None	102 (51.3)	97 (48.7)	0.298
Stadium I	0 (0.0)	1 (100.0)	
Stadium II	2 (100.0)	0 (0.0)	
Stadium III	1 (100.0)	0 (0.0)	
Stadium IV	0 (0.0)	0 (0.0)	
Stadium V	15 (62.5)	9 (37.5)	
Cerebrovascular Disease			
None	116 (52.0)	107 (48.0)	0.124
Yes	4 (100.0)	0 (0.0)	
Chronic Liver Disease			
None	117 (52.5)	106 (47.5)	0.624
Yes	3 (75.0)	1 (25.0)	
Immunodeficiency			
None	119 (52.9)	106 (47.1)	1.000
HIV	1 (50.0)	1 (50.0)	
Obesity			
None	111 (52.1)	102 (47.9)	0.544
Severe (stage 3)	9 (64.3)	5 (35.7)	
Malignancy			
None	112 (52.6)	101 (47.4)	0.956
Yes	8 (57.1)	6 (42.9)	

Note: CAD=Coronary Artery Diseasel; HHD=Hypertensive Heart Disease; CHF=Congestive Heart Failure; COPD=Chronic Obstetric Pulmonary Disease; HIV=Human immunodeficiency virus

The association between the types of comorbidities and the length of stay of confirmed COVID-19 patients can be seen in Table 2. The three most common comorbidities in this study are diabetes mellitus, hypertension, and cardiovascular disease.

Tabel. 3 Association between Comorbid Types and the End of Treatment Outcome of COVID-19 Patients

Comorbid Types	End of Treatment Outcome			P
	Recovered n (%)	Recovered with Sequelae n (%)	Died n (%)	
Cardiovascular Disease				
None	115 (60.8)	10 (5.3)	64 (33.9)	0.483
CAD	14 (58.3)	2 (8.3)	8 (33.3)	
HHD	1 (20.0)	0 (0.0)	4 (80.0)	
CHF	5 (55.6)	1 (11.1)	3 (33.3)	
Hypertension				
None	93 (64.6)	9 (6.3)	42 (29.2)	0.315
Mild	20 (57.1)	2 (5.7)	13 (37.1)	
Moderate	21 (45.7)	2 (4.3)	23 (50.0)	
Hypertensive Crisis	1 (50.0)	0 (0.0)	1 (50.0)	
Diabetes mellitus				
None	104 (68.4)	8 (5.2)	40 (26.4)	<0.001*
Controlled	8 (61.5)	0 (0.0)	5 (38.5)	
Uncontrolled	23 (37.1)	4 (6.5)	35 (56.4)	
Chronic Lung Disease				
None	129 (59.4)	13 (6.0)	75 (34.6)	0.703
Pulmonary Tuberculosis	3 (42.9)	0 (0.0)	4 (57.1)	
Asthma	2 (100.0)	0 (0.0)	0 (0.0)	
COPD	1 (100.0)	0 (0.0)	0 (0.0)	
Chronic Kidney Disease				
None	125 (62.8)	9 (4.5)	65 (32.7)	0.101
Stadium I	0 (0.0)	0 (0.0)	1 (100.0)	
Stadium II	1 (50.0)	0 (0.0)	1 (50.0)	
Stadium III	1 (100.0)	0 (0.0)	0 (0.0)	
Stadium V	8 (33.3)	4 (16.7)	12 (50.0)	
Cerebrovascular Disease				
None	134 (60.1)	12 (5.4)	77 (34.5)	0.155
Yes	1 (25.0)	1 (25.0)	2 (50.0)	
Chronic Liver Disease				
None	133 (59.6)	12 (5.4)	78 (35.0)	0.245
Yes	2 (50.0)	1 (25.0)	1 (25.0)	
Immunodeficiency				
None	134 (59.6)	13 (5.8)	78 (34.7)	0.869
HIV	1 (50.0)	0 (0.0)	1 (50.0)	
Obesity				
None	130 (61.0)	12 (5.6)	71 (33.3)	0.165
Severe (stage 3)	5 (35.7)	1 (7.1)	8 (57.1)	
Malignancy				
None	127 (59.6)	11 (5.2)	75 (35.2)	0.352
Yes	8 (57.1)	2 (14.3)	4 (28.6)	

Note: *=statistically significant (P<0.05); CAD=Coronary Artery Diseasel; HHD=Hypertensive Heart Disease; CHF=Congestive Heart Failure; COPD=Chronic Obstetric Pulmonary Disease; HIV=Human immunodeficiency virus

The association between the types of comorbidities and the length of stay of confirmed COVID-19 patients carried out statistical tests with the results of all comorbidities showing no significant results (P>0.05), so there was no association between certain types of comorbidities and the length of stay of confirmed COVID-19 patients.

The association between the types of comorbidities and the end of treatment outcome for confirmed COVID-19 patients can be seen in the Table 3. Underlying diseases of uncontrolled diabetes mellitus became the most comorbid deaths (56.5%). Patients who recovered with the most sequelae were found in stage 5 chronic kidney disease (16.7%) and uncontrolled diabetes mellitus (6.5%). Coronary artery disease, moderate hypertension, and uncontrolled diabetes mellitus had the highest end-of-care status, namely (58.3%), (45.7%), and (37.1%).

The association between the types of comorbidities and the end of treatment outcome for confirmed COVID-19 patients carried out statistical tests as in Table 3. There was a significant association beetween the types of comorbid diabetes mellitus and end of treatment outcome confirmed COVID-19 patients with P<0.001.

The association between the number of comorbidities and the length of stay of confirmed COVID-19 patients can be seen in Table 4. A hundred twenty-two patients with length of stay of 21 days, more than half of the total patients (66.7%) had >1 comorbid, no comorbid (49.0%), and 1 comorbid (41.8%). The results of the statistical test showed that there was a significant association between the number of comorbidities and the length of stay of confirmed COVID-19 patients (P<0.05).

The association between the number of comorbidities and the outcome of confirmed COVID-19 patients which can be seen in Table 5. Of the 79 patients who died, less than half of patients (47.1%) had >1 comorbid, 1 comorbid (33.0%), and no comorbid (16.3%). The results of the statistical test showed that there was a significant association between the number of comorbidities and the final status of care for confirmed COVID-19 patients (P<0.05).

Tabel 4. Association between the Number of Comorbidities and the Length of Hospitalization of COVID-19 Patients

Number of Comorbidities	Length of Stay		Total n (%)	P
	≥21 Days n (%)	<21 Days n (%)		
None	24 (49.0)	25 (51.0)	49 (100.0)	
1 Comorbid	38 (41.8)	53 (58.2)	91 (100.0)	0.003*
>1 Comorbid	58 (66.7)	29 (33.3)	87 (100.0)	
Total	120 (52.9)	107 (47.1)	227 (100.0)	

Tabel 5. Association between the Number of Comorbidities and the End of Treatment Outcome for COVID-19 Patients

Number of Comorbid	End of Treatment Outcome			Total n (%)	P
	Recovered n (%)	Recovered with Sequelae n (%)	Died n (%)		
None	38 (77.6)	3 (6.1)	8 (16.3)	49 (100.0)	
1 Comorbid	57 (62.6)	4 (4.4)	30 (33.0)	91 (100.0)	0.005*
>1 Comorbid	40 (46.0)	6 (6.9)	41 (47.1)	87 (100.0)	
Total	135 (59.5)	13 (5.7)	79 (34.8)	227 (100.0)	

DISCUSSION

This study found the highest incidence of COVID-19 at the age of more than 50 years as many as 146 people. A study by Verma found that the highest age group was in the range of 50-75 years as much as 46.7%, followed by >75 years at 32% and age <50 years at 21.2%.[12] Older people who suffer from COVID-19 are more susceptible to worsening clinical conditions, even death, due to decreased function of T cells and B cells, and excessive cytokine production resulting in a prolonged inflammatory response.[9]

Based on the gender characteristics of COVID-19 patients, the majority are women. The results are different from those obtained in study by Surendraet et al in Jakarta, in that study mostly in men (52%).[13] The results of other studies conducted by Verma et al, Giannouchos et al, also found that the prevalence of males was the highest.[12,14] Males are more susceptible to infection which is associated with increased immune reactivation to viral infections. This situation is different for females due to antibody production was increase, so that they are effectively resistant to infection.[15] Women are less susceptible than men due to innate immunity, steroid hormones, and factors related to sex chromosomes.[16]

Comorbidity is a condition that is susceptible to infection due to a prolonged pro-inflammatory state and dysfunction of innate and adaptive immunity. In patients with obesity, diabetes, or cardiovascular disease, increased ACE2 expression was found to increase the susceptibility to SARS-CoV-2 infection. In addition, pulmonary function abnormalities and microangiopathy associated with obesity and diabetes will increase viral diversity and titer, and prolong viral shedding.[17] In this study, some patients had comorbid CAD (10.6%), HHD (2.2%), and CHF (4%). Verma et al's study found comorbid CAD 6.1% and CHF 6.0%.[12] Patients with mild hypertension were 15.4%, moderate was 20.3%, and a hypertensive crisis was 0.9%. Research conducted by Verma et al, Giannouchos et al, Wei et al, and Surendra et al found that hypertension comorbidities were 34.7%, respectively; 20.9%; 16.3%, and 19%.[12–14,18]

Patients who had diabetes mellitus were controlled as much as 5.7% and uncontrolled as many as 27.3%. The results of the study of Giannouchous et al, Surendra et al, and Wei et al are almost similar to the results of this study, which found the number of COVID-19 patients with comorbid DM was 17.5%; 12%; 8.6%.[13,14,18]

In diabetic patients there will be an accumulation of activated innate immune cells in metabolic tissues resulting in the release of inflammatory mediators, especially interleukin (IL)-1β and tumor necrosis factor (TNF)-α which will lead to insulin resistance and B cell damage. Furthermore, metabolic diseases can reduce immune function by disrupting macrophage function and lymphocytes so that a person is susceptible to disease.[19]

The percentage of patients who have chronic lung diseases such as tuberculosis is around 3.1%, asthma is 0.9%, and COPD is 0.4%. A total of 10.6% of patients with chronic kidney disease are at stage 5. Study by Verma showed that patients with comorbid renal failure were about 20.6%,[12] on the other hand, Giannouchos et al., Surendra et al., Fresan et al. only had 2.3%; 3%; 2.3%.[13,14,20] Stroke in this study was found to be 1.8%. Only 1.8% of patients in this study had chronic liver disease. The research conducted by Surendra et al. showed that the number of COVID-19 patients with liver disease was 0.7%.[13]

There were 6.2% of patients with severe obesity. Surendra et al research found that obese patients were around 0.8%. A total of 6.2% of patients in this study had malignancy. COVID-19 patients with malignancy in the study of Surendra et al were 0.5%.[13] Only 0.9% of patients in this study had HIV. Similar results were obtained in the studies of Giannouchos et al, Surendra et al, COVID-19 patients with comorbid immunosuppression of about 1.6%; 0.7%.[13,14]

This study showed that most of them were treated for 21 days or more, namely 52.9%. The results of study by et al found that the median length of patient care was 24 days with a range of 13 to 36 days.[13] The median length of stay in the Sanyaolu study was about 12 days.[21] Outcomes of patients obtained in this study, more than half recovered with a percentage of 59.5%, followed by death by 34.8%, and recovery with sequelae of 5.7%. Research by Osibogun et al. showed that 3.34% of patients died and 78.98% recovered.[22]

Based on the severity of COVID-19, patients with severe COVID-19 effects will increase the mortality rate. The statement is in line with the results of the study by Osibogun which got a mortality rate at a critical degree of 100%, severe 23.53%, moderate (2.67%), and mild (0.37%).[22] The mortality rate was significantly increased in cases with comorbidities in Khedr et al's study (P<0.001).[9] In this study, it was found that the comorbidity that had a significant relationship to the outcome was diabetes mellitus, while the length of stay did not have a significant relationship with each comorbid.

COVID-19 patients who have comorbid cardiovascular disease in study by Fresan et al showed that cardiovascular disease was correlated with a statistically high risk of COVID-19 hospitalization and severity (OR=1.33; 95% CI=1.13-1.58; P<0.001 and aRR=1.61; 95% CI=1.13-2.30, P=0.008).[20] Previous cardiovascular disease contributed to 5 times higher risk to experience severe COVID-19. Meta-analysis showed that cardiovascular disease comorbidities were at high risk for severe COVID (OR=3.15; 95% CI=2.34-4.25), death (OR=3.23; 95% CI=2.28-4.57) and outcome fatal in patients in all age groups (OR=3.11; 95% CI=2.55-3.79).[23]

Patients with a history of cardiovascular disease become unstable and caused an increased incidence of

coronary disease, heart failure, and arrhythmias in SARS-CoV-2 infection. It's caused by an imbalance between metabolic demands and decreased cardiac work and is associated with an inflammatory response and myocardial damage.[17]

Study by Fresan et al showed that hypertension was associated with COVID-19 treatment and severity but was not statistically significant (OR=1.22; 95% CI=1.06-1.41; P=0.005; OR=1.53; 95% CI=1.11-2.10; P=0.009).[20] Meta-analysis showed that hypertension was at high risk for severe COVID (OR=2.42; 95% CI=1.98-2.96), death (OR=2.60; 95% CI=2.11-3.20) and fatal outcome in patients in all ages (OR=2.50; 95% CI=2.49-4.88).[23]

Dysregulation of the immune system in hypertensive patients is related to the severity of COVID-19. Monocytes in hypertensive patients are pre-active which produce more IL-6 after stimulation by angiotensin II or lipopolysaccharide and found an increase in CD8+ T cells that produce TNF. These CD8+ T cells are unable to fight off viral infections and result in the overproduction of cytokines.[24]

Patients with diabetes died in study by Wen et al as much as 11%. On the other hand, those who did not have diabetes experienced death as much as 3% with P<0.001.[15] Patients with diabetes mellitus 3.69 times the risk of dying from COVID-19.[22] Meta-analysis showed that comorbid diabetes mellitus was at higher risk for severe COVID (OR=2.47; 95% CI=1.86-3.27), death (OR=2.11; 95% CI=1.63-2.73) and the outcome was fatal in patients in all age groups (OR=2.25; 95% CI=1.89-2.69).[23]

Diabetes is one of the most common and most dangerous metabolic diseases characterized by chronic inflammatory conditions that lead to metabolic and vascular abnormalities that affect the response to pathogens.[24] Type 2 diabetes mellitus is associated with chronic inflammation induced by excess visceral adipose tissue. This inflammatory condition affects glucose homeostatic regulation and peripheral insulin sensitivity. Chronic hyperglycemia and inflammation can cause an abnormal and ineffective immune response by stimulating the synthesis of proinflammatory cytokines and oxidative markers that cause tissue inflammation. In addition, diabetic patients are at high risk of developing an uncontrolled hypercoagulable state and inflammatory response.[25]

Potential mechanisms that make diabetic patients more susceptible to the risk and severity of COVID-19 include the role of hyperglycemia, high cellular affinity binding, efficient viral entry, decreased viral clearance, impaired T cell function, hyper inflammation, cytokine storm syndrome, and the presence of cardiovascular disease.[24,25]

Pulmonary disease can be a strong predictive comorbid predictor of poor outcome and death (OR=4.17; 95% CI=2.67-6.50 and OR=3.23; 95% CI=2.55-4.32, respectively).[17] Studies Alwafi et al and published reports of similar

studies found that patients with chronic lung diseases, particularly COPD, was found as a higher risk factor to the outcome of patients COVID-19 heavier. This is because the patient's lung function has decreased.[26]

Study by Fresan et al showed that chronic kidney disease was associated with a high risk of hospitalization and severity of COVID-19 (OR=1.52; 95% CI=1.21-1.91; P<0.001 and OR=1.78; 95% CI=1.14-2.76, P=0.010).[20] Study by Osiboguns showed that patients with kidney disease were 12.53 times more likely to die from COVID-19.[22] Chronic kidney disease is associated with inflammation and dysregulation of immune function which increases the risk of mortality in COVID-19. This is due to overexpression of tubular cells in COVID-19 patients with kidney disease characterized by elevated serum creatinine and urea nitrogen.[27]

Study by Fresan et al showed that cerebrovascular disease was associated with a high risk of hospitalization and severity of COVID-19 (aRR=1.41; 95% CI=1.04-1.92; P=0.025 and aRR=1.91; 95% CI=1.13-3.25; P=0.016).[23] This is caused by cerebrovascular disease that can cause disability. SARS-CoV-2 can cause direct damage to nerves or vascular events such as stroke, and increased proinflammatory cytokines will damage vascular endothelium and increase blood coagulability.[28]

Previous studies have described a higher mortality rate in a chronic liver disease infected with COVID-19. The results of the logistic regression analysis of Alwafi et al study showed the odds ratio of death was 1.92 with 95% CI=1.65-8.63.[27] Study by Zhou et al found that there was no significant association between comorbid chronic liver disease and the severity of COVID-19 (OR=1.54 95% CI=0.95-2.49).[17] COVID-19 patients with chronic liver disease are prone to adverse outcomes such as death or longer hospital stays compared to patients without chronic liver disease. Laboratory findings emphasize the negative impact of SARS-CoV-2 infection on liver function.[26]

Patients with obesity experienced 7% mortality and those without obesity experienced approximately 4% mortality (P<0.001). Obesity is associated with impaired lung function that occurs due to a decrease in lung compliance, expiratory reserve volume and functional capacity, and an increase in cytokines.[15]

The study findings of Alwafi et al stated that mortality was high and the hospital stay period was longer in COVID-19 patients with malignancy. The nature of cancer and the therapeutic use of antineoplastic agents that attack the immune system will increase fatal outcomes and more severe COVID-19 infections.[26]

Patients with HIV are 12.21 times at risk of dying from COVID-19.[27] Patients with HIV have decreased TCD4+ cells and develop T-cell dysfunction and inflammation, which increases the risk of severe outcomes in viral infection.[29]

The findings of Richardson et al showed that patients had more than one comorbid as many as 88%, followed by having 1 comorbid at 6.3%, and those without comorbid at 6.1%.[8] Study by Giannochous showed that approximately 40% of patients had one or more comorbidities.[14] This study found a significant association between the number of comorbidities on length of stay and outcome (P=0.003). Research conducted by Osibogun showed that 8,47% of patients with 1 comorbid died and 91.53% recovered, while 28.86% of patients with 2 or more comorbidities died and 71.74% recovered with an OR=4.25; 95% CI=2.31-7.84; P<0.001.[24]

Patients with two or more comorbidities were four times more likely to die than patients with one comorbid.[22] Having one or more comorbidities is closely related to a poor outcome, this is because multiple comorbidities contribute to the complexity of the disease and patients are more susceptible to adverse effects.[14]

Jang's study in Korea showed that more comorbidities were associated with a longer length of stay (P<0.001) with a mean length of stay for no co-morbidities, one co-morbidity, two co-morbidities, and three or more co-morbidities, respectively, which was 20.7±13.4; 24.1±15.8; 26.8±17.8; and 26.2±17.9.[30]

In this study, there are several limitations including this study using a retrospective cohort design with data collection through medical records.

CONCLUSION

The characteristics of the most COVID-19 patients at Dr. M. Djamil General Hospital Padang were female and more than 50 years old. There was no correlation between the type of comorbid and the length of stay, while there was a relationship between the number of comorbidities with the length of stay and the final status of the patient's care. Diabetes mellitus is related to end-of-care status. Thus, a multidisciplinary team is needed in the treatment and close monitoring of inflammatory markers is carried out so that the outcome of COVID-19 patients with comorbid diabetes mellitus can be better.

REFERENCES

1. Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. *Int J Antimicrob Agents*. 2020;55(5).
2. Wang R, Pan M, Zhang X, et al. Epidemiological and clinical features of 125 Hospitalized Patients with COVID-19 in Fuyang, Anhui, China. *Int J Infect Dis*. 2020;95:421-428.
3. Satuan Tugas Penanganan COVID-19. Analisis Data Covid-19 Indonesia Update Per 28 Februari 2021. Satuan Tugas Penanganan COVID-19. https://covid19.go.id/p/berita/analisis-data-covid-19-indonesia-update-28-februari-2021. Published 2012.
4. Tim IT DISKOMINFO Sumbar. Data pantauan COVID-19 provinsi sumatera barat. Pemerintah Provinsi Sumatera

Barat. https://corona.sumbarprov.go.id/. Published 2021. Accessed March 13, 2021.
5. Pemerintah Kota Padang. Kondisi Covid-19 Kota Padang. Pemerintah Kota Padang. http://corona.padang.go.id/. Published 2021. Accessed September 19, 2022.
6. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. *J Chinese Med Assoc*. 2020;83(3):217-220.
7. Ejaz H, Alsrhani A, Zafar A, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. *J Infect Public Health*. 2020;13(12):1833-1839.
8. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA*. 2020;323(20):2052-2059.
9. Khedr EM, Daef E, Mohamed-Hussein A, et al. Impact of comorbidities on COVID-19 outcome. *medRxiv Prepr Serv Heal Sci*. 2020.
10. Thiruvengadam G, Lakshmi M, Ramanujam R. A Study of Factors Affecting the Length of Hospital Stay of COVID-19 Patients by Cox-Proportional Hazard Model in a South Indian Tertiary Care Hospital. *J Prim Care Community Health*. 2021;12.
11. Guan W, Liang W, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55(5):640.
12. Verma AA, Hora T, Jung HY, et al. Characteristics and outcomes of hospital admissions for COVID-19 and influenza in the Toronto area. *CMAJ*. 2021;193(12):E410-E418.
13. Surendra H, Elyazar IR, Djaafara BA, et al. Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: A hospital-based retrospective cohort study. *Lancet Reg Heal - West Pacific*. 2021;9:100108.
14. Giannouchos T V., Sussman RA, Mier JM, Poulas K, Farsalinos K. Characteristics and risk factors for COVID-19 diagnosis and adverse outcomes in Mexico: an analysis of 89,756 laboratory–confirmed COVID-19 cases. *Eur Respir J*. 2021;57(3).
15. Wen S, Prasad A, Freeland K, et al. Clinical Characteristics and Outcomes of COVID-19 in West Virginia. *Viruses*. 2021;13(5).
16. Das SK. The Pathophysiology, Diagnosis and Treatment of Corona Virus Disease 2019 (COVID-19). *Indian J Clin Biochem*. 2020;35(4):385-396.
17. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: A systematic review and meta-analysis. *Int J Infect Dis*. 2020;99:47-56.
18. Wei ZY, Qiao R, Chen J, et al. The influence of pre-existing hypertension on coronavirus disease 2019 patients. *Epidemiol Infect*. 2021;149.

19. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91-95.
20. Fresán U, Guevara M, Trobajo-Sanmartín C, Burgui C, Ezpeleta C, Castilla J. Hypertension and Related Comorbidities as Potential Risk Factors for COVID-19 Hospitalization and Severity: A Prospective Population-Based Cohort Study. *J Clin Med*. 2021;10(6):1-12.
21. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its Impact on Patients with COVID-19. *SN Compr Clin Med*. 2020;2(8):1069-1076.
22. Osibogun A, Balogun M, Abayomi A, et al. Outcomes of COVID-19 patients with comorbidities in southwest Nigeria. *PLoS One*. 2021;16(3):e0248281.
23. Bae SA, Kim SR, Kim MN, Shim WJ, Park SM. Impact of cardiovascular disease and risk factors on fatal outcomes in patients with COVID-19 according to age: a systematic review and meta-analysis. *Heart*. 2021;107(5):373-380.
24. Mitra P, Suri S, Goyal T, et al. Association of Comorbidities with Coronavirus Disease 2019: A Review. *Ann Natl Acad Med Sci*. 2020;56(2):102-111.
25. Corrao S, Pinelli K, Vacca M, Raspanti M, Argano C. Type 2 Diabetes Mellitus and COVID-19: A Narrative Review. *Front Endocrinol (Lausanne)*. 2021;12.
26. Alwafi H, Naser AY, Qanash S, et al. Predictors of Length of Hospital Stay, Mortality, and Outcomes Among Hospitalised COVID-19 Patients in Saudi Arabia: A Cross-Sectional Study. *J Multidiscip Healthc*. 2021;14:839-852.
27. Biswas M, Rahaman S, Biswas TK, Haque Z, Ibrahim B. Association of Sex, Age, and Comorbidities with Mortality in COVID-19 Patients: A Systematic Review and Meta-Analysis. *Intervirology*. 2021;64(1):36-47.
28. Siepmann T, Sedghi A, Barlinn J, et al. Association of history of cerebrovascular disease with severity of COVID-19. *J Neurol*. 2021;268(3):773-784.
29. Rossouw TM, Boswell MT, Nienaber AG, Moodley K. Comorbidity in context: Part 1. Medical considerations around HIV and tuberculosis during the COVID-19 pandemic in South Africa. *South African Med J*. 2020;110(7):621-624.
30. Jang SY, Seon JY, Yoon SJ, Park SY, Lee SH, Oh IH. Comorbidities and Factors Determining Medical Expenses and Length of Stay for Admitted COVID-19 Patients in Korea. *Risk Manag Healthc Policy*. 2021;14:2021-2033.

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

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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.

REFERENCES

1. La Marca A, Capuzzo M, Paglia T, Roli L, Trenti T, Nelson SM. Testing for SARS-CoV-2 (COVID-19): a systematic review and clinical guide to molecular and serological in-vitro diagnostic assays. *Reprod Biomed Online*. 2020;41(3):483-499.
2. Böger B, Fachi MM, Vilhena RO, Cobre AF, Tonin FS, Pontarolo R. Systematic review with meta-analysis of the accuracy of diagnostic tests for COVID-19. *Am J Infect Control*. 2021;49(1):21-29.
3. Ahn DG, Shin HJ, Kim MH, et al. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). *J Microbiol Biotechnol*. 2020;30(3):313-324.
4. Adhikari SP, Meng S, Wu YJ, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis poverty*. 2020;9(1).
5. Tim IT DISKOMINFO Sumbar. Data pantauan COVID-19 provinsi sumatera barat. Pemerintah Provinsi Sumatera Barat. https://corona.sumbarprov.go.id/. Published 2021. Accessed March 13,

2021.

6. Kashyap VK, Dhasmana A, Massey A, et al. Smoking and COVID-19: Adding Fuel to the Flame. *Int J Mol Sci*. 2020;21(18):1-22.
7. Cai G, Bossé Y, Xiao F, Kheradmand F, Amos CI. Tobacco smoking increases the lung gene expression of ACE2, the Receptor of SARS-CoV-2. *Am J Respir Crit Care Med*. 2020;201(12):1557-1559.
8. Patanavanich R, Glantz SA. Smoking is Associated with COVID-19 Progression: A Meta-Analysis. *medRxiv*. 2020.
9. Badan Nasional Penanggulangan Bencana. Merokok Meningkatkan Potensi Terjangkit COVID-19 - BNPB. Badan Nasional Penanggulangan Bencana. https://bnpb.go.id/berita/merokok-meningkatkan-potensi-terjangkit-covid19. Published 2020.
10. Shastri MD, Shukla SD, Chong WC, et al. Smoking and COVID-19: What we know so far. *Respir Med*. 2021;176:106237.
11. WHO. *WHO Global Report on Trends in Prevalence of Tobacco Use 2000-2025, Third Edition*. Geneva: WHO; 2019. https://www.who.int/publications/i/item/who-global-report-on-trends-in-prevalence-of-tobacco-use-2000-2025-third-edition.
12. Salah HM, Sharma T, Mehta J. Smoking Doubles the Mortality Risk in COVID-19: A Meta-Analysis of Recent Reports and Potential Mechanisms. *Cureus*. 2020;12(10).
13. Surendra H, Elyazar IR, Djaafara BA, et al. Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: A hospital-based retrospective cohort study. *Lancet Reg Heal - West Pacific*. 2021;9:100108.
14. Zhang J jin, Dong X, Cao Y yuan, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020;75(7):1730-1741.
15. Sharma G, Volgman AS, Michos ED. Sex Differences in Mortality From COVID-19 Pandemic: Are Men Vulnerable and Women Protected? *JACC Case Reports*. 2020;2(9):1407.
16. Schurz H, Salie M, Tromp G, Hoal EG, Kinnear CJ, Möller M. The X chromosome and sex-specific effects in infectious disease susceptibility. *Hum Genomics*. 2019;13(1):2.
17. Schroeder M, Tuku B, Jarczak D, et al. The majority of male patients with COVID-19 present low testosterone levels on admission to Intensive Care in Hamburg, Germany: a retrospective cohort study. *medRxiv*. 2020:2020.05.07.20073817.
18. Montopoli M, Zumerle S, Vettor R, et al. Androgen-deprivation therapies for prostate cancer and risk of infection by SARS-CoV-2: a population-based study (N = 4532). *Ann Oncol*. 2020;31(8):1040.
19. Chen J, Jiang Q, Xia X, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. *Aging Cell*. 2020;19(7).

20. Gao M, Piernas C, Astbury NM, et al. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. *Lancet Diabetes Endocrinol*. 2021;9(6):350-359.
21. Jayanama K, Srichatrapimuk S, Thammavaranucupt K, et al. The association between body mass index and severity of Coronavirus Disease 2019 (COVID-19): A cohort study. *PLoS One*. 2021;16(2).
22. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: A systematic review and meta-analysis. *Int J Infect Dis*. 2020;99:47-56.
23. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
24. CDC. Current Cigarette Smoking Among Adults in the United States. CDC. https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm. Published 2020.
25. Umnuaypornlert A, Kanchanasurakit S, Lucero-Prisno DE, Saokaew S. Smoking and risk of negative outcomes among COVID-19 patients: A systematic review and meta-analysis. *Tob Induc Dis*. 2021;19.
26. Monteiro AC, Suri R, Emeruwa IO, et al. Obesity and smoking as risk factors for invasive mechanical ventilation in COVID-19: A retrospective, observational cohort study. *PLoS One*. 2020;15(12).
27. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242.
28. Guo A, Lu J, Tan H, et al. Risk factors on admission associated with hospital length of stay in patients with COVID-19: a retrospective cohort study. *Sci Reports 2021 111*. 2021;11(1):1-7.
29. Osibogun A, Balogun M, Abayomi A, et al. Outcomes of COVID-19 patients with comorbidities in southwest Nigeria. *PLoS One*. 2021;16(3):e0248281.

Original Article

Characteristics of Albumin Levels and Liver Function in Patients With COVID-19 at H. Adam Malik Hospital, Medan

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Abstract

Background: COVID-19 (Corona Virus Disease-2019) pandemic has a high mortality rate especially in Medan, Indonesia. Serum albumin and liver function tests are believed to be predictive biomarkers for prognosis in patients with infectious diseases, including COVID-19. This study aimed to investigate the association between the mortality events and severely ill COVID-19 patients' serum albumin and liver enzymes.

Method: This is a cross-sectional study using secondary data from the medical records of H. Adam Malik Hospital patients with COVID-19 who were confirmed by RT-PCR from August to December 2020. All patients were analyzed for age, sex, hypoalbuminemia, increased liver enzymes and outcome using Chi-square tests (P<0.05).

Results: The average age of severe COVID-19 patients at H. Adam Malik Hospital ranged from 41 to 60 years, with more women prevalence than men. Most of the patients had hypoalbuminemia (84.2%), an increase in AST (59.4)% and ALT (45.5%). There was no significant association between hypoalbuminemia and the disease outcome (P=0.12). There was a significant association between elevated liver enzymes and mortality in severely ill COVID-19 patients (P<0.001).

Conclusion: We found that hypoalbuminemia is common in patients with severe COVID-19. However, we found that albumin levels had no association with the patients' mortality rate. Liver enzymes levels appear to be a predictive biomarker for outcomes in COVID-19 patients of H. Adam Malik Hospital. We found that higher ALT and AST levels were associated with significantly higher mortality.

Keywords: COVID-19, hypoalbuminemia, liver enzymes.

INTRODUCTION

In March 2020, COVID-19 (Corona Virus Disease-2019) was officially designated by WHO as a pandemic case with a mortality rate far exceeding MERS (Middle East Respiratory Syndrome) and SARS (Severe Acute Respiratory Syndrome).[1] In Indonesia, the city of Medan is the region with the most

extensive distribution of COVID-19 cases, namely 8,000 confirmed cases, 6,692 recovered cases and 326 death cases.[2]

In recent years, research has shown that specific biomarkers can provide additional information in determining pneumonia severity, aetiology, complications, and prognosis. Serum albumin is an examination that is often performed and is believed to be able to predict the prognosis in patients with infectious diseases. Low serum albumin levels are associated with morbidity and mortality in various diseases.[3]

In addition, the hepatocellular severity in COVID-19 patients was reported due to systemic inflammatory response, hypoxemia due to pneumonia (secondary infection) and liver injury due to side effects of drugs such as antibiotics, NSAIDs, herbal products and anti-viral agents.[4]

In a study conducted by J. Huang et al.,[5] severe COVID-19 patients with hypoalbuminemia at presentation increased the risk of death. The potential therapeutic value of albumin in COVID-19 needs urgent further evaluation.

Therefore, this study aims to assess albumin levels and liver function in severe COVID-19 patients at H. Adam Malik Hospital, Medan.

METHOD

This cross-sectional study was conducted in H. Adam Malik Hospital, starting from August to December 2020. This study was approved by the Ethics Committee of medical faculty of Universitas Sumatera Utara. The subjects were a population of 101 patients who were confirmed to be positive for COVID-19. Cross-sectional investigation of the correlates of COVID-19 outcome identified the following correlates: age, gender, low serum albumin and high liver enzyme levels. These data were obtained from the patients' medical records.

We applied 2 inclusion criteria: (i) all adult patients (>18 years of age) were diagnosed as having severe COVID-19 and were confirmed by real-time polymerase chain reaction (RT-PCR) (ii) patients with definite outcome of either survive or die due to COVID-19. Patients will be excluded for incomplete medical records.

Initial laboratory values on the day of admission were collected, including albumin, aspartate transaminase (AST) and alanine transaminase (ALT). Hypoalbuminemia was defined as a decreased albumin level below 3.5 g/dL, while a value above this was considered as normal. The normal range of values for ALT is about 0-55 u/L, while AST is about 5-34 u/L. Elevations were 2-3 times higher than the normal range. Outcomes recorded included discharges with no remaining symptoms and in-hospital mortality events.

Categorical variables were presented as frequencies and percentages. Univariate analyses were conducted using Chi-square tests, as well as Fisher's exact test to compare groups of patients with each variable to identify any significantly association with adverse outcomes. Tha value of $P<0.05$ was considered statistically

significant. Multivariate analysis was conducted using logistic regression.

RESULTS

The baseline characteristics of 101 patients with severe COVID-19 are provided in Table 1.

Table 1. Basic Characteristics of COVID-19 Patients

Characteristics	N	f (%)
Sex		
Male	48	47.5
Female	53	52.5
Age (years)		
18-40	27	26.7
41-60	53	52.5
>60	21	20.8
Laboratory values Albumin		
Decreased	85	84.2
Normal	16	15.8
ALT		
Elevated	46	45.5
Normal	55	54.5
AST		
Elevated	60	59.4
Normal	41	40.6
Clinical outcome		
Discharged	76	75.2
Died	25	24.8

Forty-eight (47.5%) patients were male. There were 53 (52.5%) patients included in 41 to 60 years of age group, and 27 (26.7%) patients in 18 to 40 years of age group. Among the patients, 85 (84.2%) subjects had a low serum albumin level. Most patients had normal ALT value (55 of 101 subjects: 54.5%). In terms of AST, the 60 (59.4%) had an elevated AST level. Mortality events were found on the 25 (24.8%) of subjects.

We examined the association of clinical outcomes with serum albumin, ALT, and AST levels using statistical analysis (Table 2). The outcomes showed no significant association with serum albumin (P=0.12). A significant association was found between the clinical outcomes and ALT levels, as well as AST levels.

DISCUSSION

Several studies demonstrated that serum albumin levels are predictive of adverse outcomes in patients with confirmed COVID-19. Decreased albumin levels were associated with poor outcomes, including more venous thromboembolism events, ARDS development, ICU admissions, readmissions within 90 days, and total adverse events.[6,7]

Table 2. Serum albumin and liver enzymes levels of patients with severe COVID-19.

Characteristics	Outcome		P
	Died	Survived	
Albumin			
Decreased	25 (100%)	60 (78.9%)	0.012
Normal	0 (0%)	16 (21.1%)	
ALT			
Elevated	23 (92%)	23 (30.2%)	<0.001
Normal	2 (8%)	53 (69.8%)	
AST			
Elevated	23 (92%)	37 (48.7%)	<0.001
Normal	2 (8%)	39 (51.3%)	

A study conducted by Violi et al.[8] also found that serum albumin of less than 35 g/L was detected in 74% of the COVID-19 patients with a higher ICU prevalence and is associated with vascular disorders.[7]

The mechanism of hypoalbuminemia in COVID-19 has not been thoroughly studied. Albumin is a protein produced by the liver with a serum half-life of approximately 21 days.[5] Serum albumin levels can be decreased by many factors, including hepatocellular injury, malnourishment, inflammation, and renal losses.[6]

Albumin is synthesized less and extravasated into the interstitial space due to capillary leakage during a state of severe illness. Adequate albumin levels appear to have significant antioxidant properties, such as scavenging oxygen free radicals (OFR), which is critical in preventing tissue ischemia, reperfusion injury, and intense systemic inflammatory response. This implies that severely ill COVID-19 patients with hypoalbuminemia may have a diminished immunological response and can lead to mortality.[6]

In this study, the results showed that severe COVID-19 patients had a higher rate of decreased albumin levels (84.2%) than normal albumin levels. This is in line with the previous research conducted by Zhang,[4] which showed that hypoalbuminemia was seen mainly in severe cases of COVID-19 compared to mild cases.[4]

In addition, the study of J. Huang et al.[5] also showed that severe COVID-19 patients with hypoalbuminemia had a mortality rate of 13.2%. In this study, the survival rate for severe COVID-19 patients with hypoalbuminemia was 70.5% (P=0.12), which means that there was no significant association between hypoalbuminemia and the mortality rate in severe cases of COVID-19. The increased survival rate is caused by albumin therapy that have been administered in COVID-19 patients in H. Adam Malik Hospital.

Elevation of ALT and AST levels have also been noted in patients with COVID-19. Evidence suggests a strong correlation between the severity of liver impairment caused by viral infections and the degree of liver enzyme elevation. Up to 11% of patients with COVID-19 have liver comorbidities, and 14% to 53% show elevated transaminase levels (ALT and AST) during the progression of the illness. Patients with a mild illness may have normal or only slightly elevated aminotransferase levels, while those with more severe cases can present with higher elevations.[9,10]

In this study, we also found that the value of ALT and AST increased in severe COVID-19 patients who died, with P<0.001, which means that there is a significant relationship between elevated transaminase levels and mortality rate of severe COVID-19 patients. This is supported by a study conducted by Zhang et al.,[4] which stated that the hepatocellular severity in COVID-19 patients is due to a systemic inflammatory response, hypoxemia and the adverse effects of hepatotoxic therapy during hospitalization.

CONCLUSION

In this research, it can be concluded that severe cases of COVID-19 are mostly experienced by women aged 41-60 years. Hypoalbuminemia and increased liver function are predictors of mortality for severe COVID-19 in H. Adam Malik Hospital, Medan.

REFERENCES

1. Livingston E, Bucher K, Rekito A. Coronavirus Disease 2019 and Influenza 2019-2020. *JAMA*. 2020;323(12):1122.
2. Satuan Tugas Penanganan COVID-19. COVID-19 SUMUT. Diskominfo Provinsi Sumatera Utara. https://covid19.sumutprov.go.id/.
3. Viasus D, Garcia-Vidal C, Simonetti A, et al. Prognostic value of serum albumin levels in hospitalized adults with community-acquired pneumonia. *J Infect*. 2013;66(5):415-423.
4. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: A retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int*. 2020;40(9):2095-2103.
5. Huang Y, Meng S, Zhang Y, et al. The respiratory sound features of COVID-19 patients fill gaps between clinical data and screening methods. *medRxiv*. 2020.
6. Kheir M, Saleem F, Wang C, Mann A, Chua J. Higher albumin levels on admission predict better prognosis in patients with confirmed COVID-19. *PLoS One*. 2021;16(3):e0248358.
7. Violi F, Ceccarelli G, Cangemi R, et al. Hypoalbuminemia, coagulopathy, and vascular disease in COVID-19. *Circ Res*. 2020;127(3):400-401.
8. Violi F, Cangemi R, Romiti GF, et al. Is Albumin Predictor of Mortality in COVID-19? *Antioxid Redox Signal*. 2021;35(2):139-142.
9. Clark R, Waters B, Stanfill AG. Elevated liver function tests in COVID-19: Causes, clinical evidence, and potential treatments. *Nurse Pract*. 2021;46(1):21-26.
10. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA*. 2020;323(16):1612-1614.

Literature Review

Effect of Chemotherapy on Quality of Life of Lung Cancer Patients: Scoping Review

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Abstract

Background: Lung cancer is a tumor originating from the lung parenchyma or in the bronchi. Lung cancer is the second most frequently diagnosed cancer. The treatment often used is chemotherapy as most lung cancers are diagnosed late. Chemotherapy can provide many benefits but also has side effects because it works by killing healthy replicating cells. Symptoms of cancer that appear as well as side effects of therapy have an impact on the patient's quality of life. Quality of life is a person's perception of his position in life in the context of values and culture. Quality of life can determine a person's general well-being and well-being is the main goal of treatment**.** This study aims to determine the effect of chemotherapy on the quality of life of lung cancer patients.

Method: This Scoping Review was compiled by conducting a literature search on the PubMed, ScienceDirect, SpringerLink databases, and manual searches on Google Scholar with the keywords "Lung Cancer" AND "Chemotherapy" AND "Quality of Life" from 2016 to 2021 publication period. Scoping This review is guided by the PRISMA-ScR checklist.

Results: As much as 30 journals were obtained based on inclusion and exclusion criteria from this process. We found that most of the literature states that chemotherapy has a positive effect in improving the quality of life of lung cancer patients, which are dominated by advanced NSCLC cancer types.

Conclusion: Aspects that can affect the quality of life of lung cancer patients undergoing chemotherapy are the available health facilities, the choice of chemotherapy regimen, the timing of the quality-of-life assessment, and the patient's socio-cultural background.

Keywords: lung cancer, chemotherapy, quality of life (QoL)

INTRODUCTION

Lung cancer or bronchogenic carcinoma is a tumor originating from the lung parenchyma or in the bronchi. The pathophysiology of lung cancer is very complex and not fully understood.[1] Globally, lung cancer is the leading cause

of death with a high prevalence.

Lung cancer is the second most frequently diagnosed cancer with a portion of 11.4% in 2020. However, lung cancer is still the leading cause of cancer death, with an estimated 1.8 million deaths each year.[2] Lung cancer is the most common type of cancer with highest mortality in men and second in women after breast cancer.[3] Lung cancer incidence and mortality also differ by region. In 2020, Asia has the highest incidence rate, 59.6%, and the highest mortality rate with a 61.9% percentage while Oceania has the lowest incidence rate (0.8%) and the lowest mortality rate (0.7%).[4]

In Indonesia, Basic Health Research (Riskesdas) data in 2013 and 2018 showed an increase in cancer prevalence from 1.4% to 1.8%.[5] In 2020 the number of new cancer cases reached 396,914 cases and the number of new lung cancer cases lung numbered 34,783 cases. This makes lung cancer in third place with the most cancer cases.[6] The prevalence of cancer in Aceh Province also increased from 2013 to 2018 from 1.4 to 2.[7,8]

Based on medical records of the Regional General Hospital dr. Zainoel Abidin Banda Aceh, recorded that there were 53 lung cancer patients in 2018 then increased in 2019 to 63 patients.[9] This high incidence requires serious efforts from all relevant parties in selecting and implementing therapy for patients.

There are several alternative therapies for patients, namely surge surgery, rugs including chemotherapy, targeted therapy and immunotherapy, and palliative care. All of them have a role in the treatment of lung cancer patients depending on the stage of cancer.[10]

This treatment plan should be based on the histologic and molecular characteristics of the tumor, disease stage at diagnosis, appearance status, and individual comorbidities.[10] Most lung cancers are diagnosed late because they are inoperable or metastatic. In this case, the treatment of choice is chemotherapy, either alone or in combination with radiotherapy.[11]

Chemotherapy is the application of chemicals or drugs to kill cancer cells and the effects are systemic.[12] Chemotherapy works by stopping or slowing the growth of cancer cells. Chemotherapy can make tumors smaller before surgery or radiation therapy, destroy any cancer cells that may remain after surgery or radiation therapy, help radiation therapy and immunotherapy work better, and can destroy cancer cells that come back (relapse) or spread to other parts of the body (metastasis).[13] Although chemotherapy can provide many benefits, chemotherapy has side effects as it also kills healthy replicating cells.[14] Common side effects include hair loss, nausea, and low blood cell counts.[15]

Cancer symptoms that manifested and the side effects of the therapy have an impact on the patient's quality of life. Quality of life is a person's perception of his position in life in the context of values and culture. It relates to the patient's goals, expectations, standards, and concerns.[16] Quality of life can determine a person's general well-being and well-being is the

one of the main goals of treatment. In addition, the patient's well-being is expected to prolong life expectancy. Therefore, quality of life is now widely used by clinical researchers as an outcome measure to evaluate the effectiveness of treatment so that it can provide the right therapy.[17]

Previous studies are showing the effect of chemotherapy on the quality of life of cancer patients. Studies conducted in patients with squamous NSCLC with four cycles of nab-paclitaxel or carboplatin showed a clinically significant improvement in quality of life and greater benefit compared to those who did not undergo these therapies.[18] However, a study conducted in patients with advanced NSCLC showed a negative effect on the quality of life of patients undergoing chemotherapy compared to the period before the start of therapy.[19]

Because there are still research gaps that explain the effect of chemotherapy on lung cancer quality of life, Therefore, the authors are interested in studying further regarding the effect of chemotherapy on the lives of lung cancer patients, which is then expected to provide a synthesis.

METHODS

The literature search was carried out using four databases of journal publications and articles in the literature search process related to the research topic. The databases used are Pubmed, Sciencedirect, Springerlink, and manual data searches on Google Scholar. The research was conducted in Banda Aceh from September to November 2021. The keywords used were "Lung Cancer" AND "Chemotherapy" AND "Quality of Life". Literature was obtained with a time limit of the last 5 years, namely from 2016 to 2021.

The literature that included is literature published on databases or international article publication sites. The contents of the literature that are relevant to the research objective, namely describing the topic of the effect of chemotherapy on the quality of life of lung cancer patients, literature published within a period of 5 years, from 2016 to 2021. The excluded literature is duplicates, literature in languages other than English, literature which is a literature review, and literature that does not provide full-text access.

The filter used all titles, abstracts, and full text independently. Then the following information was extracted: title, DOI/journal number, year of publication, country of the first author or international organization where the research was conducted, type of literature, and results and conclusions.

The analysis carried out is a descriptive analysis of the characteristics of the included literature. The source describes where found literature, year of publication, type of literature, and literature topics on the effect of chemotherapy on the quality of life of lung cancer patients to examine gaps in the study. The scoping review according to the PRISMA-ScR Checklist was conducted.

RESULTS

The search in the PubMed database uses a literature filtering function using English and the time range for publication is from 2016 to 2021. The selected types of articles are full text, associated data, case reports, clinical studies, journal articles, observational studies, Randomized Control Trials. The number of literatures obtained in the search was 574 pieces of literature. A total of 551 pieces of literature were excluded because they did not meet the inclusion and exclusion criteria so only 23 pieces of literature in the PubMed database search were reviewed at the stage of identifying duplicates and reviewing the overall contents of the literature.

Search on ScienceDirect using the filtering function of the literature publication time range from 2016 to 2021 and the type of literature in the form of research articles and case reports and using the advanced search title, abstract, keywords feature: The number of literature obtained is 137 pieces of literature, 116 of which do not meet the inclusion and exclusion criteria. The number of literatures reviewed at the stage of duplicate identification and review of the contents of the entire literature is a total of 21 pieces literature.

The search on SpringerLink uses a filtering function for the time range of literature publication from 2016 to 2021. The number of articles obtained is 5,151 literatures with article types, not chapters. A total of 5,150 of the entire literature is irrelevant and only 1 suitable literature meets the inclusion and exclusion criteria so that duplicates and the entire contents of the literature will be reviewed.

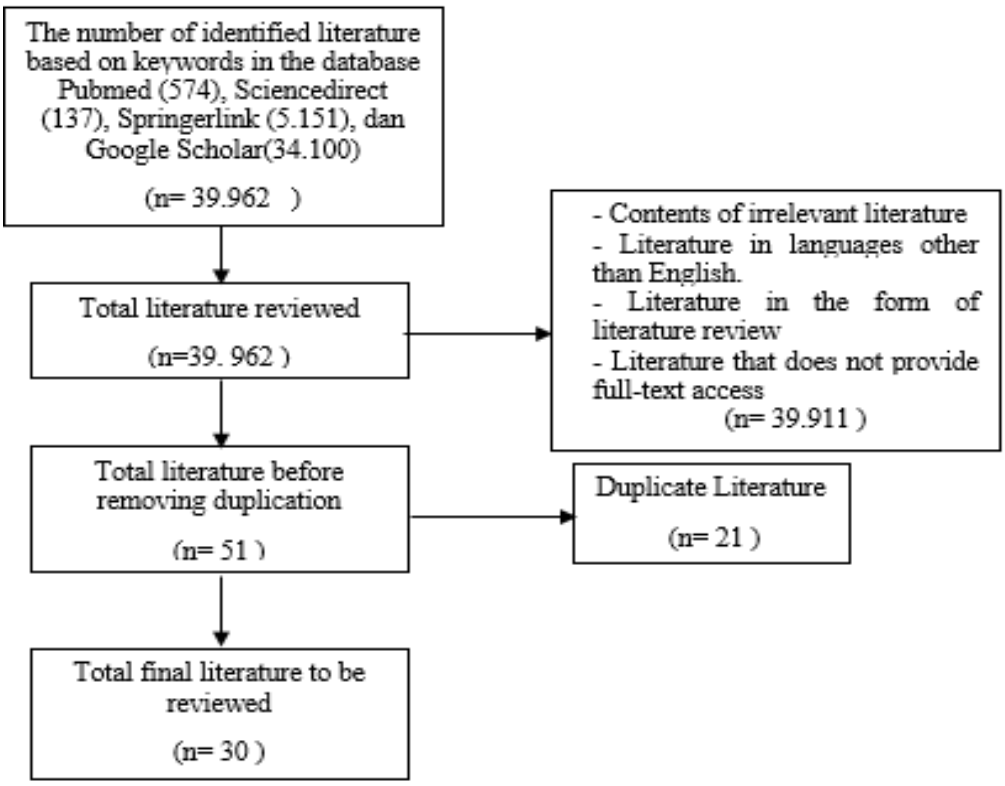

Figure 1. Flowchart of Search Results and Literature Selection

The manual search aims to obtain literature that is relevant to the research topic but unable to found in the PubMed. The number of literatures that meets the inclusion and exclusion criteria is six literature which will then be reviewed for duplicates. Furthermore, as many as 21 pieces of literature were removed as duplications of a total of 51 pieces of literature so that the remaining 30 pieces of literature will be extracted from each literature and reviewed (Figure 1).

Table 1. Characteristics of Literature

Characteristics	N	%
Journal		
Tha Lancet	3	10
European Journal of Cancer	3	10
Thoracic Cancer	3	10
Journal Lung Cancer	3	10
European Society for Medical Oncology (ESMO)	2	7
Other	16	53
First Author's Country		
China	5	17
United States	5	17
German	5	17
France	3	10
Other	12	40

Most of the literature comes from China, the United States, and Germany with a percentage of 17% in each country. Then, the journals with the highest amount of literature were The Lancet, European Journal of Cancer, Journal of Thoracic Cancer, and Lung Cancer Journal with 3 (10%) published literature (Table 1).

Figure 2 shows the cumulative amount of literature every year, starting from 2016 to 2021. During that period, there are publications of literature related to this research topic which fluctuate annually with the highest number of journal publications being in 2017 with 12 pieces of literature.

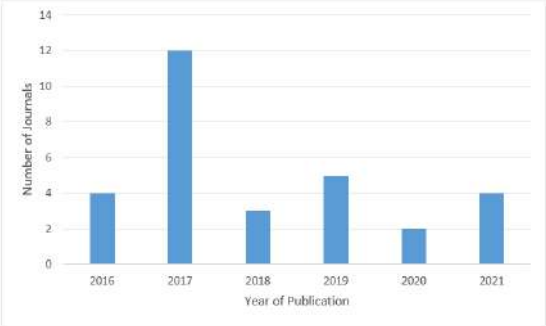

Figure 2. Number of Journals by Year of Publication

The type of literature published annually is shown in Figure 3 where the author finds literature with the type of clinical trial every year although it is fluctuating the author only gets 3 cohort studies published in 2016 and 2017 while in 2018 to 2021 there are no cohort studies.

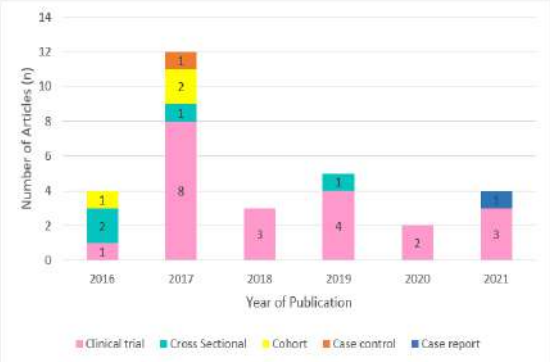

Figure 3. Types of Studies by Year of Publication

DISCUSSION

The study by Dai et al. reported that patients who achieved partial response after undergoing chemotherapy experienced stronger improvements in global quality of life and QOL emotional functional domains than patients who did not achieve a partial response. To assist

advanced NSCLC patients in optimizing their quality of life, healthcare practitioners should improve their ability to identify patients who are at high risk of experiencing poor quality of life during chemotherapy.[20]

The study was reinforced by Daroszewski et al who stated that patients who completed at least three cycles of chemotherapy had a better physical function and a good appetite compared to those who did not complete but global health status did not change in patients with advanced NSCLC.[21]

The results of another study conducted by von Verschuer et al using the The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Cancer 30 (QLQ-C30) and The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13) questionnaires stated that there was no significant difference in results in improving or maintaining the quality of life between carboplatin or cisplatin administration after 4-6 months of therapy.[22]

Another literature by Kristensen et al used the same questionnaire but with a different regimen, namely carboplatin plus vinorelbine (VC) or gemcitabine (GC) where the mean global quality of life scores showed a consistent pattern during chemotherapy. However, there were differences in mean HRQol scores between the two treatment groups at different times.[23] In contrast to the study by Juan Arraras et al, patients with advanced NSCLC showed moderate QoL scores with platinum-doublet treatment but worsened on the third assessment.[24]

The occurrence of this worsening is in line with the study by Shallwani et al who reported a decrease in the SF-36 score in advanced NSCLC patients indicating a worsening quality of life status ($P<0.05$) and the study of

Ferry et al which showed a worsening quality of life in patients who were given carboplatin or cisplatin at a low dose of 50 mg/m^2.[19,25] These results are supported by the study of

Prapa et al who found a low quality of life in lung cancer patients under chemotherapy treatment.[26]

The study was also conducted in a group of patients with advanced squamous NSCLC. The research of

Wang et al stated that there was an increase in the quality of life of lung cancer patients undergoing chemotherapy. Significant improvement in quality of life was measured by the experimental outcome index where it was seen that nab-paclitaxel improved quality of life more significantly than gemcitabine ($P<0.05$).[27]

The same result was stated by Saad et al which showed that the administration of cisplatin or carboplatin, when combined with gemcitabine in patients with advanced squamous NSCLC, had an effect in increasing the total FACTL score and TOI score significantly from baseline after administration of the regimen of three cycles and six cycles.[28] This is supported by research by Thomas et al which states that giving carboplatin can maintain or improve

quality of life.[18]

Another study using BAI chemotherapy by Zhu et al also significantly improved patients' quality of life. This study revealed that BAI chemotherapy significantly increased operative rates, prolonged PFS and OS, and improved quality of life in patients with inoperable stage III pulmonary SCC compared with intravenous neoadjuvant chemotherapy in the same group of patients.[29]

Improvements in quality of life also occurred in the non-squamous NSCLC group who were given first-line treatment to maintenance therapy.[30] However, a study by Reck et al conducted with patients with advanced squamous and non-squamous NSCLC on a regimen of docetaxel did not improve health status and did not relieve symptoms compared to nivolumab.[31,32]

In addition, there is a study comparing chemotherapy with immunotherapy, namely the comparison between nivolumab and docetaxel conducted by Reck et al who found that the docetaxel HRQoL group experienced a significant deterioration in various assessments, and the docetaxel group also experienced a significant decrease in HRQoL compared to nivolumab showing an increase in HRQoL.[33]

Research by Bordoni et al also stated that administration of docetaxel was no better in improving the patient's quality of life when compared to atezolizumab as measured using a global health status score.[34] Still in a similar study conducted by Brahmer et al also showed the same results, namely a decrease in the average score of global health status or quality of life by 0.9 points (–4.8 to 3.0) from the initial average score. before platinum-based chemotherapy. This study also showed that platinum-based chemotherapy was no better than pembrolizumab in improving or maintaining the quality of life to a better level.[35]

There are other studies comparing chemotherapy with a group of tyrosine kinase inhibitors. Chemotherapy was also shown to be no better at maintaining or improving quality of life when compared to the tyrosine kinase inhibitor group in lung cancer patients with EGFR mutations in the study of Lee et al with the administration of osimertinib and lung cancer with ALK mutations in the study of Soria et al. Ceritinib administration has been shown to improve quality of life better than chemotherapy.[36,37]

In a study conducted on the population aged over 70 years by Huerter et al, the quality-of-life assessment used the FACT-L questionnaire which is a special questionnaire to see the impact of treatment on the quality of life and performance of lung cancer patients. From this assessment, it was found that an increase in the score at week 17 in patients who had completed therapy showed an improvement in quality of life compared to the baseline, but the number of respondents who completed the questionnaire was still relatively low.[38]

A study in a similar population was also conducted by Morabito et al. The

results of the QOL response in the group with the addition of cisplatin to single-agent chemotherapy showed no signs of improvement, although the overall reduction in quality of life tended to be better when cisplatin was added (HR=0.56; 95% CI=0.31-1.01; P=0.05) so that is not sufficient to provide a positive interpretation of QOL therefore in elderly patients the addition of cisplatin does not provide any benefit.[39]

In a study conducted on NSCLC patients who had metastases by Garon et al, there were significant changes from the start of chemotherapy to week 48 which indicated an improvement or worsening.[40] The results in patients with metastatic NSCLC were strengthened in the study of Maizeres et al which showed a change after undergoing chemotherapy where for the carboplatin and paclitaxel/nab-paclitaxel group combined with placebo the average QLQ-C30 GHS/QoL score was lower than baseline. throughout the assessment until week 36.[41]

Furthermore, there was a study using docetaxel in the treatment group of NSCLC patients who had undergone previous treatment. In the study of Barlesi et al, there was a nominally significant worsening that was inversely related to pembrolizumab at a reported dose of 2 mg/kg arm and had a greater proportion of significantly improved QLQ-C30 EORTC scores across multiple domains.[42]

In the study, Nokihara et al. also described a better quality of life maintained with S-1 than with docetaxel in NSCLC patients with previous platinum-based chemotherapy treatment.[43] Similar results were also reported by the study of James Yang et al but in elderly patients who reported that administration of docetaxel did not work well in improving quality of life compared to administration of S-1.[44]

There was one literature that met the inclusion and exclusion criteria for SCLC patients conducted by Mansfield et al with the administration of atezolizumab plus Carboplatin/Etoposide group therapy. Administration of the regimen provided a significant increase in HRQoL that persisted at most visits up to week 54, whereas the initial increase in HRQoL in the placebo plus Carboplatin/Etoposide group (mostly <10 points) decreased after week 21. Health-related quality of life (HRQoL) improved in both groups after starting treatment, with a more pronounced and persistent increase in HRQoL in the atezolizumab group.[45]

The authors also found a study of adjuvant chemotherapy with vinorelbine plus cisplatin regimen compared with adjuvant gefitinib in patients with fully resected stage II-IIIA NSCLC mutant EGFR-mutants. There are similar results in studies by Zhong et al and Zeng et al. It was reported that the quality of life between the two groups fluctuated and there was a gradual improvement. However, if the logistic regression analyzed the level of OR improvement, FACT-L, TOI, and LCSS scores were significantly higher in the gefitinib treatment group and it was also stated that the timing of the decline in quality of life was delayed in the gefitinib group.[46,47]

Based on this search, research was found that examined the effect of chemotherapy on the quality of life of lung cancer patients which was dominated by advanced NSCLC cancer types, where there were variations in the quality-of-life outcomes in the study that could be influenced by several aspects, such as available health facilities, choice of chemotherapy regimen, the timing of the quality of life assessment, and the different socio-cultural backgrounds of patients.

CONCLUSION

Aspects that can affect the quality of life of lung cancer patients undergoing chemotherapy are the available health facilities, the choice of chemotherapy regimen, the timing of the quality-of-life assessment, and the patient's socio-cultural background.

Researchers who wish to conduct a similar scoping review are expected to examine other aspects that can affect chemotherapy. Health practitioners are expected to be able to choose the right regimen for lung cancer patients so that the patient's quality of life increases. Patients are expected to comply with the education provided and undergo chemotherapy to improve their quality of life.

REFERENCES

1. Siddiqui F, Vaqar S, Siddiqui AH. Lung Cancer. In: *Cambridge Handbook of Psychology, Health and Medicine, Second Edition*. StatPearls Publishing; 2022:605-606.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249.
3. Mao Y, Yang D, He J, Krasna MJ. Epidemiology of Lung Cancer. *Surg Oncol Clin N Am*. 2016;25(3):439-445.
4. The Global Cancer Observatory. Lung: Facts Sheets Cancers. *World Heal Organ*. 2020.
5. Kementerian Kesehatan RI. *Hasil Utama Riskesdas 2018*. Jakarta; 2018.
6. The Global Cancer Observatory. Indonesia: Facts Sheets Cancers. *World Heal Organ*. 2020.
7. Kementrian Kesehatan RI. *Riset Kesehatan Dasar Kementerian RI 2013*. Jakarta: Kementrian Kesehatan RI; 2013.
8. Kementerian Kesehatan RI. *Laporan Nasional Riskesdas 2018*. Jakarta; 2018.
9. Instalasi Rekam Medis RSUD dr. Zainoel Abidin. Data Rekam Medis RSUD dr. Zainoel Abidin. 2019.
10. Coakley M, Popat S. Management of lung cancer. *Med (United Kingdom)*. 2020;48(4):273-278.
11. Visconti R, Morra F, Guggino G, Celetti A. The between Now and Then of Lung Cancer Chemotherapy and Immunotherapy. *Int J Mol Sci*. 2017;18(7).
12. Huang CY, Ju DT, Chang CF, Muralidhar Reddy P, Velmurugan BK. A review on the effects of current

chemotherapy drugs and natural agents in treating non-small cell lung cancer. *BioMedicine*. 2017;7(4):12-23.

13. National Cancer Institute. *Chemotherapy and You: Support for People With Cancer*. Washington DC: National Cancer Institute; 2018.
14. McFarland DC. New lung cancer treatments (immunotherapy and targeted therapies) and their associations with depression and other psychological side effects. *Gen Hosp Psychiatry*. 2019;60:148.
15. Abbas AD. Effect of Chemotherapy upon Lifestyle for Patients with Pulmonary Carcinoma. *Iraqi J Cancer Med Genet*.
16. Binotto M, Reinert T, Werutsky G, Zaffaroni F, Schwartsmann G. Health-related quality of life before and during chemotherapy in patients with early-stage breast cancer. *Ecancermedicalscience*. 2020;14.
17. Naga Sunanda V, Priyanka M, Architha J, Shravan M, Rao AS, Hadi MA. Quality of Life Assessment in Cancer Patients of Regional Centre of Hyderabad City. *J Appl Pharm Sci*. 2018;8(01):165-169.
18. Thomas M, Spigel DR, Jotte RM, et al. nab-paclitaxel/carboplatin induction in squamous NSCLC: longitudinal quality of life while on chemotherapy. *Lung Cancer (Auckland, NZ)*. 2017;8:207-216.
19. Shallwani SM, Simmonds MJ, Kasymjanova G, Spahija J. Quality of life, symptom status and physical performance in patients with advanced non-small cell lung cancer undergoing chemotherapy: an exploratory analysis of secondary data. *Lung Cancer*. 2016;99:69-75.
20. Dai YL, Yang CT, Chen KH, Tang ST. Changes in and Determinants of Quality of Life in Patients With Advanced Non-Small-Cell Lung Cancer Undergoing Initial Chemotherapy. *J Nurs Res*. 2017;25(3):203-215.
21. Daroszewski C, Stasiewicz M, Jaźwińska-Tarnawska E, et al. Quality of Life in Patients with Advanced Non-Small-Cell Lung Cancer Receiving Palliative Chemotherapy. *Adv Exp Med Biol*. 2019;1160:11-18.
22. von Verschuer U, Schnell R, Tessen HW, et al. Treatment, outcome and quality of life of 1239 patients with advanced non-small cell lung cancer - final results from the prospective German TLK cohort study. *Lung Cancer*. 2017;112:216-224.
23. Kristensen A, Solheim TS, Amundsen T, et al. Measurement of health-related quality of life during chemotherapy – the importance of timing. *Acta Oncol (Madr)*. 2017;56(5):737-745.
24. Arraras JI, Hernandez B, Martinez M, et al. Quality of Life in Spanish advanced non-small-cell lung cancer patients: determinants of global QL and survival analyses. *Springerplus*. 2016;5(1):836.
25. Ferry D, Billingham L, Jarrett H, et al. Carboplatin versus two doses of cisplatin in combination with gemcitabine in the treatment of

advanced non-small-cell lung cancer: Results from a British Thoracic Oncology Group randomised phase III trial. *Eur J Cancer*. 2017;83:302-312.

26. Prapa P, Papathanasiou I V., Bakalis V, Malli F, Papagiannis D, Fradelos EC. Quality of Life and Psychological Distress of Lung Cancer Patients Undergoing Chemotherapy. *World J Oncol*. 2021;12(2-3):61.
27. Wang Z, Huang C, Yang JJ, et al. A randomised phase II clinical trial of nab-paclitaxel and carboplatin compared with gemcitabine and carboplatin as first-line therapy in advanced squamous cell lung carcinoma (C-TONG1002). *Eur J Cancer*. 2019;109:183-191.
28. Saad AS, Ghali RR, Shawki MA. A prospective randomized controlled study of cisplatin versus carboplatin-based regimen in advanced squamous nonsmall cell lung cancer. *J Cancer Res Ther*. 2017;13(2):198-203.
29. Zhu J, Zhang HP, Jiang S, Ni J. Neoadjuvant chemotherapy by bronchial arterial infusion in patients with unresectable stage III squamous cell lung cancer. *Ther Adv Respir Dis*. 2017;11(8):301-309.
30. Sztankay M, Giesinger JM, Zabernigg A, et al. Clinical decision-making and health-related quality of life during first-line and maintenance therapy in patients with advanced non-small cell lung cancer (NSCLC): findings from a real-world setting. *BMC Cancer*. 2017;17(1).
31. Reck M, Taylor F, Penrod JR, et al. Impact of Nivolumab versus Docetaxel on Health-Related Quality of Life and Symptoms in Patients with Advanced Squamous Non–Small Cell Lung Cancer: Results from the CheckMate 017 Study. *J Thorac Oncol*. 2018;13(2):194-204.
32. Reck M, Brahmer J, Bennett B, et al. Evaluation of health-related quality of life and symptoms in patients with advanced non-squamous non-small cell lung cancer treated with nivolumab or docetaxel in CheckMate 057. *Eur J Cancer*. 2018;102:23-30.
33. Reck M, Ciuleanu TE, Lee JS, et al. First-Line Nivolumab Plus Ipilimumab Versus Chemotherapy in Advanced NSCLC With 1% or Greater Tumor PD-L1 Expression: Patient-Reported Outcomes From CheckMate 227 Part 1. *J Thorac Oncol*. 2021;16(4):665-676.
34. Bordoni R, Ciardiello F, von Pawel J, et al. Patient-Reported Outcomes in OAK: A Phase III Study of Atezolizumab Versus Docetaxel in Advanced Non–Small-cell Lung Cancer. *Clin Lung Cancer*. 2018;19(5):441-449.e4.
35. Brahmer JR, Rodríguez-Abreu D, Robinson AG, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. *Lancet Oncol*. 2017;18(12):1600-1609.

36. Lee CK, Novello S, Rydén A, Mann H, Mok T. Patient-Reported Symptoms and Impact of Treatment With Osimertinib Versus Chemotherapy in Advanced Non-Small-Cell Lung Cancer: The AURA3 Trial. *J Clin Oncol*. 2018;36(18):1853-1860.
37. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet (London, England)*. 2017;389(10072):917-929.
38. Huerter MM, Meza JL, Copur MS, et al. Weekly vinorelbine and paclitaxel in older patients with advanced non-small cell lung cancer: A phase II Fred and Pamela Buffet Cancer Center Clinical Trials Network study. *J Geriatr Oncol*. 2017;8(1):18-22.
39. Morabito A, Piccirillo MC, Maione P, et al. Effect on quality of life of cisplatin added to single-agent chemotherapy as first-line treatment for elderly patients with advanced non-small cell lung cancer: Joint analysis of MILES-3 and MILES-4 randomised phase 3 trials. *Lung Cancer*. 2019;133:62-68.
40. Garon EB, Cho BC, Reinmuth N, et al. Patient-Reported Outcomes with Durvalumab With or Without Tremelimumab Versus Standard Chemotherapy as First-Line Treatment of Metastatic Non–Small-Cell Lung Cancer (MYSTIC). *Clin Lung Cancer*. 2021;22(4):301-312.e8.
41. Mazieres J, Kowalski D, Luft A, et al. Health-Related Quality of Life With Carboplatin-Paclitaxel or nab-Paclitaxel With or Without Pembrolizumab in Patients With Metastatic Squamous Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2020;38(3):271-280.
42. Barlesi F, Garon EB, Kim DW, et al. Health-Related Quality of Life in KEYNOTE-010: a Phase II/III Study of Pembrolizumab Versus Docetaxel in Patients With Previously Treated Advanced, Programmed Death Ligand 1–Expressing NSCLC. *J Thorac Oncol*. 2019;14(5):793-801.
43. Nokihara H, Lu S, Mok TSK, et al. Randomized controlled trial of S-1 versus docetaxel in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy (East Asia S-1 Trial in Lung Cancer). *Ann Oncol Off J Eur Soc Med Oncol*. 2017;28(11):2698-2706.
44. Yang JCH, Mok TSK, Lu S, et al. Efficacy and Safety of S-1 Compared With Docetaxel in Elderly Patients With Advanced NSCLC Previously Treated With Platinum-Based Chemotherapy: A Subgroup Analysis of the EAST-LC Trial. *JTO Clin Res Reports*. 2021;2(3):100142.
45. Mansfield AS, Każarnowicz A, Karaseva N, et al. Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial. *Ann Oncol Off J Eur Soc Med Oncol*. 2020;31(2):310-317.

46. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. *Lancet Oncol*. 2018;19(1):139-148.
47. Zeng J, Mao WM, Chen QX, et al. Quality of life with adjuvant gefitinib versus vinorelbine plus cisplatin in patients with completely resected stage II–IIIA (N1–N2) EGFR-mutant non-small-cell lung cancer: Results from the ADJUVANT (CTONG1104) study. *Lung Cancer*. 2020;150:164-171.

Literature Review

Early Diagnosis of Interstitial Lung Disease

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Abstract

Interstitial Lung Disease (ILD) includes more than 200 diseases that involve the interstitial lung. The diagnosis of ILD depends on the onset of symptoms, causes, and clinical manifestations. An anamnesis comprehensive and physical examination are essential in diagnosing ILD. In addition, laboratory tests are carried out in certain clinical conditions. The analysis of biomarkers in ILD is helpful for diagnosis, disease monitoring, and prediction of prognosis. Pulmonary function studies support the diagnosis of ILD and as a predictor of prognosis. High-resolution Computed Tomography (HRCT) is the main diagnostic procedure in ILD patients. In certain conditions, a lung biopsy may be considered. Multidisciplinary discussion (MDD) enhances accurate diagnosis. An accurate early diagnosis of ILD is necessary to ensure that patients receive optimal management, reduce the risk of developing pulmonary fibrosis and reduce the risk of death. Early diagnosis of ILD define as early identification of symptoms, laboratory and radiological findings at the early stage of the disease

Keywords: early diagnosis, fibrosis, high resolution CT, interstitial lung disease

INTRODUCTION

Interstitial lung disease (ILD) is a large group of diseases that includes more than 200 interstitial lung diseases. Most ILDs are classified as rare diseases and are associated with high morbidity and mortality rates in all age groups.[1,2] The interstitial space is the space between the capillary endothelium and the alveolar epithelium. However, this disease also involves surrounding areas such as the periphery of the airways and blood vessels.[1]

Idiopathic pulmonary fibrosis (IPF) is the most common form of ILD in older adults and has a poor prognosis. Sarcoidosis is more common in young adults and generally has a good prognosis.[1] Some patients with ILD may develop a progressive fibrotic phenotype. Progressive fibrosis is associated with worsening respiratory symptoms, decreased lung function, and a limited response to immunomodulatory therapy. Hence, there is a decrease in quality of life and worse prognosis in this phenotype.[2]

The clinical course of ILD is highly variable and is determined by the underlying cause.[1] The cause of ILD is often unknown. The most common symptoms are cough without phlegm, shortness of breath, and those associated with certain systemic diseases.[3,4] Some

forms of ILD respond well to treatment, but others are untreatable.

Early diagnosis of ILD define as early identification of symptoms, laboratory and radiological findings at the early stage of the disease. Therefore, a quick and accurate diagnosis is essential. This is to ensure that patients receive optimal management and prevent the development of pulmonary fibrosis.[1]

ILD CLASSIFICATION

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) changed the classification of ILD in 2013 based on the etiology and characteristic features of the disease. In this classification, ILD is divided into four groups: ILD with a known cause, Idiophatic Interstitial Pneumonia (IIP), granulomatous ILD, and other forms of ILD.[5] Group IIP is a term used to describe various ILDs with characteristic clinical, radiological, and pathological features.[2] The IIP group is divided into 3 parts, namely major, rare and unclassified. The major group is the most common in IIP and is divided into the chronic fibrosis group, associated with smoking and the onset of acute or subacute disease.[5] The IPF group is the most common type of IIP, accounting for 50% of all IIPs (Figure 1).[2]

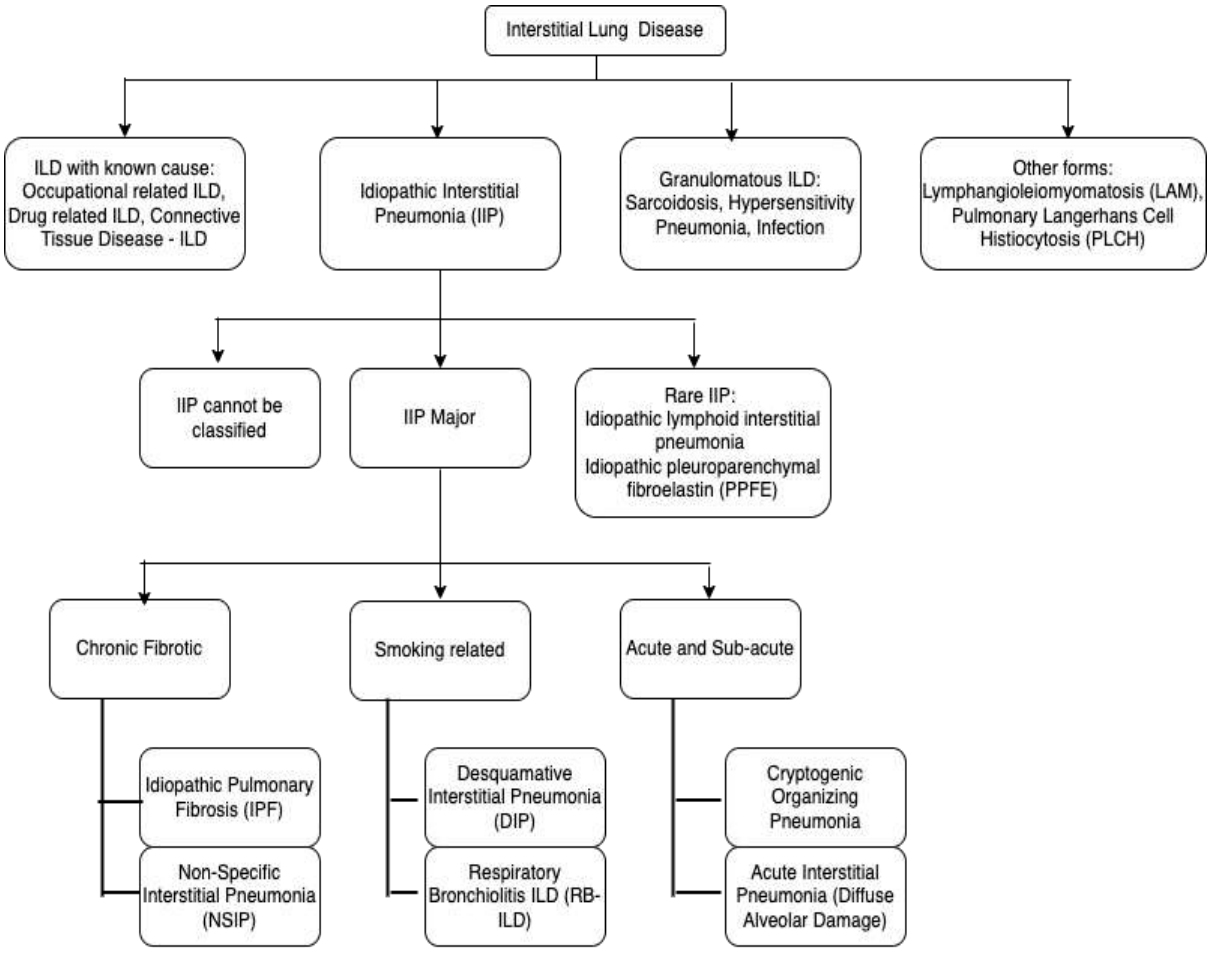

Figure 1. Interstitial Lung Disease Classification[2]

RISK FACTOR

Several risk factors for the incidence of ILD include demographics, genetics, occupational exposures, hobbies, the environment, drugs, microbes, and a history of smoking. Idiopathic pulmonary fibrosis is common in men aged 50-60 years. Sarcoidosis is more common in young people and their 40s, although it can manifest in older age.[3]

Familial interstitial pneumonia (FIP) is identified when two or more family members are diagnosed with ILD. Therefore, family history is essential in identifying patients with inherited ILD. The IIP group accounted for 2-20% of FIP.[6] A family history can be found in 1-3% of IPF patients and 6-19% of sarcoidosis patients.[3]

Occupations at risk include miners (pneumoconiosis), granite workers, welders, shipyard workers, plumbers, electricians, car mechanics, poultry farmers, bird farmers, mushroom farmers, workers in the computer, and electronics industry, nuclear industry, and related jobs. Exposure to hobbies such as bird fancier, cultivating mushrooms, or woodworking. Another risk factor of ILD is using drugs such as methotrexate, amiodarone, bleomycin, busulfan, chemotherapy, cytotoxic drugs, and narcotics. Microbial agents such as viruses, fungi, and bacteria also play an important role in developing IPF disease.[3] A history of smoking is associated with the risk of developing IPF and other pulmonary fibrotic diseases.[7,8]

DIAGNOSIS

Diagnosis of ILD depends on several categories such as the onset of symptoms (acute, subacute, chronic), etiology of the disease (known and unknown), and the clinical manifestations of the underlying systemic or extrapulmonary disease. The approach to the diagnosis of ILD is adapted to different clinical scenarios. Patients may present with specific clinical symptoms such as dry cough and shortness of breath. Patients can also be at risk for ILD because there is a history of exposure such as amiodarone, asbestos, or certain diseases in the family.[9]

Patients may also present without symptoms but have abnormalities on chest X-ray or computed tomography (CT) scans, or there are findings on pulmonary function examinations such as restriction abnormalities or impaired gas exchange on analysis of the pulmonary diffusion capacity for carbon monoxide or diffusing capacity of the lung for carbon monoxide (DLCO).[9]

Anamnesis

A comprehensive anamnesis is very important in diagnosing ILD, especially regarding the onset of respiratory symptoms, the history of the disease, the history of known exposures that can cause ILD, the history of previous systemic diseases, and the severity of the disease. The severity of the disease is known by accurately assessing the level of limitation of physical activity with the degree of perceived shortness.[9]

The most common symptoms are shortness of breath and a dry cough. Extrapulmonary symptoms include gastroesophageal reflux disease (GERD) symptoms, joint swelling or pain in rheumatoid arthritis (RA), skin thickening, Raynaud's phenomenon, and dysphagia in systemic sclerosis.[9]

Physical Examination

On physical examination, thickening of the skin and acral necrosis of scleroderma and clubbing can be seen in 40% of ILD patients to 66% of IPF patients. In addition, there may also be Livedo Racemosa in SLE patients, the vasculitis in patients with Churg Strauss syndrome, and cyanotic edematous skin in dermatomyositis. On auscultation of the lungs, 90% of IPF patients and 60% of CTD-ILD can hear a crackling sound on inspiration or called a "Velcro" sound.[9] The Velcro sound is produced by abnormal airflow into the pulmonary fibrosis tissue and can be heard in the early stages of the fibrosis process.[10]

Laboratory Tests

Laboratory tests can also be a useful adjunct when used in certain clinical conditions. Laboratory tests include complete peripheral blood, kidney function, liver function, electrolyte levels, including calcium. In addition, certain serum antibodies can also be tested to evaluate CTD-ILD and certain systemic diseases such as antinuclear antibodies (ANA) and rheumatoid factor (RF).[9]

Increased levels of matrix metalloproteinases (MMP), both serum MMP1 and MMP7, bronchoalveolar lavage (BAL) fluid and sputum, serum levels of insulin-like growth factor-binding protein (IGFBP) 2 serum levels of the chemokine CXCL13 are diagnostic biomarkers in IPF patients. In addition, elevated levels of Krebs von de Lungen (KL) 6 serum and BAL fluid were found in patients with IIP, hypersensitivity pneumonitis, sarcoidosis, asbestosis, and CTD-ILD.[11]

Pulmonary Function

Pulmonary function examination is needed to evaluate patients suspected of having ILD, which consists of blood gas analysis, spirometry, body plethysmograph, DLCO, and oximetry both at rest and activity. Examination of lung function, in general, cannot support the diagnosis of specific ILD but is needed to assess respiratory limitations, assess disease severity, monitor disease progression and response to therapy, and as a predictor of disease prognosis. Restriction abnormalities, decreased lung volume and reduced diffusion capacity are common outcomes in ILD patients.[1,3,9,12]

Radiological Examination

The chest X-ray was the first radiological examination performed but has limited sensitivity and specificity in ILD.[1] The most frequently findings on chest radiographs of ILD patients include diffuse reticulonodular, ground-glass opacities (GGO), or both. High-resolution computed tomography (HRCT) has a greater accuracy

value than chest X-ray and is the main diagnostic procedure in ILD patients.[9] We can find several typical patterns on HCRT namely reticular patterns, nodular patterns, alveolar patterns, and cystic pattern.[12]

The reticular pattern is characterized by linear opacity, forming a web-like braid, resulting from thickening of the interlobular and intralobular septa, interconnected with each other, located in the periphery and basal areas of the lung and is common in IPF patients. The nodular pattern is around discrete opacity and varies in size from a few millimetres to 3 cm, commonly found in sarcoidosis. The alveolar way is an opacity that arises due to alveolar filling consisting of GGO, consolidation and tree in the bud. A cystic way is an enlarged air space surrounded by walls of varying thickness and composition. This pattern is found in LAM and PLCH.[12,13]

Based on HRCT images, there are four categories of IPF diagnosis, namely the usual interstitial pneumonia (UIP) pattern, probable UIP, indeterminate UIP and alternative diagnoses. The UIP image is a typical IPF image (Table 1).[14] Figure 2 shows common typical pattern on HRCT of ILD patients.[15]

Table 1. Patterns of HRCT images on IPF[14]

UIP	Probable UIP	Indeterminate UIP	Alternative diagnosis
Predominant in subpleura and basal, heterogeneous distribution	Predominant in subpleura and basal, heterogeneous distribution	Predominant in subpleura and basal	The findings lead to other diagnoses namely: CT image: - Cystic - Mosaic Attenuation - Dominant GGO - Lots of micronodules - Centrilobular nodules - Nodules - Consolidation
Honeycombing with or without traction bronchiectasis/bronchiectasis in the periphery	Reticular pattern with traction bronchiectasis/bronchiolectasis in the periphery	Mild reticulation, may be accompanied by mild ARF (early UIP pattern)	Dominant distribution: - Peribronchovascular - Perilymphatic - Upper or middle lung
	May be accompanied by mild GGO	CT images or distribution of pulmonary fibrosis that do not point to a specific cause (indeterminate UIP)	Other: - Pleural plaque (leading to asbestosis) - Esophageal dilation - Erosion of the distal clavicle (leading to RA) - Enlarged lymph nodes (leads to other causes) - Pleural effusion, pleural thickening (leading to CTD/drug-induced)

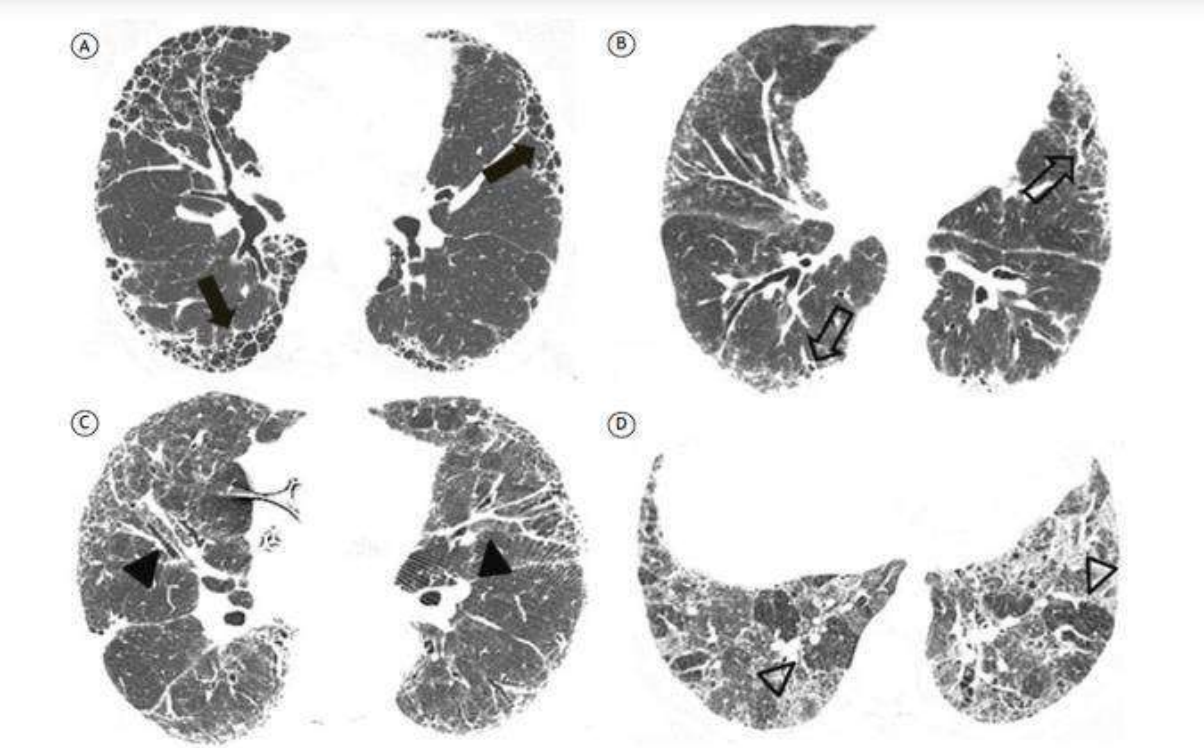

Figure 2. High-resolution CT image of IPF. A. UIP pattern: broad honeycombing in the subpleural and dominant in the basal (arrows). B. Probable UIP: reticular opacity and traction bronchiectasis (arrows) without honeycombing. C. Indeterminate UIP: central and diffuse regional abnormalities (arrows), GGO and reticular opacity. D. Alternative diagnosis: Extensive ARF and mosaic attenuation pattern (arrow).[15]

Bronchoscopy and Lung Biopsy

A lung biopsy is usually not required if a specific diagnosis can be made by history, physical examination, laboratory studies, and HRCT. However, if a specific diagnosis has not been reached, a lung biopsy may be considered. In addition to establishing a particular diagnosis, lung biopsy can also help assess prognosis and guide treatment. Furthermore, it can be determined whether lung biopsy by bronchoscopy or by surgical biopsy.[12]

Bronchoscopy can also obtain microbiological material, cytology with bronchoalveolar lavage (BAL) technique so that it can provide sufficient evidence to diagnose sarcoidosis, hypersensitivity pneumonitis, PLCH, DIP, lymphocytic interstitial pneumonia, LAM and pulmonary alveolar proteinosis (PAP). Histopathological diagnosis has an accuracy value of 90%.[12]

In IPF, histopathological examination is no longer the gold standard for diagnosis because sampling errors can occur, and there is uniformity of disease patterns in patients with advanced disease. Multidisciplinary discussion (MDD) involving pulmonologists, radiologists and anatomical pathologists has become the gold standard in diagnosing IPF. Multidisciplinary discussion is also an appropriate approach for the diagnosis of most ILD patients and holds the most promise for achieving diagnostic confidence.[9] Adequate case presentation and discussion of clinical and radiological data are essential for an accurate diagnosis.[5]

EARLY DIAGNOSIS OF ILD

Some ILDs are characterized by progressive fibrosis so that they have progressive symptoms, decreased quality of life, decreased lung function, poor response to treatment, are fatal and reach death an average of 3 years after diagnosis. IPF is the most common form of ILD and is more severe. IPF patients initially experience non-typical clinical symptoms such as dry cough and shortness of breath when active, so they are often misdiagnosed until pulmonary function examinations and radiological examinations show ILD.[16,17]

Determining the diagnosis of ILD with confidence is a big challenge because of the heterogeneous variety of diseases that often experience delays in diagnosis.[18] A cohort study of delayed diagnosis of ILD in 129 patients who met the IPF criteria according to the ATS found an average delay of diagnosis of 2.2 years with a range of 1.0-3.8 years. The delay in diagnosing ILD was defined from the onset of symptoms until a tertiary health centre visit. Delay in diagnosis is associated with an increased risk of death.[16] On the other hand, an accurate early diagnosis will have significant implications for treatment and prognosis and reduce death risk.[16,17]

The delay in diagnosing ILD can be caused by several factors, such as atypical symptoms causing patients to arrive late to health facilities. In addition, it can also be caused by a misdiagnosis by clinicians in the community so that they are late in referring to a tertiary health centre. Therefore, it is hoped that primary health services and pulmonary doctors can consider the diagnosis of ILD in patients with symptoms of shortness of breath of unknown cause and then involve other expertise in diagnosing and managing ILD early in the course of the disease.[16,19]

Currently, screening for ILD is limited to patients with known risk factors for ILD or a history of familial IPF. Another factor is the delay in obtaining a final diagnosis at a tertiary health centre. All of these contribute to the delay in the diagnosis of ILD. Research on biomarkers and quantitative imaging methods currently being developed can be the key to identifying ILD as early as possible.[16,19]

Screening for ILD in patients with systemic sclerosis with HRCT shows that 60% of whom has normal lung function. In this case, pulmonary function examination alone performs less well than HRCT in detecting ILD. High-resolution CT analysis and concurrent and serial lung function studies have shown that screening with HRCT as a baseline for predicting the risk of developing pulmonary fibrosis, the rate of fibrosis progression and lung function decline.[20]

Further studies on the examination of biomarkers such as CCL18 and non-radiative pulmonary imaging modalities such as ultrasonography (USG) and magnetic resonance imaging (MRI) are expected to serve as a support for the early detection of ILD.[20]

The American Thoracic Society and emergency response system (ERS) emphasize the need for a dynamic

integrated diagnostic process among pulmonologists, radiologists and pathologists, by exchanging information in determining the diagnosis in patients with suspected ILD. A study examining the importance of MDD shows that MDD improves accurate diagnosis because more data are available. The patient may be decided not to have a lung biopsy based on clinical symptoms and high-resolution CT results that are convincing for the diagnosis of IPF. In addition, for ILD patients other than IPF, it can be agreed to perform a lung biopsy as a final diagnosis.[21]

CONCLUSION

The diagnosis of ILD depends on several categories such as the onset of symptoms, the cause of the disease and the clinical manifestations of the underlying disease. A comprehensive history and physical examination are very important in diagnosing ILD. Laboratory tests are needed as support in certain clinical conditions. Analysis of biomarkers in ILD is useful for diagnosis, disease monitoring and prediction of prognosis.

Examination of lung function can support the diagnosis of ILD and also as a predictor of disease prognosis. High-resolution computed tomography is the main diagnostic procedure in ILD patients. Multidisciplinary discussion (MDD) enhances accurate diagnosis. A real early diagnosis of ILD is necessary to ensure that patients receive optimal management, reduce the risk of developing pulmonary fibrosis and reduce the risk of death.

REFERENCES

1. Ward J, McDonald C. Interstitial lung disease - An approach to diagnosis and management. *Aust Fam Physician*. 2010;39(3):106-110.
2. Cottin V, Hirani NA, Hotchkin DL, et al. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. *Eur Respir Rev*. 2018;27(150).
3. Saha K. Interstitial lung disease: Diagnostic approach. *J Assoc Chest Physicians*. 2014;2(1):3.
4. Nogee LM. Interstitial lung disease in newborns. *Semin Fetal Neonatal Med*. 2017;22(4):227.
5. Antoniou KM, Margaritopoulos GA, Tomassetti S, Bonella F, Costabel U, Poletti V. Interstitial lung disease. *Eur Respir Rev*. 2014;23(131):40-54.
6. Sgalla G, Iovene B, Calvello M, Ori M, Varone F, Richeldi L. Idiopathic pulmonary fibrosis: pathogenesis and management. *Respir Res*. 2018;19(1).
7. Baumgartner KB, Samet JM, Stidley CA, Colby T V., Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1997;155(1):242-248.
8. Flaherty KR, Hunninghake GG. Smoking: an injury with many lung manifestations. *Am J Respir Crit Care Med*. 2005;172(9):1070-1071.
9. Behr J. Approach to the diagnosis of interstitial lung disease. *Clin Chest Med*. 2012;33(1):1-10.
10. Pancaldi F, Sebastiani M, Cassone G, et al. Analysis of pulmonary sounds for

the diagnosis of interstitial lung diseases secondary to rheumatoid arthritis. *Comput Biol Med*. 2018;96:91-97.

11. Inoue Y, Kaner RJ, Guiot J, et al. Diagnostic and Prognostic Biomarkers for Chronic Fibrosing Interstitial Lung Diseases With a Progressive Phenotype. *Chest*. 2020;158(2):646-659.
12. Ryu JH, Daniels CE, Hartman TE, Yi ES. Diagnosis of interstitial lung diseases. *Mayo Clin Proc*. 2007;82(8):976-986.
13. Jawad H, Chung JH, Lynch DA, Newell JD. Radiological approach to interstitial lung disease: a guide for the nonradiologist. *Clin Chest Med*. 2012;33(1):11-26.
14. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68.
15. Torres PPTES, Rabahi MF, Moreira MADC, Escuissato DL, Meirelles G de SP, Marchiori E. Importance of chest HRCT in the diagnostic evaluation of fibrosing interstitial lung diseases. *J Bras Pneumol*. 2021;47(3).
16. Lamas DJ, Kawut SM, Bagiella E, Philip N, Arcasoy SM, Lederer DJ. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. *Am J Respir Crit Care Med*. 2011;184(7):842-847.
17. Wong AW, Ryerson CJ, Guler SA. Progression of fibrosing interstitial lung disease. *Respir Res*. 2020;21(1):1-10.
18. Walsh SLF, Devaraj A, Enghelmayer JI, et al. Role of imaging in progressive-fibrosing interstitial lung diseases. *Eur Respir Rev*. 2018;27(150).
19. van der Sar IG, Jones S, Clarke DL, et al. Patient Reported Experiences and Delays During the Diagnostic Pathway for Pulmonary Fibrosis: A Multinational European Survey. *Front Med*. 2021;8.
20. Molberg Ø, Hoffmann-Vold AM. Interstitial lung disease in systemic sclerosis: progress in screening and early diagnosis. *Curr Opin Rheumatol*. 2016;28(6):613-618.
21. Flaherty KR, King TE, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med*. 2004;170(8):904-910.

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