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Original Article

Original Article

Characteristics of EGFR Gene Mutation in Lung Adenocarcinoma at Adam Malik General Hospital

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Abstract

Background: Epidermal growth factor (EGFR) is a transmembrane receptor that plays an important role in the development of cancer phenotypes. Some patients with lung cancer have genetic mutations. Several studies have found a close correlation of EGFR gene mutation with 15-20% of lung adenocarcinoma cases. This study aimed to determine the EGFR profile in adenocarcinoma lung cancer patients at Haji Adam Malik General Hospital.

Methods: This was a prospective cohort study conducted at Haji Adam Malik General Hospital, Medan. This study used patients data for 3 years, starting from January 1, 2014 to D[1]ecember 31, 2016. The sample size in this study was 34 patients. The data were then analyzed using SPSS.

Results: All patients were adenocarcinoma lung cancer patients with positive EGFR mutation. There were 9 subjects with EGFR mutation in exon 19; 11 subjects with exon 21 L858R mutation; and 3 subjects with exon 21 L861Q mutation. Meanwhile, there were 3 subjects with uncommon EGFR mutations, namely exon 18 mutation. Majority of subjects with exon 19 mutation were male, aged >60 years, smokers with mixed types of cigarettes and severe brinkmann index. In subjects with exon 21 L858R mutation, most of the patients were male, aged 50-60 years, smokers with mixed cigarette types and severe brinkmann index. The same characteristics were also observed in subjects with exon 18 mutation. However, for exon 21 L861Q mutation, the majority of subjects were female with varying ages, and were not smokers.

Conclusion: Most of the study subjects profiles were male, aged over 60 years, smokers, with mixed types of cigarettes, and with severe Brinkman Index. The EGFR mutations most commonly occured in exon 21, followed by exon 19 (ins/del exon 19), exon 18, and a combination of 2 exons.

Keywords: Adenocarcinoma, EGFR, Lung cancer

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INTRODUCTION

Lung cancer is the leading cause of malignancy globally, accounting for up to 11.4% of all cancer diagnoses in both sex. Lung cancer is also the second most common cancer worldwide with total cases around 2.21 million cases and highest mortality among all type of cancers (1.8 million deaths per year). The incidence and mortality are higher in male compare with female with ratio 2:1 and varies across region.[1] According to GLOCOBAN 2020, lung cancer is the third rank of highest incidence of lung cancer with the highest mortality in both sex. Every year, 34.783 new cases of lung cancer with 30.843 deaths detected in Indonesian population.[2] This is why lung cancer must be considered as in Indonesia's health issue that need special attention and research concentration in the treatment and outcome aspect.

Lung cancer is generally classified into two histologic types: non-small cell carcinoma (NSCLC) and small cell carcinoma (SCLC). NSCLC is the most common type of lung cancer, accounting for about 85% of all lung cancer cases, and consists of several subtypes, including squamous carcinoma (epidermoid carcinoma), adenocarcinoma, and large cell carcinoma.[3,4] Further, these types of lung cancer has the their own molecular characteristics of which adenocarcinoma is known as the histology type of lung cancer that has the most oncogenes and tumor supressor genes related lung carcinogenesis.[5–7]

Some people with lung cancer have genetic mutations. Several studies have found a close correlation between mutations in the Epidermal Growth Factor (EGFR) gene with 15–20% of lung adenocarcinoma cases. In East Asia, the percentage of EGFR gene mutations in lung adenocarcinoma cases was higher at 38%[8] while Asia-Pasific showed the highest prevalence of EGFR mutations.[9] Meanwhile, EGFR gene mutations were expressed in 89% of lung adenocarcinoma cases in India.[10] EGFR is a transmembrane receptor of the ErbB family, consisting of four closely related members: HER1/ErbB1, HER2/neu/erbB2, HER3/ErbB3, and HER4/ErbB4.[11] EGFR activation can trigger signal transduction and subsequent intracellular cancer cells proliferation, inhibition of apoptosis, neoangiogenesis, and distant metastasis, all of which are important for the development of cancer phenotypes.[12]

Based on the description above, the researcher conducted a study to determine the EGFR profile in patients with adenocarcinoma lung cancer at Haji Adam Malik General Hospital.

METHODS

This was a prospective cohort study conducted at the Department of Pulmonology and Respiratory Medicine at Haji Adam Malik General Hospital, Medan. This study used patient data for 3 years, starting from January 1, 2014, to December 31, 2016.

The sample size in this study was 34 patients. The inclusion criteria in this study were: all patients diagnosed with mutation-positive adenocarcinoma, were examined for EGFR mutations using PCR method with specific alleles targeting specific EGFR mutations at exons 19 and 21 in subjects who had an established cytological or histopathological diagnosis, and had consumed tyrosine kinase inhibitor (TKI) drugs for at least 3 months. The exclusion criteria were incomplete patient data.

The molecular examination process is broadly divided into two parts, namely the preparation of manual examination materials to obtain deoxyribonucleic acid (DNA) from cytological slide scrapings or deparaffinization of paraffin blocks through FFPE and amplification of detection from DNA using the principle of allele-specific detection with Cobas z 480 (Roche, Switzerland). The minimum tumor percentage is 5% of the total examination material. The kit used for material preparation was the Cobas® DNA Sample Preparation Kit (P/N: 05985536190). The kit used for amplification and mutation detection was the Cobas® EGFR Mutation Test Kit (P/N: 06471463190).

Data on medical record (MR) numbers and patient names were obtained using the International Classification of Diseases and Related Health Problems 10 (ICD – 10). The data were then copied into data collection sheet. The data collected were demographic data, which included: MR number, name, gender, age, smoker, type of cigarette, Brinkman Index (BI), and exon data. The data were then analyzed using SPSS.

RESULTS

The characteristics of adenocarcinoma lung cancer patients can be seen in Table 1. Adenocarcinoma lung cancer patients with favorable gene mutations were mostly male with as many as 24 patients (70.6%) while the female were 10 patients (30.6%). Subjects aged 60 years were 14 patients (41.2%), followed by those aged 51–60 years with as many as 13 patients (38.2%), and the least was aged 41–50 years with 7 patients (20.6%). There were no patients under 41 years of age.

Based on smoking status, the number of smokers was higher than the non-smokers, namely 24 patients (70.6%) vs 10 patients (30.4%).

Table 1. Characteristics of the subjects

Profile	N	Percentage (%)
Gender		
Male	24	70.6
Female	10	30.4
Age		
<30 years	-	-
31–40 years	-	-
41–50 years	7	20.6
51–60 years	13	38.2
>60 years	14	41.2
Smoking Status		
Smokers	24	70.6
Non-smokers	10	30.4
Type of cigarettes		
Filtered	8	33.3
Non-filtered	-	-
Mixed	16	66.7
Brinkman Index (BI)		
Mild	-	-
Moderate	-	-
Severe	24	100

Most of the smokers smoked mixed type of cigarettes (66.7%) while the rest smoked only filtered cigarettes (33.3%). None of the subjects consumed non-filtered cigarettes. All patients had severe BI.

Table 2. Profile of EGFR mutations by exons

EGFR	N	Percentage (%)
Exon 18		
G719A	2	5.9
G719C	-	-
G719D	-	-
G719S	2	5.9
G719V	-	-
Exon 19		
Ins/del exon 19	13	38.2
Exon 21		
L858R	11	32.4
L816Q	5	14.7
2 Exons		
Ins/del exon 19 and exon 21 L858R	1	2.9
Total	34	100

The profile of EGFR mutations based on exons in Table 2 shows that the percentage of Exon 18 with G719A and G719S types was 5.9%. The percentage of Exon 19 with type insertion/deletion 19 was 38.2%. Exon 21 with L858R type was 32.4%, while the L86Q type was 14.7%. Meanwhile, the percentage of 2 Exons with ins/del exon 19 and exon 21 L858R types was 2.9%.

Based on Table 3, the percentage of pattern combinations of Exon 18 or Exon 19 or Exon 21 were 11.8%, 38.2%, and 47.1%, respectively. Meanwhile, the percentage of the combination of 2 Exons (Exon 18 and Exon 21) was 2.9%.

Table 3. EGFR combination patterns

Combination pattern	N	Percentage (%)
Exon 18 or exon 19, or exon 21		
Exon 18	4	11.8
Exon 19	13	38.2
Exon 21	16	47.1
2 exons combination		
Exon 18 and exon 21	1	2.9
3 exons combination	-	-
Total	34	100

The characteristics of patients with EGFR mutations based on the type of exon that experienced mutations were not much different. There were 9 subjects with exon 19 EGFR mutations, 11 subjects with exon 21 L58R mutation, and 3 subjects with exon 21 L861Q mutation. Nevertheless, there were 3 subjects with uncommon EGFR mutations, namely exon 18 mutations.

Table 4. Clinical characteristics by type of exon

Characteristic	Exon 19	Exon 18	Exon 21 L858R	Exon L861Q
Gender				
Female	3	0	2	2
Male	6	3	9	1
Age (years)				
40–50	3	0	2	1
51–60	2	0	5	1
>60	4	3	4	1
Smoking Status				
Smokers	6	0	2	1
Non-Smokers	3	3	9	2
Types of cigarettes				
Filter	2	0	4	1
Non-filter	-	0	0	0
Mixed	4	3	5	0
Brinkmann Index				
Mild	-	0	0	0
Moderate	-	0	0	0
Severe	6	3	9	1

The majority of subjects with exon 19 mutations were male, aged >60 years, smokers with mixed types of cigarettes and severe BI.

In subjects with mutations in exon 21 L858 R, most patients were male, aged 50-60 years, smokers with mixed cigarette types and severe BI. The same characteristics were also found in subjects with exon 18 mutations. However, for exon 21 L861Q mutations, most subjects were females of various ages and were non-smokers. More detailed information regarding the characteristics of subjects based on the type of exon that undergoes mutations can be seen in Table 4.

DISCUSSION

The development of lung cancer studies towards biomolecular aspects makes targeted therapy a promising therapeutic option. EGFR is an oncogene mutation that has been discussed in numerous clinical studies and meta-analyses. Overall, the presence of EGFR mutations suggests a good prognosis in patients with lung cancer. Various meta-analyses have shown that EGFR mutations were more common in the type of adenocarcinoma, the elderly, and non-smokers.[13] This study obtained that most patients with lung adenocarcinoma who received targeted therapy were men (70.6%) compared to women. A similar result was pointed out in a study conducted in Indonesia (61% of male subjects with EGFR mutations).[14]

Data at Haji Adam Malik Hospital Medan from January 2010 to May 2012 revealed that around 143 (85.62%) lung cancer patients were male, while 24 patients (14.37%) were female. This study observed that female had the most EGFR mutations in exon 19 and exon 21 of 35.7% and 38.1%, respectively.[15] It was thought that this was due to differences in the epidemiological distribution of lung cancer. According to Tseng, et al. in 2017, lung adenocarcinoma patients with EGFR mutations were predominantly female, non-smokers, and already terminally ill.[16] However, Jang, et al. stated that there were no significant differences in clinical characteristics of age, sex, smoking status, and body surface area in lung cancer patients with exon 19 and exon 21 L858R mutations.[13] To date, there have been no studies which describe the pathobiology of a gender-specific predisposition to the presence of EGFR mutations in lung cancer, so the available data were only epidemiological from various countries.[8,16,17]

Based on smoking habits in this study, it was asserted that 70.6% of the patients were active smokers with heavy BI. A study on 199 patients in China expressed an opposite result that patients with EGFR mutations were more commonly non-smokers compared to those who smoked.[17] EGFR mutations appeared to be more common in subjects who were women, with adenocarcinoma histology, Japanese, and have never smoked.[18]

Similarly, meta-analyses and other global epidemiological studies explained that this EGFR mutation was more dominant in the non-smoking population. Furthermore, current smokers or ex-smokers with a high number of cigarettes/year in patients with EGFR mutations suggested a poor prognosis.[17] The differences in clinical characteristics of EGFR mutations for the North Sumatra population are still debatable. Further studies are expected to explain it in more detail. Common oncogene mutations in lung cancer and their association with smoking status were significant risk factors for lung cancer.

EGFR mutations are currently divided into 2 types, namely common mutations such as mutations in exon 19 as well as exon 21 L858R; and uncommon mutations such as mutations in exon 18 and exon 20.[17] This study only described the prevalence of common mutations such as exon 19 and exon 21 due to limited facilities. This study discovered that exon 19 was the exon that experienced the most mutation among the other 2 exons, namely 38.2% (ins/deletion 19), while exon 21 experienced the second most mutation (14.7%). Another study conducted in 2018

also indicated that exon 19 deletion was the most common mutation, followed by mutations of exon 21.[19]

Another study with a wider population also explained that 51% of EGFR mutations were exon 19, followed by exon 21 of 28%, exon 20 of 6%, and exon 18 of 5%.[8] Globally, differences in the clinical characteristics of lung cancer patients with EGFR mutations were also differentiated based on the type of mutation, in which patients with an exon 19 dominant mutation were more frequently associated with the non-smoker population and higher levels of life expectancy when compared to exon 21 L858R and exon 20.[17,18,20]

LIMITATIONS

The limitation of the research in this study is this study only described the prevalence of common mutations such as exon 19 and exon 21 due to limited facilities.

CONCLUSION

Most of study subjects were male, aged over 60 years, smokers with mixed types of cigarettes, and with heavy BI. The most common EGFR mutation were exon 21 mutation.

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CONFLICT OF INTEREST

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Original Article

Factors Affecting the Outcomes of COVID-19 Patients Treated at Dr. M. Djamil Padang General Hospital

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Abstract

Background: COVID-19 has spread rapidly throughout the world with high morbidity and mortality. This study aimed to determine the factors that influenced the outcomes of COVID-19 patients treated at RSUP. Dr. M. Djamil Padang.

Methods: This was an observational analytic study conducted with a retrospective cohort design on COVID-19 patients at RSUP Dr. M. Djamil Padang. Data were taken from medical records from January to March 2021. Association between comorbidities and the outcome of COVID-19 patients were analyzed using Chi- Square/Fisher Exact Test.

Results: Majority of the patients were female (56.4%) and aged above 50 years (64.3%). Hypertension was the most common comorbidity (41.1%). Diabetes mellitus affected the final outcome of treatment. The number of comorbidities the patients had was associated with a worse outcome for COVID-19.

Conclusion: Most of COVID-19 patients at RSUP Dr. M. Djamil Padang were male and more than 50 years old. There was a correlation between age, gender, and comorbidities in COVID-19 patients with the outcomes.

Keywords: Comorbidities, COVID-19, Outcome COVID-19

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a new type of outbreak that is currently a global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2).[1,2] Reports of COVID-19 cases in Indonesia at the end of February 2021 obtained that there was a decrease of 8.5% with increased mortality rate by 74.80%. The number of confirmed cases recorded on March 11, 2021 was around 1,403,722 cases, with 38,049 mortality cases and 611,097 cases were declared cured.[3] Data in West Sumatra province as of March 11, 2021, there were 29,985 confirmed cases of COVID-19, 659 of them died and 28,297 were recovered, while in Padang City there were 14,820 confirmed cases of COVID-19, 288 of them died and 14,188 were declared cured.[4,5]

The mortality rate due to COVID-19 in Indonesia was still relatively higher than the world average mortality rate set by the World Health Organization (WHO), which was 2%.[3] Several risk factors that have been studied as factors related to death include comorbidities, older age, and male gender. Signs and symptoms suggestive of respiratory failure or organ damage assessed from laboratory markers or radiological features are also considered potential risk factors for death in COVID-19. Izcovich et al. in their study concluded that laboratory values such as increased procalcitonin, increased D-Dimer, decreased lymphocytes, increased IL-6, and extensive infiltrates on chest X-ray could increase the risk of death in COVID-19.[6]

Currently, data regarding risk factors related to the outcome of COVID-19 patients in Indonesia and West Sumatra in particular were still very limited, therefore the authors were interested in

examining the factors that affect the outcome of COVID-19 patients at RSUP Dr. M. Djamil, Padang.

METHODS

This was an observational analytic study with a retrospective cohort design conducted in the COVID-19 isolation room at RSUP Dr. M. Djamil Padang. The study population was all COVID-19 patients treated in the COVID-19 isolation room of RSUP. Dr. M. Djamil Padang from January 1, 2021 to March 31, 2021.

The inclusion criteria were: COVID-19 patients treated in the COVID-19 isolation room, had complete medical record data, aged >18 years. Meanwhile, the exclusion criteria were subjects discharged at their own will and subjects with mild clinical degrees.

Data analysis was carried out descriptively and analytically. Bivariate analysis was used to find association between independent and dependent variables using Chi-square test (or Fisher's Exact Test if the data obtained did not meet the requirements for the test Chi-square).

RESULTS

The characteristics of the study subjects are presented in Table 1. The most common age group was found to be under 50 years old, as many as 35 subjects (35.6%). Based on gender, the majority of subjects were male for as many as 46 subjects (51.1%). Based on the presence of comorbidities in confirmed COVID-19 patients, hypertension was the most common comorbidity, which was observed in 37 subjects (41.1%).

The association between age and patient outcomes was found at a younger age that had a greater chance of recovering, namely at age <50 years with the prevalence of recovered patients of 75.7%, and aged 50-59 years of 47% (*P* <0.001).

Comorbiditiy with uncontrolled diabetes mellitus was the most often caused death, namely 35 subjects (56.5%). Outcomes of recovered patients with the most sequelae were found in stage 5 chronic kidney disease in as many as 4 subjects (16.7%) and uncontrolled diabetes mellitus in 4 subjects (6.5%). Comorbidities of CAD, moderate hypertension, and uncontrolled diabetes mellitus had the highest recovery outcomes, namely 14 subjects (58.3%), 21 subjects (45.7%) and 23 subjects (37.1%) respectively.

Table 1. Characteristics of Confirmed COVID-19 Patients Treated at RSUP Dr. M. Djamil Padang

Patient Characteristics	Total n= 90	%
Ages		
<50 years	35	35.6%
50–59 years	25	27.8%
60–69 years	17	18.9%
≥70 years	14	15.6%
Gender		
Male	46	51.1%
Female	44	48.9%
Comorbidities		
Cardiovascular Disease	16	17.8%
Hypertension	37	41.1%
Diabetes Mellitus	30	33.3%
Pulmonary Tuberculosis	2	2.22%
Asthma	2	2.22%
Cerebrovascular Disease	2	2.22%
Chronic Liver Disease	3	3.33%
Chronic Kidney Disease	8	8.9%
Immunodeficiency	1	1.11%
Malignancy	6	6.7%
Nutritional Status		
Obesity	3	3.3%
Laboratory Finding		
NLR		
<3.13	36	40%
≥3.13	54	60%
ALC		
<500	26	28.9%
500–900	32	35.6%
>1000	32	35.6%
End of Treatment Outcome		
Died	26	28.9%
Recovered	64	71.1%

The correlation between the types of comorbidities and the outcome of COVID-19 patients was confirmed using statistical tests with the results of all comorbidities showing significant results (*P* <0.05). Diabetes mellitus and chronic kidney disease had *P*-values of 0.0001 and 0.024 respectively, indicating that there was a correlation between each diabetes mellitus and chronic kidney disease with the outcome of confirmed COVID-19 patients.

Table 2. Association between Comorbidities Types and the End of Treatment Outcome of Confirmed COVID-19 Patients at RSUP Dr. M. Djamil Padang

Comorbidities Types	End of Treatment Outcome			*P*
	Recovered	Recovered with Sequelae	Died	
	n (%)	n (%)	n (%)	
Cardiovascular Disease				
CAD	14 (58.33)	2 (8.33)	8 (33.34)	
HHD	1 (20.00)	0	4 (80.00)	0.483
CHF	5 (55.56)	1 (11.11)	3 (33.33)	
Hypertension				
Mild	20 (57.14)	2 (5.71)	13 (37.15)	
Moderate	21 (45.65)	2 (4.35)	23 (50.00)	0.315
Hypertensive Crisis	1 (50.00)	0	1 (50.00)	
Diabetes mellitus				
Controlled	8 (61.53)	0	5 (38.47)	<0.001*
Uncontrolled	23 (37.09)	4 (6.45)	35 (56.46)	
Chronic Lung Disease				
Pulmonary Tuberculosis	3 (42.85)	0	4 (57.15)	
Asthma	2 (100.0)	0	0	0.703
COPD	1 (100.0)	0	0	
Chronic Kidney Disease				
Stage I	0	0	1 (100.0)	
Stage II	1 (50.00)	0	1 (50.00)	0.101
Stage III	1 (100.0)	0	0	
Stage V	8 (33.33)	4 (16.67)	12 (50.00)	
Cerebrovascular Disease				
Yes	1 (25.00)	1 (25.00)	2 (50.00)	0.155
Chronic Liver Disease				
Yes	2 (50.00)	1 (25.00)	1 (25.00)	0.245
Immunodeficiency				
HIV	1 (50.00)	0	1 (50.00)	0.869
Obesity				
Severe (stage 3)	5 (35.71)	1 (7.14)	8 (57.14)	0.165
Malignancy				
Yes	8 (57.14)	2 (14.28)	4 (28.58)	0.352

DISCUSSION

In this study, the largest age group found was under 50 years old, for as many as 35 subjects (35.6%). Study from Verma obtained that the most common age group was in the range of 50-75 years (46.7%), followed by >75 years (32%) and <50 years (21.2%).[7] Siordia in the study noticed that the highest COVID-19 cases were in the range of 30-79 years (87%).[8] The elderly people suffering from COVID-19 are more susceptible to worsening clinical conditions, even death, due to decreased function of T and B cells, as well as excessive cytokine production resulting in a prolonged inflammatory response.[9]

According to gender, the majority of subjects were male in as many as 128 subjects (56.4%). The result was similar to a study from Surendra in Jakarta in line with this study which stated that the highest prevalence of COVID-19 was in men (52%).[10] Males are more susceptible to infection associated with increased immune reactivation to viral infections compared to the females due to increased antibody production so that they are effectively resistant to infection.[11] Females are less susceptible than males related to innate immunity, steroid hormones and other factors associated with sex chromosomes. Immune regulatory genes encoded by the X chromosome in women will lead to decreased viral load and inflammation compared to men, in addition to higher CD4+ T cells and a better immune response. TLR7 levels in women are also higher while biallellic expression allows a better immune response and increases resistance to viral infections than in men.[12]

Comorbidities are conditions that are susceptible to infection due to a prolonged proinflammatory state and dysfunction of innate and adaptive immunity. Based on data from early 2020, this pandemic was associated with multiple comorbidities, many of which affected older age, hypertension, diabetes mellitus, coronary heart disease, obesity, and cerebrovascular disease. In patients with obesity, diabetes, or cardiovascular disease, an increased expression of ACE2 was found to increase the susceptibility to SARS-CoV-2 infection. In addition, lung function abnormalities and microangiopathy associated with obesity and diabetes might increase viral diversity and titer, as well as prolonged viral shedding (41.1%). Verma et al. observed comorbidities of CAD in 6.1% and CHF in 6.0%.[7] Patients with mild hypertension were 15.4%, moderate hypertension of 20.3%, and hypertensive crisis of 0.9%. Studies conducted by Verma et al., Giannouchos et al., and Surendra et al. found that hypertension was 34.7%, 20.9%, and 19%; respectively.[7,10,13]

Patients who had comorbidity of controlled diabetes mellitus were 5.7% while the uncontrolled were 27.3%. The results of the studies from Giannouchous et al. and Surendra et al., were almost close to the results of this study, which obtained that the number of COVID-19 patients with DM comorbidity of 17.5%; 12%.[10,13] Diabetic patients are susceptible to infections including COVID-19.[14] In diabetic patients there will be accumulation of activated innate immune cells in metabolic tissues resulting in the release of inflammatory mediators, especially IL-1β and TNF-α which will lead to insulin resistance and damage. B cells and metabolic diseases can lower immune function by interfering with the function of macrophages and lymphocytes so that a person is susceptible to disease.

The percentage of patients with chronic lung diseases such as tuberculosis was 3.1%, asthma of 0.9%, and COPD of 0.4%. There was a total of 10.6% patients with stage 5 chronic kidney disease. Verma pointed out that patients with comorbidity of renal failure were about 20.6%, while on the other hand, Giannouchos et al. and Surendra et al., only had 2.3% and 3% chronic kidney disease respectively.[7,10,13]

Comorbidity of stroke in this study was found to be 1.8%. Phelps stated that the prevalence of stroke was around 9.5%.[15] Only 1.8% of patients in this study had chronic liver disease. Study conducted by Surendra et al. discovered that the number of COVID-19 patients with liver disease was only 0.7%.[10]

There were 6.2% of patients with severe obesity. Surendra found 0.8% of obese patients in their study.[10] A total of 6.2% of patients in this study had malignancy. COVID-19 patients with malignancy in the studies of Surendra et al., Siordia et al., Phelps et al. were 0.5%; 4.3%; and 10.3%, respectively.[8,10,15] Only 0.9% of the patients in this study had HIV. Similar results were obtained in the studies of Giannouchos et al., Surendra et al., and Siordia et al. of 1.6%; 0.7%; and 0.2%, respectively.[8,10,11]

Osibogun observed that more men died (4.79%) with an OR of 1.81 (95% CI=1.04-3.14; *P*=0.036).[16] The results of the meta-analysis conducted by Biswas et al. pointed out that male gender significantly had increased mortality in COVID-19 patients compared to the female (RR=1.86; 95% CI=1.67-2.07; *P*<0.00001). Male patients have high ACE2 expression because ACE2 expression is encoded by the ACE2 gene on the X chromosome which can be regulated by male sex hormones so that they are more at risk and have poorer clinical outcomes. Hormonal factors also play a role, chemotactic factors on neutrophil and monocyte uptake such as CXCL1 and CCL20 are regulated by androgen receptors. On the other hand, the immune response to estrogen receptor regulation is to intensify interferon production and antiviral response.[17]

A cross-sectional study conducted by Alwafi et al. achieved that age was one of the risk factors associated and had a significant impact with a high risk of death and an increase in length of hospital stay.[18] Mortality rates in study from Verma et al. were based on the age group <50 years, 50–75

years, and more than 75 years of around 5.1%, 13.5%, and 38.9%, respectively.[7]

Age was assessed to be significantly associated with mortality both without treatment and with treatment (OR=1.07; *P*<0.0001 and OR=1.06; *P*<0.0001). The increased risk of death at the age of 50 years and over was 15.4 times compared to the age of 50 years and under (RR=15.44; 95% CI=13.02-18.31; *P*<0.00001). Aging process will trigger an imbalance of functions in various systems including the immune system so that it is more susceptible to inflammation and death. Patients aged 50 years and over have a higher expression of ACE2 which is encoded by the ACE2 gene with other factors such as decreased immunity, low organ function or previous comorbidities that increase the risk of death.[19]

Based on the degree of severity, the more severe the disease, the more increasing the mortality rate. According to Osibogun, the mortality rate at critical level was 100%, severe level was 23.53%, moderate level was 2.67%, while mild was 0.37%.[16] In this study, it was found that the comorbidity which had a significant correlation with the outcome was diabetes mellitus, while the length of stay did not have a significant correlation with each comorbidities.

COVID-19 patients who had cardiovascular disease in study from Fresan pointed out 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). Previous cardiovascular disease had a high risk of developing severe COVID-19 up to 5 times.[20] Meta-analysis showed that cardiovascular 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 fatal outcome in patients at all age groups (OR=3.11; 95% CI=2.55-3.79).[21] A history of cardiovascular disease becomes unstable with an increased incidence of coronary disease, heart failure, and arrhythmias in SARS-CoV-2 infection caused by an imbalance between metabolic demands and decreased cardiac work and is associated with an inflammatory response and myocardial damage.[12]

As stated by Fresan, hypertension was associated with COVID-19 treatment (OR=1.22; 95% CI=1.06-1.41; *P*=0.005) and severity OR=1.53; 95% CI=1.11-2.10; *P*=0.009) but was not statistically significant.[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 at all age groups (OR=2.50; 95% CI=2.49-4.88).[15] Immune system dysregulation in hypertensive patients is related to the severity of COVID-19. Monocytes in hypertensive patients are pre-active which produce more IL-6 after being stimulated by angiotensin II or lipopolysaccharide and found an increase in CD8+ T cells that produce TNF. These CD8+ T cells are unable to fight viral infections and result in the overproduction of cytokines.[22]

Diabetics died in study of Wen et al. were as much as 11%, on the other hand, those who did not have diabetes experienced death as much as 3% with *P*<0.001. Patients with diabetes mellitus had 3.69 times the risk of death from COVID-19.[11] Meta-analysis showed that diabetes mellitus was at high risk for severe COVID (OR=2.47; 95% CI=1.86-3.27), death (OR=2.11; 95% CI=1.63-2.73) and fatal outcome in patients at all age groups (OR=2.25; 95% CI=1.89-2.69).[21]

Diabetes is one of the most common and most dangerous metabolic diseases characterized by chronic inflammatory conditions that lead to metabolic and vascular abnormalities which affect the response to pathogens.[22] Type 2 diabetes mellitus is associated with chronic inflammation produced 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 create tissue inflammation. In addition, diabetic patients are at high risk of developing an uncontrolled hypercoagulable state and inflammatory response.[24]

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.

Pulmonary disease can be a strong predictive comorbidity predictor of poor outcome and death with ORs 4.17 (95% CI=2.67-6.50) and 3.23 (95% CI=2.55-4.32).[23] In opinion of Alwafi et al. and published reports of similar studies, it was known that patients with chronic lung diseases, particularly COPD were found to be a high-risk factor for the outcome of more severe COVID-19 patients. This was because the patient's lung function has decreased.[18]

On a report of Fresan, it was stated 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] Osibogun noticed that patients with kidney disease were 12.53 times more likely to die from COVID-19.[16] 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.[17]

Fresan argued 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).[20] This is due to cerebrovascular disease which can produce disability, SARS-CoV-2 can generate direct nerves damage or vascular events such as stroke, and an increase in proinflammatory cytokines which will damage the vascular endothelium and increase blood coagulability.[24]

Previous studies have described high mortality rates in chronic liver disease infected with COVID-19. The results of the logistic regression analysis in study from Alwafi et al. revealed that the odds ratio of death was 1.92 with 95% CI 1.65-8.63.[18] According to Zhou et al. there were no significant associations between chronic liver disease and the severity of COVID-19 (OR=1.54; 95% CI=0.95-2.49).[23] COVID-19 patients with chronic liver disease are prone to adverse outcomes such as death or longer hospitalization compared to patients without chronic liver disease. Laboratory findings emphasize the negative impact of SARS-CoV-2 infection on liver function.[17]

Patients with obesity had a mortality of 7% and those without obesity had a mortality of about 4% with *P*<0.001.[16] Obesity is associated with impaired lung function that occurs due to decreased lung compliance, expiratory reserve volume and functional capacity, as well as an increase in cytokines.[12]

Alwafi et al denoted that mortality rate 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 which attack the immune system will escalate fatal outcomes and more severe COVID-19 infections.[18]

Patients with HIV are 12.21 times at risk of dying from COVID-19.[18] The study found that the incidence of COVID-19 living with HIV was 0.9% of cases, 14% of cases became severe and 4% of cases reported death.[25] Patients with HIV have decreased TCD4+ cells and develop T-cell dysfunction and inflammation, which increases the risk of severe outcomes in viral infection.[26]

LIMITATION

There were several limitations in this study, including the retrospective cohort design, data collection using medical records, and some of the obtained data still required manual categorization.

CONCLUSION

Most of COVID-19 patients at RSUP Dr. M. Djamil Padang were male and more than 50 years old. There was a correlation between age, gender, and comorbidities in COVID-19 patients with the outcomes.

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Conflict of Interest

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Original Article

Correlation of Antibiotic Resistance with Sepsis Incidence, Hospital Mortality, and Time of Sepsis Onset in Community Acquired Bacterial Pneumonia

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Abstract

Background: Community acquired pneumonia is associated with high morbidity and mortality. Treatment of multidrug-resistant organisms (MDRO) infection in pneumonia is a challenge. Antibiotic resistance is a major factor determining clinical treatment unresponsiveness and rapid progression to sepsis. Septic patients with MDRO have a higher hospital mortality. The correlation of antibiotic resistance with the incidence of sepsis and hospital mortality is yet to be known. This study analyzed the correlation of antibiotic resistance with sepsis incidence, hospital mortality, and time of sepsis onset.

Methods: Retrospective cohort study of patients with community acquired bacterial pneumonia from July-December 2019 at RSUD Dr. Moewardi. The correlation between antibiotic resistance and incidence of sepsis, hospital mortality was tested by using Chi Square and Fisher's exact test correction. Association between two variables with relative risk. Survival analysis and log rank test were used to examine the time differences of sepsis onset.

Results: There was a correlation between antibiotic resistance and incidence of sepsis in community acquired bacterial pneumonia (r = 0.417, p = 0.000) with RR = 4,294 (95% CI 2,886-6,390). The median time of sepsis onset was day 0 in the MDRO group and day 4 in non-MDRO group (p = 0.000).

Conclusion: There is a correlation between antibiotic resistance and incidence of sepsis in community acquired bacterial pneumonia with a fairly strong and significant correlation value. The presence of antibiotic resistance increases the incidence of sepsis fourfold. Antibiotic resistance also affects the time of sepsis onset.

Keywords: Hospital mortality, MDRO, Sepsis, Time of sepsis onset

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INTRODUCTION

Pneumonia is a global health issue. Community pneumonia is associated with high morbidity and mortality. Pneumonia is the leading cause of death from infectious diseases in the United States, with approximately 5–6 million cases of community pneumonia, with 1.1 million patients being treated and 45 thousand patients dying from pneumonia each year. Community pneumonia caused by bacterial infection is the leading cause of mortality in Asia and the most common cause of sepsis. The estimated incidence of community pneumonia is 0.2–1.1% in adult patients, with a mortality rate of 2–14% in developing countries and 7.3% in Asia. Basic health research data in 2013 stated that the incidence and prevalence of pneumonia were 1.8% and 4.5% in Indonesia, respectively. Pneumonia is among the top 10 diseases requiring hospitalization with a crude fatality rate of 7.6%, the highest compared to other diseases in Indonesia. The mortality rate for community pneumonia in outpatients is 2%, inpatients is 5–20%, and even higher in intensive care patients, which is >50%.[1–4]

Pathogens normally present only in the hospital setting have emerged in the community in the last twenty years, including methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant Pseudomonas aeruginosa, or extended-spectrum β lactamase producing Enterobacteriaceae (ESBL).[2]

Antibiotic resistance is a natural phenomenon in bacteria which is unstoppable. The antibiotic resistance crisis occurs because antibiotics tend to lose their efficacy due to the spread of resistance among pathogenic bacteria. This resistance is mainly due to the overuse and inappropriate use of antibiotics and their widespread use in agriculture and the food industry. The increasing elderly population makes the use of antibiotics increase with the number of patients being hospitalized. This makes patients more prone to the hospital environment, causing an increase in the number of nosocomial pathogen infections.[2,5]

Pneumonia therapy in multi-drug resistant organism (MDRO) infection is a current challenge. Antibiotic resistance is a significant factor determining clinical unresponsiveness to treatment and the rapid sepsis and septic shock progression. Septic patients with MDRO infection had a higher risk of in-hospital mortality. Drug resistance is common in gram-negative infections. Gram-negative bacterial infection in community pneumonia often causes respiratory failure, acute respiratory distress syndrome (ARDS), sepsis, and septic shock.[2,5,6]

Zilberberg MD et al. found that MDRO infection was an important determinant of inadequate therapy associated with a threefold increase in in-hospital mortality.[7] Tores A et al. (2015) found that sepsis in MDRO infection was significantly associated with inadequate therapy. In addition, the mortality rate for sepsis with drug resistance has doubled.[8] Prina E et al stated that MDRO infection was significantly associated with increased mortality.[9]

Study addressing relationship between antibiotic resistance and sepsis and hospital mortality in community-acquired bacterial pneumonia has never been carried out, so it is interesting to conduct research.

METHODS

This study is a retrospective cohort study by collecting medical record data of patients with community acquired bacterial pneumonia from July through December 2019 at Dr. Moewardi General Regional Hospital Surakarta. Total sampling method was applied with the inclusion criteria of patients aged 18–64 years, undergoing hospitalization with a diagnosis of community pneumonia, and having sputum culture results and antibiotic resistance. The exclusion criteria were incomplete medical records, currently undergoing treatment for pulmonary tuberculosis, on steroid and oral chemotherapy, having a Charlson comorbidity index (CCI) score of 4, receiving empiric antibiotic therapy, not following the community pneumonia antibiotic guidelines of the Indonesian Lung Doctors Association (Indonesian Lung Doctors Association) receiving initial therapy for sepsis which did not comply with The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).

The dependent variable in this study was sepsis, hospital mortality, and the time of onset of sepsis, while the independent variable was antibiotic resistance. The relationship between two nominal variables was tested by using the Chi-Square test with Fisher's exact test correction. The magnitude of association between two variables was estimated with a relative risk (RR). Survival analysis and log-rank test were used to examine the differences between the two-time curves for the onset of sepsis. All statistical tests used a 95% confidence interval value or a value limit of the significance of $P<0.05$.

RESULTS

The study included 220 patients who met the inclusion criteria. The research subjects were assigned into two groups, the MDRO group and the non-MDRO group respectively. Each group was evaluated for the occurrence of sepsis, the time of sepsis, and death in the hospital. The flow of the results of this study can be seen in Figure 1.

Participant’s characteristics of this study included gender, age, CCI score, and type of germ. Non-MDRO group had the highest number of male patient (64.8%), while MDRO group had the highest number of female participant (39.5%). The mean age in the MDRO group was 47.24 years, while in the non-MDRO group was 49.32 years.

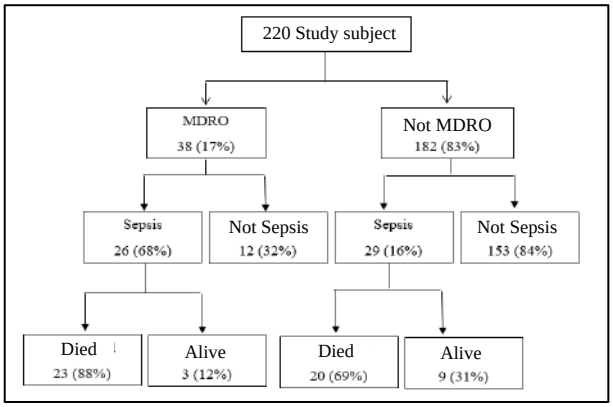

Figure 1. Flow of research results

The highest CCI score in the MDRO group was 1 at 34.2%, while in the non-MDRO group, the highest CCI score was 0. The MDRO group had the most comorbid of cerebrovascular disease at 15.8%. The non-MDRO group had the most comorbid of diabetes mellitus without complications at 16.5%. All of the above baseline data did not have a significant correlation in the two groups except for the CCI scores for the moderate and severe chronic liver disease, which, although it had a significant correlation (*P*=0.023), the correlation was very weak (r=0.152).

The most common type of MDRO bacteria was Acinetobacter baumannii at 21.1%, followed by Klebsiella pneumonia ESBL (+) and Escherichia coli with the same number at 18.4%. The non-MDRO group had the most types of bacteria, Klebsiella pneumonia at 37.9%, followed by Pseudomonas aeruginosa at 12.6% and Enterobacter cloacae at 9.9%. Participant's characteristics is presented in Table 1.

Table 2. Correlation between antibiotic resistance and sepsis

Antibiotic resistance	Sepsis		Total	r	*P*
	Yes	No			
MDRO	26 (47,3%)	12 (7,3%)	38 (17,3%)	0,417	0,0001
Not MDRO	29 (52,7%)	153 (92,7%)	182 (82,7%)		
Total	55 (100%)	165 (100%)	220 (100%)		

The correlation test between antibiotic resistance and sepsis in this study revealed r=0.417 and *P*=0.0001, which implies a significant correlation with a fairly strong correlation value (r=0.417) with a unidirectional relationship and RR=4.294 (95% CI=2.886–6.390). The correlation between antibiotic resistance and sepsis is outlined in Table 2.

The correlation test between antibiotic resistance and hospital mortality in this study revealed r=0.229 and *P*=0.081, which implies no significant correlation with the RR=1.283 (95% CI=0.969–1.699). The correlation between antibiotic resistance and hospital mortality is presented in Table 3.

Table 3. Correlation between antibiotic resistance and mortality in hospital

Antibiotic resistance	Died in the hospital		Total	r	*P*
	Died	Alive			
MDRO	23 (53,5%)	3 (25%)	26 (47,3%)	0,229	0,081
Not MDRO	20 (46,5%)	9 (75%)	29 (52,7%)		
Total	43 (100%)	12 (100%)	55 (100%)		

The median occurrence of sepsis in the MDRO group was 0 days (95% CI=0.000–0.000), while the non-MDRO group was 4 days (95% CI=3.402–4.598), with the log-rank test results revealed *P*=0.0001 which suggests that there was a difference in the median time of occurrence of sepsis in both groups.

Table 4. Median and log-rank test for the time of sepsis

Antibiotic resistance	Median		*P*
	95% *Confidence Interval*		
	Lower Bound	*Upper Bound*	
MDRO	0.000	0.000	0,0001
Not MDRO	3.402	4.598	
Total	0.683	3.317	

The median and log-rank test for the time of sepsis is delineated in Table 4. The Kaplan Meier curve for the time of sepsis is described in Figure 2.

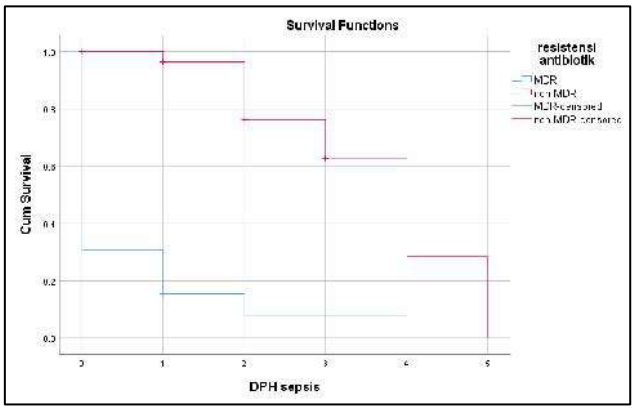

Figure 2. Kaplan Meier curve at the time of sepsis

Table 1. Characteristics of participants

Variables	MDRO n=38 (%)	Not MDRO n=182 (%)	r	*P*
Gender				
Male	23 (60.5%)	118 (64.8%)	0,034	0,615
Female	15 (39.5%)	64 (35.2%)		
Mean age	47.24	49.32	-	0,346
CCI Score				
Score 0	12 (31.6%)	75 (41.2%)	-	
Score 1	13 (34.2%)	67 (36.8%)	-	0,220
Score 2	8 (21.1%)	31 (17.0%)	-	
Score 3	5 (13.2%)	9 (4.9%)	-	
Myocardial infarction	0 (0%)	10 (5.5%)	0,099	0,139
Congestive heart failure	5 (13.2%)	23 (12.6%)	0,006	0,930
Peripheral artery disease	0 (0%)	1 (0.5%)	0,031	0,647
Dementia	0 (0%)	0 (0%)	-	-
Cerebrovascular disease	6 (15.8%)	28 (15.4%)	0,004	0,950
Chronic obstructive pulmonary disease	2 (5.3%)	9 (5%)	0,005	0,941
Connective tissue disease	0 (0%)	1 (0.5%)	0,031	0,647
Uncomplicated diabetes mellitus	5 (13.2%)	30 (16.5%)	0,034	0,610
Decubitus ulcer	0 (0%)	2 (1.1%)	0,044	0,516
Mild chronic liver disease (Child Pough A)	0 (0%)	0 (0%)	-	-
Hemiplegia	0 (0%)	0 (0%)	-	-
Chronic renal failure	4 (10.5%)	6 (3.3%)	0,130	0,052
Diabetes mellitus with complications	1 (2.6%)	2 (1.1%)	0,050	0,459
Malignant tumor without metastases	2 (5.3%)	2 (1.1%)	0,117	0,081
Leukemia	2 (5.3%)	7 (3.8%)	0,027	0,688
Lymphoma	1 (2.6%)	5 (2.7%)	0,003	0,968
Moderate and severe chronic liver disease (Child Pough B-C)	2 (5.3%)	1 (0.5%)	0,152	0,023
Malignant tumor (cancer), metastases	0 (0%)	0 (0%)	-	-
AIDS	0 (0%)	0 (0%)	-	-
Types of germs				
Klebsiella pneumoniae	2 (5.3%)	69 (37.9%)	-	-
Klebsiella pneumoniae ESBL (+)	7 (18.4%)	0 (0%)	-	-
Pseudomonas aeruginosa	4 (10.5%)	23 (12.6%)	-	-
Acinetobacter baumanii	8 (21.1%)	14 (7.7%)	-	-
Staphylococcus aureus	1 (2.6%)	9 (4.9%)	-	-
MRSA	2 (5.3%)	0 (0%)	-	-
Staphylococcus haemolyticus	4 (10.5%)	9 (4.9%)	-	-
Escherichia coli	7 (18.4%)	13 (7.1%)	-	-
Escherichia coli ESBL (+)	2 (5.3%)	0 (0%)	-	-
Enterobacter cloacae	1 (2.6%)	18 (9.9%)	-	-
Others	0 (0%)	27 (14.8%)	-	-
Sepsis	26 (68.4%)	29 (15.9%)	-	-
Sepsis and died	23 (88.4%)	20 (68.9%)	-	-
Time of onset of sepsis (median)	0	4	-	-

DISCUSSION

The MDRO group had 81.5% gram-negative bacteria (31 patients), while the non-MDRO group had 87.3% (159 patients). Gram-negative bacteria affected majority of patients in both groups. The result is comparable to SARI sentinel surveillance data which obtained from several hospitals in Indonesia (2012), and Luan Y et al., which stated that gram-negative bacteria are the most common cause of community pneumonia.[1,3,4]

MDRO infection in this study was 17% which is higher than result reported by Prina E et al. (2015), which found 6% of the causes of community pneumonia were MDRO bacteria but almost similar to a study by Capsoni N et al. which found MDRO

infection up to 17% in community pneumonia. Sepsis caused by MDRO in this study was 47% higher than a study by Tores A et al., which revealed that MDRO caused only 10% of the incidence of sepsis in community pneumonia patients. This may be due to the differences in the germ map in each region.[8–10]

This study found a significant correlation (*P*=0.0001) between antibiotic resistance and the incidence of sepsis with a fairly strong correlation value (r=0.417) and a unidirectional relationship in which if antibiotic resistance increased, the incidence of sepsis also increased. The presence of risk factors for antibiotic resistance increased the risk of sepsis by four times (RR=4.294; 95% CI=2.886-6.390) compared to those without risk factors for antibiotic resistance.

This may be due to ineffective therapy in eliminating MDRO germs, as reported by Torres A et al., which stated that MDRO sepsis was significantly associated with the administration of therapy that was ineffective in eliminating bacteria (*P*<0.001). Zilberberg MD et al. also revealed that MDRO infection had a strong relationship with the administration of inappropriate therapy (AOR=13.05; 95% CI=7.00-24.31). Failure to eliminate bacteria keeps the inflammatory process running and causes sepsis. Study that addresses the link between risk factors of antibiotic resistance with sepsis has never been conducted.[7,8]

This study found no significant correlation between antibiotic resistance and hospital mortality (*P*=0.081). A relative risk value of 1 (RR=1.283;95% CI=0.969-1.699) indicated that antibiotic resistance was not a risk factor for in-hospital mortality. The result disproves a study conducted by Capsoni et al., which stated that MDRO infection was an independent risk factor related to death in hospitals in sepsis patients (OR=4.6; *P*<0.001). In addition, the study by Prina et al. stated that MDRO infection was independently associated with an increased risk of 30-day mortality (AOR=2.51; 95% CI=1.20-5.25; *P*=0.015), they also only included MDR bacteria of Pseudomonas aeruginosa, ESBL, and MRSA in their study while in this study it was not limited to those three. In addition, in Prina et al.'s study, the mortality criteria used were mortality from any cause. In contrast, in this study, death in the hospital was used as the leading cause of sepsis.[9,10]

The absence of correlation between antibiotic resistance and hospital mortality in this study suggests that there may be other factors affecting hospital mortality. Firmansyah MA at Cipto Mangunkusumo Hospital reported significant independent predictors of mortality in multivariate analysis, including severe pneumonia (OR=29.42; 95% CI=20.81-41.58), sepsis (OR=3.65; 95% CI=2.57-5.19), respiratory failure (OR=3.2; 95% CI=1.9-5.37), CCI score 5 (OR=2.25; 95% CI=1.6-3.15) and albumin levels <3 g/dL (OR=1.42; 95% CI=1.04-1.95) in community pneumonia patients.[11] Presence of sepsis, the severity of sepsis, or severity of comorbidities may influence in-hospital mortality in this study.

Most MDRO germs in this study were Acinetobacter baumannii at 21.1%, where a study by Zilberberg MD et al. stated that MDR Acinetobacter baumannii increased the risk of ineffective therapy more than five times (ARRR=5.5; 95% CI=4.0-7.7; *P*<0.001) and inappropriate therapy almost doubled hospital mortality (ARRR=1.8; 95% CI=1.4-2.3; *P*<0.001). Busani S et al. also found in a multivariate analysis of MDR infection with Acinetobacter baumannii an increased risk of 30-day mortality (OR=3,197) in septic shock due to MDRO infection.[12,13] The presence of Acinetobacter baumannii infection, which was commonly found in the MDRO group, may have a relationship with hospital mortality in this study.

The median time of occurrence of sepsis in this study in the MDRO group was 0 days (95% CI=0.000-0.000), while in the non-MDRO group was 4 days (95% CI=3.402-4.598) with the log-rank test revealed a significant difference in the median time of occurrence of sepsis in both groups (*P*=0.0001). The incidence of sepsis in the MDRO group on day 0 was more than 50% after having risk factors for antibiotic resistance, while more than 50% of the incidence of sepsis in the non-MDRO group was on day 4. This study shows that the MDRO group had a higher risk of developing sepsis faster than the non-

MDRO group, although, in this study, the early onset of sepsis was difficult to predict with certainty because participants might have had sepsis for several days before being hospitalized. Administration of antibiotics before participant is hospitalized may also affect the onset of sepsis, which was not included in study analysis. The survival analysis of sepsis has never been done before.

LIMITATION

The limitation of this study is the retrospective cohort design in which observations were made indirectly, only relying on medically recorded data, which cannot be controlled for data quality. In addition, indirect observations make it difficult to accurately determine onset of sepsis. This study also does not rule out the influence of genetic factors, microbiome factors, or environmental factors that may influence the occurrence of sepsis and hospital mortality.

CONCLUSION

This study suggests that there was a relationship between antibiotic resistance and the incidence of sepsis in community-acquired bacterial pneumonia, but there was no significant relationship between antibiotic resistance and hospital mortality. Antibiotic resistance affects the timing of sepsis in community-acquired bacterial pneumonia.

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CONFLICT OF INTEREST

None.

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REFFERENCES

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Original Article

Factors Affecting the Treatment Success of Short-Term Regimen for Drug Resistant Tuberculosis (DR TB) Patients at Dr. Saiful Anwar General Hospital Malang

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Abstract

Background: Tuberculosis/TB is a major health problem in the world. Indonesia ranks 3rd in TB cases and 7th in drug resistant (DR) TB cases in the world. In 2016, WHO recommended short term (9–11 month) regimen treatment with a success rate of 84% in several Asian and African countries. The purpose of this study was to determine factors that influence the success and failure of treatment using short-term regimen for DR TB patients at Dr. Saiful Anwar General Hospital Malang.

Methods: This was an analytic observational study with retrospective cohort design on 85 short-term regimen DR TB patients who started treatment on October 1, 2017 to September 30, 2018 at the DR TB ward of Dr. Saiful Anwar General Hospital Malang. Data analysis used chi square test with alternative fisher exact test and logistic correlation test.

Results: Education level had a significant correlation with treatment success (*P*=0.036; OR=2.746; CI 95%=1.053-7.165) while Pre XDR TB sputum drug susceptibility test had a significant correlation with treatment failure (*P*=0.037; OR=1.556; CI 95%=1.180-2.050). Based on logistic correlation test, the predictive variables for treatment outcomes were age, education, criteria for suspected DR TB and drug susceptibility test results of pre XDR TB.

Conclusion: The level of education affected the success treatment of DR TB short-term regimen. The results of Pre XDR TB sputum drug susceptibility test influenced the failure of DR TB short-term regimen.

Keywords: Drug Resistant TB, Short Term Regimen, Success Treatment

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INTRODUCTION

Tuberculosis (TB) is one of the world's health problems and is one of the leading cause of death among the 10 most common diseases in the world. WHO data in 2018 mentioned that Indonesia ranked 3rd of highest TB case in the world after India and China.[1]

Resistance to first-line Anti-Tuberculosis Drugs (ATD) is an obstacle in achieving TB targets. About 5% of all TB cases are drug resistant (DR) TB. WHO data in 2007 stated that the percentage of primary resistance worldwide had 17.0% cases of polyresistance, 10.3% monoresistance, and 2.9% multidrug resistance (MDR). Meanwhile, in Indonesia, the primary resistance to MDR TB was 2%.[2] WHO data in 2018 pointed out that Indonesia ranked 7th of the highest DR TB prevalence in the world.[1]

Currently in Indonesia, there has been a decline in the success rate for DR TB treatment, from 67.9% (2010) to 51.1% (2013), and an increase in the rate of loss to follow-up (LFU) from 10.7% (2009) to 28.7% (2013).[3] Data at Dr. Saiful Anwar General Hospital Malang from January 2014 to December 2016 of 57 patients receiving DR TB treatment, 17 patients recovered (29.82%), 15 patients died (26.32%), and 25 patients dropped out of treatment (43.86%).[4]

The current management of DR TB takes a long time and requires high costs, both for the program and for patients. Worldwide DR TB surveillance data also showed unsatisfactory results in terms of the long-term standardized treatment success rate, which was around 62%. In 2016, WHO issued a recommendation for using standardized short-term treatment combinations of

9–11 months which indicated promising outcomes based on the results of various observational studies in several Asian and African countries with treatment success rate of 84%. Currently, there are two combinations of treatment in Indonesia, namely a combination of standard short-term treatment and a combination of individual treatment. Treatment success for DR TB patients can be seen from several factors: health workers and TB control programs, patients, drugs, economy, comorbidity factors, HIV/AIDS factors, and drug adverse effects.[3]

In general, this study aimed to determine the treatment success rate of patients with standard short-term regimen for DR TB and specifically to identify the factors that influence the success and failure of standard short-term regimen for DR TB patients at Dr. Saiful Anwar General Hospital Malang.

METHODS

This study used an analytic observational design with a cohort retrospective approach. The study subjects were all DR TB patients on short-term combination treatment who met the inclusion and exclusion criteria.

Inclusion criteria were patients aged 18 years and patients who had at least one day of treatment with a short-term combination of DR TB recorded in the MDR clinic medical record of Dr. Saiful Anwar General Hospital Malang on October 1, 2017 to September 30, 2018. Exclusion criteria were patients who did not meet the requirements for DR TB short-term combination treatment.

The study used secondary data (review of medical record documents and e-TB manager data) at the MDR TB clinic of Dr. Saiful Anwar General Hospital Malang from January 2019 to June 2019. The ethics committee had approved every procedure.

The independent variables of the study were age, gender, education level, occupation, income, domicile, criteria for suspected DR TB, nutritional status, comorbidities, smoking history, results of investigations, drugs adverse effects, and HIV status of patients with short-term standard treatment for DR TB. The dependent variable was the treatment success of patients with DR TB short-term treatment.

The recorded data were then processed, analyzed, and interpreted. The analysis used in this study were univariate, bivariate, and multivariate analysis. Chi-square test was used to evaluate the correlation between the independent and dependent variables, while the alternative Fisher exact test was used if requirements were not met. Logistic regression was applied to determine the most influential correlation between the independent and dependent variables. These measurements of variables were carried out using Microsoft Office Excel 2010 program and SPSS 25.0.

RESULTS

The sociodemographic characteristics of the study subjects and the sociodemographic correlation to the success of DR TB short-term treatment are shown in Table 1. Based on the sociodemographic characteristics of the study subjects, the majority were male (61.2%), the mean age of subjects in the treatment group was 40.08 years with a median of 42 years (Figure 1), had low education (61.2%), risk occupation group (84.7%), had low income (62.3%), domiciled outside Malang (52.9%), had a history of smoking (55.3%), had diabetes melitus (DM) comorbidity (41.2%), came from the criteria for non-relapse cases (54.1%), and had non-underweight BMI (55.3%).

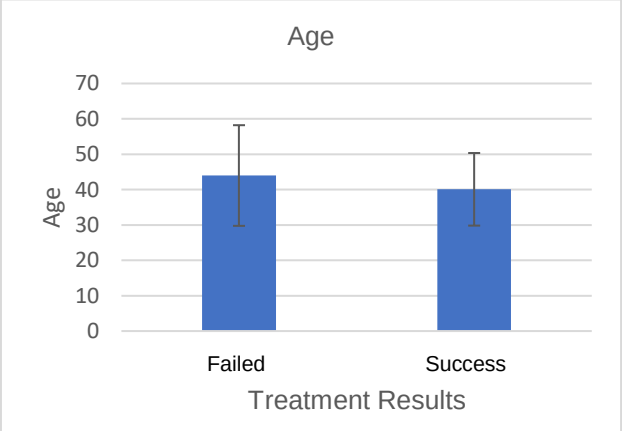

Figure 1. Age Difference in Failed Treatment and Successful Treatment Groups

Table 1. Characteristics and Sociodemographic Effects on Treatment Success

Variable		Treatment Results						*P*
		Failure		Successful		Total		
		n	%	n	%	n	%	
Occupation	No Risk	11	84.6	2	15.4	13	15.3	0.328*
	At Risk	49	68.1	23	31.9	72	84.7	
Gender	Male	39	75	13	25	52	61.2	0.262
	Female	21	63.6	12	36.4	33	38.8	
Income	Low	36	67.9	17	32.1	53	73.6	0.705
	High	12	63.2	7	36.8	19	26.4	
Education	Low	41	78.8	11	21.2	52	61.2	0.036
	High	19	57.6	14	42.4	33	38.8	
Smoking Status	Smoker	35	74.5	12	25.5	47	55.3	0.383
	Non-smoker	25	65.8	13	34.2	38	44.7	
Area	Malang	26	65.0	14	35.0	40	47.1	0.286
	Outside Malang	34	75.6	11	24.4	45	52.9	
BMI	Underweight	25	65.8	13	34.2	38	44.7	0.383
	Non-Underweight	35	74.5	12	25.5	47	55.3	
Criteria for Suspected DR TB	Relapsed	30	76.9	9	23.1	39	45.9	0.238
	Non-Relapse	30	65.2	16	34.8	46	54.1	
Comorbid	Existed	27	73	10	27	37	43.8	0.811*
	Non-existent	33	68.8	15	31.2	48	56.5	
HIV	Existed	1	100	0	0	1	1.2	1.00*
	Non-existent	59	70.2	25	29.8	84	98.8	
DM	Existed	25	71.4	10	28.6	35	41.2	0.887
	Non-existent	35	70	15	30	50	58.8	

Table 2. The Effect of Supportive Examination Results and Drugs Adverse Effects on Treatment Success

Variable		Treatment Results						*P*
		Failure		Successful		Total		
		n	%	n	%	n	%	
Sputum AFB Conversion Time	Mean	1.318		1.40		1.351		0.511*
	Median	1		1		1		
Sputum Culture Conversion Time	Mean	1.407		1.50		1.449		0.950*
	Median	1		1		1		
Chest X-Ray	Extensive	59	67.9	25	32.1	84	91.8	0.100
	Minimum	1	100	0	0	1	8.2	
Sputum drug susceptibility test	Monoresistance	0	0	1	100	1	1.6	0.379
	RR	13	60.9	9	31.7	22	36.5	0.802
	MDR	19	64.3	10	35.7	29	44.4	Reff
	Pre-XDR	11	100	0	0	11	17.5	0.037
Drugs Adverse Effects	Exist	41	66.1	21	33.9	62	72.9	0.139
	None	19	82.6	4	17.4	23	27.1	

To determine the correlation between sociodemography and the success of short-term standardized treatment for DR TB, the chi-square test and the Mann Whitney test were carried out. In this study, based on the results of the chi-square test, it was found that gender (*P*=0.262), occupation (*P*=0.328), income (*P*=0.705), domicile (*P*=0.286), smoking history (*P*=0.383), criteria for suspected DR TB (*P*=0.238), BMI (*P*=0.383), comorbid status (*P*=0,811), DM comorbidity (*P*=0.887) and HIV status (*P*=1.00) were not significantly associated with the success of short-term treatment regimen for DR TB. Meanwhile, the Mann Whitney test results indicated that age was not significantly related to the success of short-term DR TB treatment (*P*=0.218). Only the patient education variable was significantly related to the success of short-term treatment for DR TB (*P*=0.036).

The characteristics of AFB sputum conversion time and culture, chest X-ray (CXR) results, sputum examination results for first line and second line drug sensitivity tests, drugs adverse effects, and

their effects on the success of DR TB treatment can be seen in Table 2. Percentage of treatment results the effect of supporting examination results and drug side effects on success treatment: the most extensive CXR results (91.8%), the results of sputum examinations for line 1 and 2 drug sensitivity tests with the most MDR (34.1%), many have side effects of treatment (72.9%).

Table 3. Treatment Outcome, Causes of Switching to Individualized Regimens, Treatment Dropout, Drugs Adverse Effects

Parameter	n	Percentage (%)
Treatment End Result		
Complete treatment	11	12.9
Recovered	14	16.5
Dropout	26	30.6
Treatment failure	2	2.4
Died	13	15.3
Switched to individualized regimen	19	22.3
Causes of Switching to individualized regimen		
Pre XDR	11	12.9
Drugs adverse effects	8	9.4
Causes of treatment dropout		
Drugs adverse effects	20	23.5
No family supports	2	2.4
Refusing treatment	4	4.7
Drugs adverse effects		
Nausea/vomiting	56	65.9
Injection site pain	10	11.8
Weakness	2	2.4
Vertigo	12	14.1
Anorexia	3	3.5
Visual impairment	5	5.9
Hearing disorder	10	11.8
Headache	10	11.8
Electrolyte disturbance	7	8.2
Impaired kidney function	4	4.7
Arthralgia	2	2.4
Peripheral neuropathy	4	4.7
Insomnia	4	4.7

The Mann Whitney test was used to analyze the effect of AFB sputum conversion time and sputum culture conversion time on the success of DR TB treatment. On the other hand, the CXR results and sputum drug susceptibility test results affected the success of DR TB treatment, as confirmed by the Chi-Square test. AFB sputum conversion time (*P*=0.511), sputum culture conversion time (*P*=0.950), CXR results (*P*=0.100), sputum results from monoresistance drug sensitivity test (*P*=0.379), rifampicin resistance/RR (*P*=0.802) and drug adverse effects (*P*=0.139) were not significantly related to the success of DR TB short-term treatment. Only pre-XDR drug susceptibility test results were significantly associated with DR TB short-term treatment failure (*P*=0.037).

The final results of treatment, causes of switching individual regimens, causes of treatment discontinuation, and drug adverse effects of study subjects are shown in Table 3.

Most of the treatment outcome was treatment dropout (30.59%), while the most common cause of switching from standard short-term treatment regimens to individualized treatment regimens was the pre-XDR result of sputum susceptibility test in first and second lines (12.9%). The cause of treatment dropout of short-term combinations was mostly due to drugs adverse effects (23.5%), while the most common adverse effect was nausea/vomiting (65.9%).

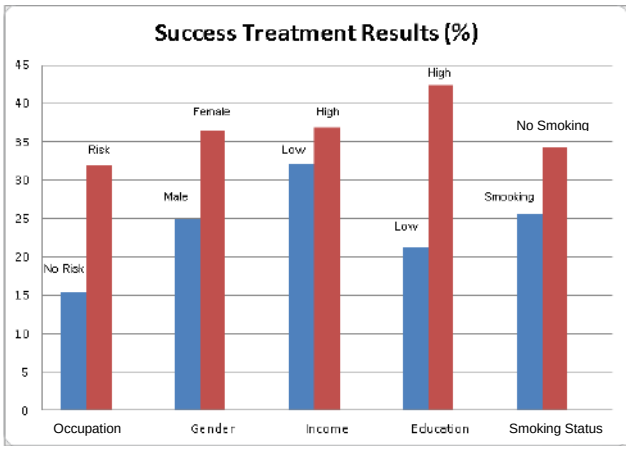

Figure 2. Successful treatment results in multiple variable groups

Table 4. Logistics Regression Test for Treatment Success of Standard Guidelines for DR TB Short-Term Regimen

Parameter	B	S.E.	Wald	df	*P*	OR	95% CI	
							Lower	Upper
Age	-0.002	0.030	0.004	1	0.950	0.998	0.941	1.059
Education	-0.309	0.825	0.140	1	0.708	0.734	0.146	3.701
Criteria for suspected DR TB	-0.470	0.801	0.345	1	0.557	0.625	0.130	3.002
Pre XDR	-20.879	12059.579	0.000	1	0.999	0.000	0.000	-
Constant	-0.045	1.577	0.001	1	0.977	0.956	-	-

The variables included in the multivariate analysis were variables with *P*-value of <0.25 in the bivariate analysis, namely age, education level, criteria for suspected DR TB and pre-XDR (Table 4).

DISCUSSION

Based on this study results, most of DR TB patients was male (61.2%), and the gender variable was not significantly correlated to the DR TB treatment success (*P*=0.262). There were no clear correlations that could explain the incidence of DR TB with gender. Men are more at risk for developing DR TB because women tend to seek health services more and are considered to be more obedient in taking medications.[5]

Descriptively, it could be seen that patients with risk of failure were in the mean age of 43.98 years with a median of 45.5 years, and for those who recovered, the mean age was 40.08 years with a median age of 42 years. From this study, it was observed that age was not associated with DR TB treatment success (*P*=0.218). This result was similar to study from Elisabeth et al. that the mean age of DR TB patients was 42.76 years. In the productive age, the rate of TB transmission is very high and extensive because the patient's interactions with other people and high work mobility might induce the patients to tend not to adhere to ATD in their previous TB treatment.[6]

Based on the occupations of DR TB patients, it was noticed that most of them had risky jobs (84.7%), and the work variable was not related to the success of DR TB treatment (*P*=0.328). Elisabeth et al. obtained no association between occupational status and treatment success, while on the contrary, patients who worked reduced the DR TB treatment success (OR=0.87; 95% CI 0.67–1.14; *P*=0.314).[7] All types of work which account study subjects to be exposed to substances that interfere with lung function and works that allow study subjects to have contact with TB patients are considered as risky jobs. A person's occupation reflects the amount of information received about illness as well as health services and helps a person to make decisions about the use of existing health services and the views about treatment.[8]

We also observed that most of the DR TB on treatment had low income (73.6%), and the income variable was not related to the success of DR TB treatment (*P*=0.705). This result was the same as study from Tirtana which stated that there was no correlation between level of income and the DR TB treatment success (*P*=1.00).[9] Resistance to ATD is broadly developed in countries with poor socio-economic conditions, where the condition of incompetent purchasing power affects the fulfillment of nutritional needs. Resistance causes M.Tb to multiply easily and ultimately inhibits sputum conversion.[10]

Based on the education status, it was observed that most of the patients with DR TB treatment had low education (61.2%), and the level of education was significantly related to DR TB treatment success (*P*=0.036). According to Kondoy et al., education level was related to medication adherence, which increased the treatment success for TB patients.[11] Higher education will support a person to understand the knowledge given.[12] Absorption of knowledge about DR TB greatly influences patients compliance behavior and leads the patient to optimize and pay more attention to their health and nutrition, including the prevention and treatment of DR TB.[13]

In this study, most DR TB patients on treatment had a history of smoking (55.3%), and the smoking history variable was not associated with the success of DR TB treatment (*P*=0.383). Khan et al. concluded that smoking was a risk factor for developing DR TB (*P*<0.05), and cases of multiple drug resistance were more common in smokers than in non-smokers. In smokers, macrophage disruption increases airway resistance and pulmonary epithelial permeability. Cigarette smoking will reduce the responsiveness to antigens. The incidence and severity of TB were related to smoking.[14]

The study subjects were DR TB patients mostly from outside Malang (52.9%), and the variable of domicile was not related to the success of DR TB treatment (*P*=0.286). It was similar to

study from Elisabeth et al. which pointed out that the distance from which the patient lived was not related to the DR TB treatment success (OR=1.01; 95% CI=0.57-1.77; *P*=0.973).[7] Most patients chose health facilities that were relatively close to their homes. The distance from home to health facilities is indeed an important factor.[15]

We also found that most DR TB patients on treatment had non-underweight BMI (55.35%), and the BMI variable was not associated to DR TB treatment success (*P*=0.383). According to Elisabeth et al., nutritional status of patients was not associated with successful treatment of DR TB (OR=2.07; 95% CI=0.47-3.02; *P*=0.718).[7] Tuberculosis patients who were underweight had a higher risk of relapse after completion of treatment. Drug resistant TB treatment has more severe side effects than drug sensitive-TB treatment, thus affecting the patient's poor nutritional status. Therefore, regular monitoring of patients' nutritional status is very important.[16]

Based on research data, the criteria for suspected DR TB were mostly non-relapse case (54.1%). The criteria for suspected DR TB were not associated with DR TB successful treatment (*P*=0.238). The incidence of DR TB is mostly caused by secondary resistance from primary resistance, and recurrence of TB patients allows drug resistance to occur. Resistant organisms can arise due to several factors, and human error is the biggest contribution.[17]

In this study, the most common comorbidity of DR TB patients was DM (41.2%), and the comorbidities variables were not related to the DR TB treatment success (*P*=0.672). According to Manurung et al., comorbidities (DM and HIV) did not affect the success rate of DR TB patients (OR=0.73; 95% CI=0.27-1.97; *P*=0.53). Comorbidities in DR TB patients cause a worse quality of life than patients without comorbidities. DM is a risk factor for DR TB, and patients with DM have deficiencies of cellular immunity.[6]

Our study obtained the mean AFB sputum conversion time of 1.351 months with a median of 1 month. There was no significant association between sputum smear conversion time with the success of DR TB treatment (*P*=0.511). The sputum culture conversion time was 1.449 months with a median of 1 month. There was also no significant association between sputum culture conversion time and the success of DR TB treatment (*P*=0.950). This result was the same as study from Sinaga which stated that among 85 study subjects, the largest AFB growth occurred in the fourth week of 43 samples (50.59%).[18]

A high conversion rate will be followed by a high cure rate.[19] Factors that could prolong sputum conversion time such as bacterial load at the start of treatment, lung cavities, smoking, chronic symptoms, age, inappropriate medication, gender, BCG score, and erythrocyte sedimentation rate, could also affect the length of conversion.[20]

Based on CXR lesions, most of the CXR lesions obtained were extensive (91.8%), and the CXR lesion variable was not associated with the success of DR TB treatment (*P*=0.100). Cha et al.mentioned that radiographic features in CXR of patients with MDR TB and XDR TB were multiple cavities, nodules, and bronchial dilatation. Both radiographic features of MDR TB and XDR TB patients were not significantly different and had various forms, which were called multiforms.[21]

The resistance pattern of the sputum results of drug susceptibility tests on first and second lines was mostly MDR (44.4%). Based on the pattern of resistance, the results of monoresistance and RR had no significant correlation to treatment success (*P*=0.379; *P*=0.802) while patients with pre-XDR pattern were associated with treatment failure for DR TB (*P*=0.037) .[22]

Marais et al. in their study pointed out that polyresistance and RR did not have significant success rate, meaning that as long as DR TB patients received the appropriate therapeutic regimen, the success rate was not much different from patients diagnosed with RR and polyresistance.[22] DR TB patients with sputum drug susceptibility test results of resistant (or intolerance) to fluoroquinolones and/or second-line injection drugs do not meet the criteria to continue short-term

standardized treatment and will be switched to individualized treatment.[23]

Most of the study subjects experienced drugs adverse effects (72.9%), and the drugs adverse effects variable was not related to the success of DR TB treatment (*P*=0.139). Deshmuck et al. expressed that many factors affected the adherence to DR TB treatment, including the adverse effects of drugs experienced by DR TB patients.[24] Management of adverse effects starts with patient education. Prior to starting treatment, patients should be well informed in detail about the potential side effects of the ATD regimen and when to report them to healthcare professionals. Even for the harmless adverse effects, the evaluation, diagnosis, and treatment should be carried out promptly.[25]

LIMITATION

This study used secondary data from patients medical records with some incomplete medical record data so that it could affect the final results of the study. The study was conducted in a limited time. The study only analyzed patients factors, investigations results, adverse effects, and HIV status on the treatment success. In contrast, microbial factors, other TB control program factors, as well as environmental and behavioral factors were not evaluated.

CONCLUSION

The success rate of short-term standardized treatment for DR TB patients was 29.4%, consisting of recovered (16.5%) and complete treatment (12.9%). The patient's education level had a significant correlation with the success of DR TB short-term treatment. Patients with pre-XDR sputum susceptibility test results of first lines and second lines had a significant correlation with DR TB short-term treatment failure (*P*=0.037). Variables that could be used as predictors of the success of short-term DR TB treatment were age, education level, criteria for suspected DR TB, and the presence of pre XDR TB.

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CONFLICT OF INTEREST

None.

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Original Article

The Difference in Serum Levels of IP-10 in Pulmonary Tuberculosis Patients with Positive AFB and AFB Conversion

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Abstract

Background: Tuberculosis (TB) is caused by Mycobacterium tuberculosis, which most commonly infects the lungs. Diagnostic modalities are required in smear-negative TB. IP-10 is a potent chemokine for detecting the presence of TB infection. This study aimed to determine the difference in serum IP-10 levels in patients with smear-positive pulmonary TB and pulmonary TB patients with AFB conversion after two months of therapy.

Methods: This was an analytic observational study with a cross-sectional approach. Sampling was carried out by consecutive sampling methods. AFB examination was performed using Ziehl-Neelsen staining, and serum IP-10 was measured using ELISA.

Results: The study results obtained mean IP-10 levels in TB patients with smear positive and AFB conversion after two months of treatment of 459 pg/mL and 204.4 pg/mL, respectively. Statistical analysis using independent t-test received *P*<0.0001. The optimal cut-off value was 306,1 pg/ml (90% sensitivity; 95% specificity; area under the curve: 0.948, 95% CI=0.88-1; *P*=0.0001).

Conclusion: There was a significant difference between IP-10 levels in TB patients with smear positive and AFB conversion.

Keywords: AFB, IP-10, Pulmonary tuberculosis

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INTRODUCTION

Tuberculosis (TB) is a disease caused by Mycobacterium tuberculosis.[1] As many as 1.5 million people die from TB every year. This makes TB an infectious disease with a very high mortality rate. The World Health Organization (WHO) 2019 reports concluded that Indonesia was in the third highest position in the world for the number of TB cases after India and China.[2]

Indonesia is a country with a large private health sector that is not very well connected to the NTP (National Tuberculosis-control Program) reporting network. In 2016, about only 360,565 TB cases were reported to national level authorities, while the estimated TB incidence was 1,020,000. The Minister of Health Decree, which came into effect in Indonesia in 2017, established TB notification a mandatory nationwide. A national TB inventory study was carried out in 2017 under the NTP and the Indonesian National Institute of Health Research and Development. The aim was to directly measure the rate of reported TB cases detected in the national TB surveillance system (SITT, Integrated Tuberculosis Information System) managed by the NTP. It was observed that the annual incidence rate for 2017 was estimated at 319 per 100,000 population per year.[3]

In clinical application, the TB diagnosis process encountered various difficulties and obstacles where the findings of TB cases with sputum smear examination were only 44% in adult cases and 15–20% in children. The gold standard examination for the diagnosis of TB is to detect the presence of Mycobacterium tuberculosis from culture examination, but it practically takes a longer time that prolongs the diagnosis process. The decision to diagnose and manage TB has become more difficult if the sputum AFB (acid fast bacilli) examination shows a negative result, especially for patients with suspected TB who are difficult or unable to expel

sputum so that sputum AFB examination cannot be performed.[4]

In such cases, a rapid diagnostic test modality is needed, such as tuberculin skin test (TST), chest X-ray, Mycobacterium tuberculosis nucleic acid amplification examination and/or pathological examination of biological specimens. However, this examination has a diagnostic significance level that is not better than the smear examination or sputum culture. Likewise, the TST has low specificity in individuals receiving the Bacille Calmette – Guérin (BCG) vaccination and in individuals living in countries with high TB prevalence.[4]

Currently, many experts have been developing new diagnostic modalities, especially in the field of TB immunodiagnostics. IFN-γ inducible protein 10 (IP-10) is one of the most studied alternative biomarkers for TB diagnostics. This protein is a pro-inflammatory chemokine secreted by monocytes, neutrophils, macrophages, and endothelial inflammatory cells of Th1 lymphocytes into the foci of inflammation.

IP-10 expression is stimulated by several T-cell signals, notably IFN γ and TNF α but also IL-2, type II IFN, IL-27, IL-17/IL-23 and IL-1β which favor pathogen-specific adaptive immune responses by positive feedback. In-vitro, IP-10 is released at a rate 100 times higher than IFN γ.[5] IP-10 can provide a dynamic response to any kind of inflammation, making it important for further clinical investigations in patients who have experienced a decrease of IP-10 due to treatment failure, TB relapse or co-occurring comorbidities.[6,7]

IP-10 has been found to be elevated in plasma in both children and adults with active TB, and has been evaluated by various methodologies. Interestingly, IP10 can also be detected in the urine of adults and children with active TB. IP-10 levels dropped after potent therapy. Compared to blood, urine biomarkers offer the advantage of non-invasive sample collection, especially in Indonesian children, and also pose a lower safety risk for healthcare workers.[8,9]

As an effort to reduce the burden and impact of TB globally and nationally, early identification and adequate management of TB are the main objectives of TB control programs. Rapid TB diagnostic modalities are still very much needed considering that the currently available diagnostic modalities are not effective enough to quickly diagnose cases with smear negative TB, therefore a new diagnostic modality is needed.[4] The purpose of this study was to determine the difference in serum IP-10 levels in patients with smear positive and negative TB at RSUDZA Banda Aceh.

METHODS

This was an analytic observational study with a cross-sectional design. The subjects in this study were taken at the Integrated Tuberculosis Service (PTT) clinic of RSUDZA Banda Aceh. This study was conducted from July 2019 to May 2020. Data collection for this study was performed from November to December 2019. The target population of this study were pulmonary TB patients in Aceh province, while the affordable population were pulmonary TB patients who came to the PTT clinic of RSUDZA from November to December 2019.

The inclusion criteria of this study were patients aged 18–60 years who were diagnosed as new TB cases with positive smear, positive sputum culture, and positive molecular rapid test (GeneXpert), as well as new cases of pulmonary TB patients with AFB conversion after two months of therapy. Patients with sepsis, immunocompromised, drug resistant TB, and extrapulmonary TB were excluded.

We used a quota sampling technique where a sample size of 40 people had previously been determined. All patients who met the study criteria would be included as study subjects until the required number of subjects is met. The number of samples in this study were 40 people with 20 people in each group. The data were analyzed using the IBM SPSS Statistics 21 application using independent t-test and the cut-offs were analyzed using the ROC (receiver operating characteristic) curve to maximize sensitivity and specificity.

RESULTS

Data collection in this study was carried out from November to December 2019. The samples in the study were patients diagnosed with TB at PTT clinic of RSUDZA Banda Aceh. There were 41 patients enrolled, while 1 patient was excluded because of HIV positive.

Table 1. Demographic Characteristics and General Characteristics of Subjects

Characteristics	TB Smear Positive		TB AFB Conversion	
	n	%	n	%
Gender				
Male	13	65	13	65
Female	7	35	7	35
Age				
18–45 years old	12	60	15	75
46–65 years old	8	40	5	25
Smoking Status				
Yes	9	45	9	45
No	11	55	11	55
Body Mass Index				
Low (<18.5)	1	5	20	100
Normal (18.5–24.9)	17	85	0	0
Overweight (25–29.9)	2	10	0	0

The study subjects were divided into two groups, namely TB patients with smear positive and TB patients with AFB conversion after two months of treatment with 20 subjects each.

Table 2. Differences in IP-10 Levels on Subject Demographic Characteristics

Characteristics	IP-10 (Mean±SD)	*P*
Gender		
Male	330.1±157.9	0.163
Female	334.6±230.3	
Age		
18–45 years old	324.3±179.2	0.793
46–65 years old	347.2±198.6	
Smoking Status		
Yes	325.1±151	0.174
No	336±209.8	
Body Mass Index,		
Low (<18.5)	-	
Normal (18.5–24.9)	316.7±175.4	0.107
Overweight (25–29.9)	596.5±237.3	
AFB examination at the beginning of the diagnosis (Group of Smear Positive)		
1+	486.7±196.9	
2+	325.1±10.8	0.482
3+	448.2±129.6	

Characteristics of the subjects in this study were grouped based on gender, age, smoking status, body mass index (BMI), blood glucose levels and the AFB value of TB patients at the time of initial diagnosis. Table 1 shows the frequency distribution of study subjects.

This study obtained no differences in IP-10 levels between gender, age, smoking status, BMI, and AFB values with *P*-values of 0.163, 0.793, 0.174, 0.107, 0.482, respectively. There was no significant difference between IP-10 levels and AFB values in smear positive patients (*P*=0.482). The IP-10 examination was performed at the beginning of the diagnosis of TB in the smear positive group and after the patients took antituberculosis drugs (ATD) in the AFB conversion group, therefore the AFB value data in the conversion group could not be analyzed because the time for AFB examination and the time for taking IP-10 serum was different. There was no statistically significant difference between IP-10 levels and blood glucose levels. There was no difference in IP-10 levels in TB patients with positive and negative BTA

Table 3. Differences in IP-10 Levels on Blood Glucose Levels

Indicator	Mean±SD	*P*
Levels of IP-10	331.7±183.5	0.258
Blood Glucose Levels	109.7±10.6	

In this study, the optimal cut-off was determined by ROC analysis of serum IP-10 levels in pulmonary TB patients with smear positive and AFB conversion after two months of therapy. The cut-off value was selected to maximize sensitivity and specificity.

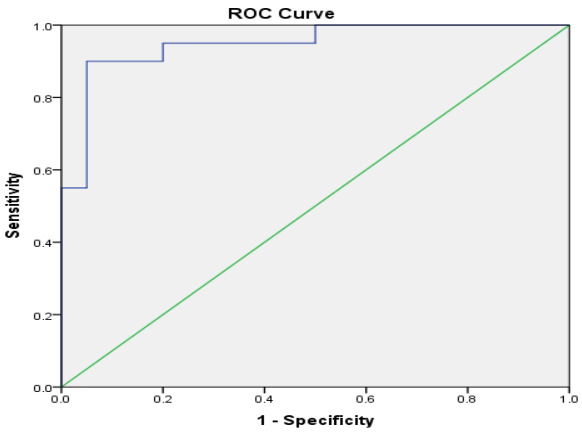

Figure 1. ROC Curve

The optimal cut-off value in this study was

306.1 pg/ml with a sensitivity of 90% and a specificity of 95% (area under curve 0.948; 95% CI=0.88-1; *P*=0.0001). This cut-off value indicates that TB patients with AFB conversion had an IP-10 level lower than 306.1 pg/ml.

Table 4. Difference in IP-10 levels in TB patients with smear positive and smear negative

	TB AFB Positive (Mean±SD)	TB AFB Negative (Mean±SD)	*P*
IP-10	459±171.1	204,4±75.69	0.0001

DISCUSSION

The data obtained pointed out that from a total of 40 subjects who met the inclusion criteria, the majority were male of 26 subjects (65%), while the rest were female of as many as 14 subjects (35%). Subjects with AFB positive and AFB conversion were 20 subjects each. The proportion of men and women in smear-positive TB patients were 13 subjects (65%) and 7 subjects (35%), respectively. The same proportion was also calculated in the number of men and women in TB patients with AFB conversion.

This study observed that the highest number of TB patients in RSUDZA occurred in the age range of 45–64 years (14 subjects), followed by ages 25–34 years (11 subjects), then ages 35–44 years (10 subjects). Subjects who had a history of smoking were 18 people or 45% of the total number of subjects, where the number was the same in TB patients with AFB positive and AFB conversion, namely 9 people each.

All TB patients with AFB conversion after two months of therapy had normal BMI with a total of 20 subjects (100%). Meanwhile, most TB patients with AFB positive had normal BMI, namely 37 subjects (92.5%). There was 1 subject (2.5%) with a low BMI and 2 subjects (10%) with overweight BMI.

Comparative analysis of IP-10 levels on the demographic characteristics of the subjects mentioned that none of the demographic characteristics had a significant correlation with IP-10 levels. The *P*-values of IP-10 for gender, age, smoking status and BMI were 0.163, 0.098, 0.174, 0.107, respectively.

Comparative analysis of IP-10 levels in TB patients with AFB positive and AFB conversion received a *P*-value of 0.00, which implied that there was a significant difference in IP-10 values among TB patients with smear positive and AFB conversion. This study stated that IP-10 is an immunodiagnostic tool which can be used to determine Mycobacterium tuberculosis infection.

IP-10 is one of the CC chemokines that escalates in polymorphonuclear monocytes and granulocytes after Mycobacterium tuberculosis infection.[10] Elevated levels of IP-10 have also been found in autoimmune diseases such as systemic lupus erythematosus,[11] and in occupational asthma.[12] So far, IP-10 was considered to only indicate the presence of inflammation and might not be very specific for use in diagnosing TB, however, Ruhwald et al. reported that IP-10 response was specific for particular antigens possessed by Mycobacterium tuberculosis and could be used to diagnose TB infection.[10]

IP-10 or CXCL-10 is encoded by chromosome number 4 in the q21 band. CXCL10 is induced by IFN-γ. CXCL10 will activate the CXCR3 receptor located on T lymphocytes, plasma cells or B cells, natural killer cells, dendritic cells and macrophage cells. When macrophages are infected by Mycobacterium tuberculosis, Th1 cells produce IFN-γ, which induces the production of various cell types that produce CXCL10. Thus, the IP-10 level is higher in tuberculosis infection. IP-10 will continue to attract and recruit Th1 cells, resulting in more CXCL10 production. Chemotaxis of immune cells continuously generates tissue damage, leaving permanent scars.[13]

The optimal cut-off value in this study was 306.1 pg/ml (90% sensitivity, 95% specificity, area under curve 0.948, 95% CI 0.88-1; *P*-value = 0.000). This cut-off value indicated that TB patients with AFB conversion had an IP-10 level lower than 306.1 pg/ml.

A study by Hong et al. in South Korea mentioned that the cut-off value of IP-10 levels in non-HIV pulmonary tuberculosis adults patients with patients without pulmonary tuberculosis or in other words adults suffering from diseases other than TB was 119 pq / mL.[14] Meanwhile, Petrone et al.

conducted a study in Uganda, reported the cut-off value for pulmonary TB patients in children compared to children without pulmonary TB was 109.1 pq/mL.[9]

LIMITATIONS

Several limitations were found in this study such as the limited number of samples, the cost and time of the study which limited the researchers using a prospective cohort study design.

CONCLUSION

There was a significant difference between IP-10 levels in TB patients with smear positive and AFB conversion after two months of treatment.

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CONFLICT OF INTEREST

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Original Article

Comparison of Serum Vitamin C Levels Between Pulmonary Tuberculosis and Healthy Controls in Medan

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Abstract

Background: Pulmonary tuberculosis infection is a high burden, especially in developing country. Vitamin C is a water-soluble micronutrient that contributes to immune defense by supporting avarietyof innate and adaptive immunity. Vitamin C protects the host from reactive oxygen and reactive nitrogen intermediates generated during Mycobacterial infection. Pulmonary tuberculosis patients have lower vitamin C levels because Mycobacterium tuberculosis infection produces reactive oxygen species for replication as well asmetabolism and also because of reduced nutrient intake. Vitamin C as an antioxidant also plays role in killing *Mycobacterium tuberculosis* by encouraging Fenton reaction.

Methods: This is a case control study of serum vitamin C levels in pulmonary tuberculosis patients and healthy controls. Vitamin C levels were measured by ELISA (Enzyme Linked Immunosorbent Assay).

Results: The number of subjects was 40 people, divided into 20 subjects of pulmonary tuberculosis as cases and 20 healthy controls, aged between 18–65 years old. Vitamin C levels according to age group were 99.03±38.60 ng/ml and 80.53±27.38 ng/mlfor18–30 years, 84.85±49.69 ng/ml and 82.70±14.93ng/ml for31–40 years, 61.34±25.36 ng/ml and 79.93±22.81 ng/ml for41–50 years, 71.43±18.36 ng/ml and 78.69±54.21 ng/ml for51–65 years. Vitamin C levels of male subjects based on case and control groups were 88.11±42.07 ng/ml and 78.36±28.95 ng/ml while for the female were 73.20±11.56 ng/ml and 83.16±23.77 ng/ml. Mean vitamin C levelin pulmonary tuberculosis patients was 83,64±35,99 ng/ml and in healthy controls was80,22±26,44 ng/ml.

Conclusion: There was no significant difference in vitamin C levels between pulmonary tuberculosis patient and healthy people.

Keywords: healthy controls, pulmonary tuberculosis, vitamin C

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INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTb) which can affect various organs, particularly the lungs. Although the DOTS strategy is very effective for TB control, the burden of TB disease in the community is still very high. In 2020 there were 10 million new cases of TB, and 1.5 million people died from this disease worldwide.[1] TB disease in Indonesia is the number one killer among infectious diseases and is the third leading cause of death after heart disease and acute respiratory disease for all ages.

The success of TB case control strategies is relatively high, and the presence of TB in various parts of the world indicates the need to identify various factors which increase the risk of TB, including age, gender, and immunity.[2] Vitamin C is a water-soluble vitamin which has antioxidant effects on body tissues. Human body cannot produce vitamin C, so it requires intake from food sources. Levels of vitamin C as an antioxidant will continue to decline due to various factors such as age, gender, lifestyle, and chronic diseases, including pulmonary TB infection.[3]

Mycobacterium tuberculosis produces free radicals in activities at cellular level such as respiration, metabolism, and replication. Reddy et al. stated that glutathione, vitamin C, and vitamin E are antioxidants that are often found to be low in pulmonary TB patients.[4]

Study by John Kennedy et al. pointed out that levels of vitamin C and vitamin E in TB patients were low. This decline in antioxidant levels will cause a

decrease in total serum antioxidant levels in TB patients. Low antioxidants can be caused by a lack of intake and an increase in free radicals during phagocytosis process of *Mycobacterium tuberculosis*.[5] Administration of antioxidants in TB patients could improve T-cell function and reduce levels of prostaglandin E2 as well as suppress free radicals. Susanto et al. observed an accelerated conversion based on sputum smear culture in pulmonary TB patients who received vitamin C supplementation.[6,7]

METHODS

This was a case control study conducted at several public health centers and special pulmonary hospitals in Medan City from November to December 2018.The subjects of this study were new cases of pulmonary TB patients who met the inclusion and exclusion criteria. The inclusion criteria were men and women aged 18–65 years, new established TB cases based on clinical, radiological and positive AFB (Acid-Fast Bacillus) smear results, signed an informed consent and were willing to participate in the study.

Exclusion criteria were diagnosed as HIV positive, extra pulmonary TB, Diabetes Mellitus (DM), liver and kidney disease based on medical records, currently taking immunosuppressive drugs and currently taking vitamin C. Inclusion criteria in the control group were men and women aged 18-65 years old, no clinical signs of active TB based on history, chest x-ray within normal limits, not diagnosed as DM and other diseases, were willing to participate in the study.

The number of study subjects were 20 pulmonary TB patients and 20 controls (no pulmonary TB). Blood sample was taken from the median cubital vein in the study subjects. Vitamin C levels were examined using the ELISA (Enzyme Linked Immunosorbent Assay) method. Data were collected and analyzed using the Kruskall Wallis and Kolmogorov Smirnov test.

RESULTS

The study subjects were 40 people divided as 20 people in the pulmonary TB group as cases and 20 healthy people as controls. It was observed among the case group that the youngest age was 21 years while the oldest was 65 years, consisted of 14 men (70%) and 6 women (30%). In the control group, the youngest age was 18 years and the oldest was 65 years with 12 men (60%) and 8 women (40%).

Table 1. Characteristics of study subjects by age and gender

Characteristic		Pulmonary TB (Case)	Healthy People (Control)
Age	18–30 years	8 (40%)	4(20%)
	31–40 years	4 (20%)	3 (15%)
	41–50 years	3 (15%)	10 (50%)
	51–65 years	5(25%)	3 (15%)
Gender	Male	14 (70%)	12 (60%)
	Female	6 (30%)	8 (40%)

In table 1, it is observed that the most common age group in the case group was 18–30 years, with a total of 8 people (40%), most of whom were male for as many as 14 people (70%) of the total sample of 20 people (100%). Subjects in the control group were mainly in the age group of 41-50 years for as many as 10 people (50%) with 12 male subjects (60%).

Table 2. Mean levels of vitamin C in pulmonary TB patients (cases) and healthy people (controls)

Parameter	Pulmonary TB (Case) (Mean±SD)	Healthy People (Control) (Mean±SD)	*P*
Vitamin C (ng/ml)	83.64±35.99	80.22±26.44	0.284

Table 3. Vitamin C levels in pulmonary TB and healthy people by age and gender

Characteristic	Vitamin C (Mean±SD)	
	Pulmonary TB (Case)	Healthy People (Control)
Age		
18–30 years	99.03±38.60	80.53±27.38
31–40 years	84.85±49.69	82.70±14.93
41–50 years	61.34±25.36	79.93±22.81
51–65 years	71.43±18.36	78.69±54.21
Gender		
Male	88.11± 42.07	78.36±28.95
Female	73.20±11.56	83.16±23.77

Table 2 shows that vitamin C levels in the pulmonary TB group were higher than in the control group, but this difference was not significant (*P*>0.05). Table 3 denotes that vitamin C levels decreased with age in both cases and controls.

DISCUSSION

Vitamin C (ascorbic acid) is a water-soluble vitamin and is included in antioxidant vitamins which could counteract various extracellular free radicals. It was discovered in 1928 and was first used to prevent canker sores. Subsequent studies obtained that vitamin C had the effect of maintaining and increasing immunity against infection.[3]

Vitamin C is an antioxidant that neutralizes free radicals, able to work inside as well as outside the cells, and also able to protect DNA damage from free radicals and mutagens in humans. Vitamin C is not produced by the body and its level depends on dietary intake. The role of vitamin C as an antioxidant controls the Fenton reaction, where *Mycobacterium tuberculosis* releases reactive oxygen species (ROS), namely superoxide, hydroxyl peroxide, and hydroxyl radical.[8]

In addition to smoking, infection, alcohol and lack of nutritional intake in pulmonary TB patients can reduce serum antioxidant levels. A study by Reddy et al. mentioned that low levels of antioxidants were glutathione, vitamin C, and tocopherol (vitamin E), so a suitable antioxidant therapy may prove beneficial and nutritional antioxidant supplementation may represent a novel approach to fast recovery. Increased levels of ROS will lessen serum antioxidant levels as a consequence of phagocytosis during *Mycobacterium tuberculosis* infection, where at the time of infection, the body will respond in inflammation as a protection against tissue damage.[2]

This study observed that vitamin C levels in men were lower than in women, both in the pulmonary TB patient group and healthy controls. This might be because men had habits of smoking and consuming alcohol. Smoking provides the formation of free radicals in the body, resulting in cell damage. Vitamin C as an antioxidant and the body's defense mechanism will prevent it by donating electrons to free radicals to make it stable. This situation causes antioxidant levels to drop. Smoking habits can increase the failure of sputum smear conversion in patients with pulmonary TB, as mentioned in a previous study by Wahyuni et al.[9]

Alcohol consumption induces low vitamin C levels due to the acetaldehyde in alcohol metabolism and an increase in the ratio of NADPH and NAD, reducing iron absorption.[10] A study from Sinaga in Medan pointed out that smoking and alcohol increased the risk of pulmonary TB.[11] Smoking and alcohol consumption habits lead to damage of pulmonary cilia function, so that it will facilitate the occurrence of infections in the respiratory tract. Rosemary et al. obtained that vitamin C levels in men were lower than in women due to different lifestyle and activity.[12]

In this study, there was a tendency for vitamin C levels to decrease with age. In the elderly, vitamin C levels decrease due to the influence of the body's absorption ability, escalated oxidative stress due to age, and muscle weakness (decreased adipose tissue).[13] Another study on vitamin C levels in a population aged over 60 years conducted in India by Ravilla D. Ravindran et al. found that vitamin C levels were influenced by age and were lower in men than women.[14]

LIMITATION

This study did not mention about the daily food intake of the subjects which could affect the vitamin C levels.

CONCLUSION

Vitamin C levels were higher in pulmonary TB patients compared to the control group, although the difference was not significant. Based on gender, men had lower levels of vitamin C than women. Vitamin C levels tended to decrease with age. The results of this study are expected to be used as a reference in further research with more in-depth interviews regarding food intake, smoking habits, and alcohol consumption.

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CONFLICT OF INTEREST

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Original Article

Clinical Characteristic and Outcome of COVID-19 Patient Using High Flow Nasal Cannula in Persahabatan Hospital, Jakarta

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Abstract

Background: Severe and critical COVID-19 patient need intensive care and even invasive mechanical ventilation. The use of high flow nasal cannula (HFNC) in acute hypoxemic respiratory failure on non-COVID-19 patient can reduce the need for intubation, meanwhile there is still inadequate data for COVID-19 patients.

Methods: This is a retrospective cohort study in 62 confirmed COVID-19 patients using HFNC and treated at Persahabatan General Hospital from March to July 2020. Demographic, clinical and laboratory data before HFNO and vital sign, respiratory index after 24 hours of HFNC was taken from medical record.

Results: Majority of patients are men (67%), mean age 57.6 years, comorbidity is mostly hypertension and diabetes. HFNC success outcome is 45.2%. Statistically significant difference between success and failure group is noted on respiratory rate (24 vs 28.5), pulse rate (88.14 vs 100), oxygen saturation (98 vs 94), PaO2/Fio2 (139.27 vs 73), SpO2/FiO2 (116.98 v 102.78) and ROX index (4.97 vs 3.5). Vital sign and respiratory index measured after 24 hours of HFNC showed statistically significant improvement in success group.

Conclusion: HFNC can reduce intubation rate in patient with COVID-19. Vital sign and respiratory index are significantly improved in HFNC success group.

Keywords: COVID-19, High flow nasal cannula (HFNC), ROX index

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by Severe acute respiratory syndrome-coronavirus2 (SARS-CoV2), which is an RNA virus in the beta coronavirus family and has phylogenetic similarities to the severe acute respiratory syndrome-coronavirus (SARS-CoV) and middle east respiratory coronavirus (MERS-CoV).[1] The World Health Organization (WHO) in March 2020 declared COVID-19 a pandemic.[2] Patients with COVID-19 can have different clinical presentations. Data from China concludes that 81% will experience mild symptoms, 14% with severe symptoms, and 5% with a critical condition.[3]

Patients with severe and critical symptoms generally experience severe acute respiratory infection (SARI) symptoms that require hospitalization and oxygen therapy. Occasionally, respiratory failure will occur, requiring mechanical ventilation and treatment in the intensive care unit (ICU).[4]

The use of high flow nasal cannula (HFNC) in patients with impending respiratory failure has the advantages of ease of operation, administration of a constant and maintained oxygen fraction, positive end expiratory pressure (PEEP), decreased anatomic dead space, decreased work of breathing and improved mucociliary clearance. This will lead to an improvement in respiratory rate, oxygen saturation and oxygenation.[5,6]

At the beginning of the pandemic, research on the characteristics of patients with COVID-19 using HFNC and their role in reducing intubation rates and mechanical ventilation is still limited, so research is needed to determine patient characteristics, intubation rates, and mortality of COVID-19 patients using HFNC.

METHODS

This study is a retrospective cohort of confirmed COVID-19 patients with inclusion criteria of 18 years of age or older, using HFNC and being treated at Persahabatan Hospital Jakarta in March-July 2020. Patients with incomplete data and a history of previous COVID-19 treatment is excluded. The initial data were demographic, clinical factors (the duration and type of previous oxygen therapy, duration of use of HFNC, and treatment regimen), and laboratory data before using HFNC. Vital signs and respiratory index data were taken before the patient used HFNC and 24 hours after HFNC. These two data were then compared between the success and failure groups using T-test or Mann-Whitney test.

Failed outcomes were defined as death or invasive mechanical ventilation after using HFNC, while successful outcomes were patients who did not experience failed outcomes. The outcome was determined on the 21st day of observation. The required data were taken from patients' medical records who met the inclusion criteria after obtaining approval from the research ethics committee.

RESULTS

Data from medical records in the March – July 2020 period showed that 69 COVID-19 patients used HFNC, five people were not included in the sample because the data was incomplete, while two people were not included because the use of HFNC was <24 hours, so that the total patients who could be analyzed were as many as 62 people.

The research subjects consisted of 67.7% men and 32.3% women. The mean age of the research subjects was 57.6 years, and the age group with the most subjects was <65 years (73.7%). Most subjects are recorded as not smoking (73%). The most common comorbidities were hypertension (58.1%), diabetes mellitus (51.6%), and cardiovascular disease (19.4%). There were 23 subjects (37.1%) had multiple comorbidities, while 11 subjects (17.7%) did not have any comorbidities.

All patients confirmed COVID-19 through Reverse transcription polymerase chain reaction (RT-PCR) swab. Based on WHO clinical criteria, 25.8% subjects were in severe conditions, while 74.2% subjects were in critical conditions. Also, based on respiratory distress criteria, there were 24.2% subjects in moderate conditions, and 75.8% were in severe conditions; all patients used non-rebreathing masks before using HFNC. The average length of treatment was 16.5±9.9 days, while the median length of HFNC use was four days. Oseltamivir was the most used treatment regiment, followed by azithromycin and chloroquine.

Table 1. Demographic and clinical characteristics

Variable	N (%)
Age	
<65	45 (73.7)
≥65 years	17 (27.4)
Gender	
Male	42 (67.7)
Female	20 (32.3)
Smoking Habit (n=45)	
Smoke	12 (26.7)
Do not smoke	33 (73)
Comorbid	
No comorbid	11 (17.7)
Diabetes Mellitus	32 (51.6)
Hypertension	36 (58.1)
Cardiovascular	12 (19.4)
Cerebrovascular	1 (1.6)
Obstructive Lung Disease	1 (1.6)
Pulmonary Tuberculosis	0
Malignancy	0
HIV	0
Multiple/multiple comorbid	23 (37.1)
WHO clinical level	
Heavy	16 (25.8)
Critical	46 (74.2)
Level of respiratory distress	
Moderate	15 (24.2)
Heavy	47 (75.8)

The mean hemoglobin was 13.20 g/dL with median leukocyte and platelet counts of 9315/µL and 259000/µL. The neutrophil/lymphocyte ratio (NLR) showed a median of 6.82. The mean erythrocyte sedimentation rate (ESR) was 82.06 mm from 29 subjects, the mean c-reactive protein (CRP) value was 146.8 mg/L from 57 subjects, and the median procalcitonin (PCT) value was 0.175 ng/mL. Examination of lactate as a marker of tissue hypoxia was performed on 49 subjects and obtained a median value of 2.5 mmol/L.

Table 2. Differences in the characteristics of vital signs

Variable	Outside		*P*
	Success	Fail	
Respiratory rate (x/minute)	24 (18–34)	28.5 (22–45)	0.0001
Pulse Rate (x/minute)*	88.21±10.94	99.94±10.21	0.0001 (6.343–17.111)
O_2 Saturation (%)	98 (93–100)	94 (54–100)	0.0001
SpO_2/FiO_2	116.47 (100–166.67)	102.78 (56.84–213.33)	0.0001
PaO_2/FiO_2 (n=58)	138.38 (68.84-267.29)	74.22 (36–184.4)	0.0001
ROX Index	4.94 (3.26–8.25)	3.58 (1.67–9.69)	0.0001

Note=*Normal distribution using Standard Deviation

Table 3. Differences in the Characteristics of Laboratory Values

Variable	Outside		*P*
	Success	Fail	
Hemoglobin (g/d)*	12.83±1.79	13.48±2.05	0.192 (-0.337–1.644)
Leukocytes (/µL)	8220 (3670–28450)	10175 (3870–21230)	0.218
Count the type of neutrophil	81.3 (39.6–97.8)	82.8 (53.9–94.1)	0.656
Count the type of lymphocyte	12.7 (1.2–55.9)	10.1 (4–39.2)	0.362
Neutrophil / Lymphocyte Ratio	6.14 (1.38–23.53)	8.02 (1.38–23.53)	0.380
Platelets (/µL)	255500 (141000–608000)	271500 (45000–590000)	0.276
CRP (mg/L)* (n=57)	130.74±91.64	159.35±88.51	0.238 (-19.482–76.688)
PCT (ng/ml) (n=58)	0.11 (0.03–5.68)	0.21 (0.05–7.14)	0.028
Urea(mg/dL) (n=61)	26 (11–111)	36 (8–168)	0.160
Creatinine(mg/dL) (n=61)	0.8 (0.4–5.4)	1 (0.4–4.1)	0.165
Aspartate transferase (U/L) (n=62)	38.5 (13–85)	49.5 (15–171)	0.110
Alanine Transferase (U/L) (n=62)	37 (12–143)	48.5 (15–124)	0.329
Troponin I (pg/ml) (n=47)	7.2 (0.9–1008)	18.25 (1.1–285.2)	0.052
Lactate (mmol/L) (n=49)	1.9 (1.2–6.1)	2.9 (1.2–5.4)	0.061
D-dimer (µg/L) (n=56)	1545 (380–22230)	1500 (460–48600)	0.434

Note=*Normal distribution using Standard Deviation

The median values for urea, creatinine, aspartate transferase, alanine transferase, total bilirubin and troponin I were 30 mg/dL, 0.9 mg/dL, 44 u/L, 39 u/L, 0.7 mg/dL and 12.7 pg/mL. The median value of D-dimer was 1500 g/L, while the median value of fibrinogen was 505 g/L. Profile Analysis of blood gases before using HFNC showed a picture of hypoxemia with median values of PaO_2, PaO_2/FiO_2, and median oxygen saturation of 67.95 mmHg, 111.18, and 93.5%, respectively

Demographic characteristics between patients who succeeded and failed after using 24 hours HFNC did not show a statistically significant difference between the success and failure groups. There are differences in clinical characteristics in the form of the total length of treatment and duration of use of HFNC at 24 hours, 7, 14, and 21 days of observation.

There was no significant difference in systolic blood pressure (136.33 mmHg vs 134.22 mmHg), diastolic blood pressure (80 mmHg vs 81 mmHg), respiratory rate (28 vs 28), pulse rate (97 vs 100), O_2 saturation (96 vs 95) and PaO_2/FiO_2 (119.51 vs 107.58) between the success and failure groups. The only visible difference in characteristics is the ratio of SpO_2/FiO_2 (167.91 vs. 143.94) and FiO_2 (58.5% vs 66%).

Vital signs and respiratory index after using HFNC 24 hours showed a statistically significant difference between patients with successful and failed outcomes. Significant differences were seen in respiratory rate, pulse rate, oxygen saturation, SpO_2/FiO_2 ratio, PaO_2/FiO_2 ratio and ROX index with better median or mean parameter values in the successful group compared to the failed group.

There was a significant difference in the PCT value between the successful and failed outcome groups. Still, there was no significant difference in the value of hemoglobin, leukocyte count, neutrophil type count, lymphocyte type count, neutrophil/lymphocyte ratio, platelet count, CRP, urea, creatinine, aspartate transferase, alanine transferase and D-dimer. The

values of troponin I and lactate showed significant differences at the outcomes of 24 hours and 7 days but became insignificant at the outcomes of 14 and 21 days.

DISCUSSION

The majority of the subjects in this study were male (67.7%), and the mean age of the subjects in this study was 57.6 years, with the most age group being <65 years. This is slightly different from Wang et al.'s study, which found the median age of patients was 56 years, and only 41% of patients were male.[7] Demoule et al. found that the median age of patients using HFNC was 60 years, with the majority (79%) male.[8] Patel et al.'s study showed a mean age of 55.6, with 51% male.[9]

In old age, the innate immune function decreases so that related cells (macrophages, neutrophils, and dendritic cells) are not activated effectively and efficiently when an infection occurs. this causes the adaptive immune system to be improperly and incompletely activated, thereby reducing viral clearance and increasing the possibility of immune system dysregulation. It can lead to excessive release of pro-inflammatory cytokines, resulting in a cytokine storm.[10]

The activity and expression of ACE2 in males are known to be greater than that in females, which is thought to be because estrogen causes downregulation of ACE2 expression in females. In contrast, testosterone causes an increase in the amount of ACE2.[11] Comorbidities and lifestyle-related major comorbidities in COVID (hypertension, diabetes and cardiovascular disease) such as smoking and alcohol consumption are also more common in men. These three things cause men to have a greater tendency for immune system dysregulation and worse outcomes in COVID-19.[11]

The most comorbid found in this study were hypertension (58.1%) and diabetes mellitus (51.6%). A total of 37.7% of the subjects had multiple comorbidities. Wang et al. also found that hypertension and diabetes mellitus were the most common comorbidities in patients taking HFNC. The same thing was obtained by Demoule et al. and Patel et al. The data from the above study shows that hypertension and diabetes mellitus have a relationship with the severity of COVID-19.[7–9]

In this study, only 26.7% of patients had a smoking record. Patel et al. found that almost half of the patients had a smoking habit (43.4%), while Gupta et al. found that 29.3% of patients requiring ICU care due to COVID-19 had a smoking habit or were previously smokers.[9,12] Patanavanich et al. conducted a meta-analysis of the relationship between smoking with worsening in COVID-19 patients and found that smokers have a 1.91x risk of worsening if they experience COVID-19.[13]

Demographic characteristics (age, gender, and comorbidities) between patients with successful or failed outcomes at 24 hours, 7 days, 14 days and 21 days did not show statistically significant differences in this study. Studies on COVID-19 patients using HFNC by Patel et al. and Calligaro et al. also did not find significant differences in age, gender, comorbid diabetes and hypertension between the intubated and non-intubated groups.[9,14] The findings in this study were because the two outcome groups had almost the same mean age (55.9 and 59.9 years), equal distribution of male gender and almost the same number of people with diabetes and hypertension between the groups with successful and failed outcomes.

Most of the patients using HFNC in this study had a high respiratory rate (>25), an oxygen demand of 10–15 liters per minute via non-rebreathing mask (NRM) and bilateral infiltrates with hypoxemia (median PaO_2/FiO_2 111.18 and median SpO_2/FiO_2 146.21) so that they fit the criteria. Acute and severe respiratory distress. Patel et al. also reported that patients using HFNC were patients who required oxygen supplementation of 15 liters/minute (severe hypoxemic respiratory failure). In contrast, Calligaro et al. reported that patients using HFNC had a respiratory rate of 30 breaths/minute and a saturation of 92% with O_2 15 liters/minute (severe respiratory failure).[9,14]

Patel et al. assessed the chest radiograph using the radiographic assessment of lung edema

score (RALES) with a mean value of 18.17 at the beginning of HFNC use. However, they did not explain whether the infiltrates were bilateral or unilateral.[9] Demoule et al. reported that patients who received HFNC therapy were patients with the category of severe and had the involvement of 4 quadrants on chest radiograph.[8]

Patients who fall into the critical criteria have a HFNC failure rate significantly different from the first 24 hour outcome but not significantly different from the 7, 14, and 21 day outcomes. This is because there are patients who switch from a successful outcome to a failed outcome, so overall, it can be concluded that the clinical degree is not significantly different between the two groups.

Most patients (75.8%) were admitted with severe respiratory distress before using HFNC, and the rest were admitted with moderate respiratory distress. There was no significant difference in the degree of respiratory distress between the patients who succeeded and those who failed, which may be due to the high rate of severe respiratory distress in the two groups. Wang et al. found that patients with a higher respiratory rate (26 vs. 23) and lower PaO2/FiO2 (159 vs. 223) were more likely to fail with HFNC.[7]

Administration of chloroquine/hydroxyl-chloroquine, azithromycin, and oseltamivir to patients using HFNC did not result in different outcomes. The same thing was reported by Patel et al., who found no difference in the number of intubations in the group receiving drugs from hydroxychloroquine, azithromycin, and remdesivir.[9] The SOLIDARITY and RECOVERY study conducted by WHO also did not find any difference in mortality and the need for mechanical ventilation between patients who received these drugs and those who did not.[15]

Before using HFNC, the patient's vital signs did not show a significant difference between the success and failure outcome groups. Significant differences were seen in the SpO_2/FiO_2 ratio (lower in the failed group) and the fractional requirement for inspired oxygen (higher in the failed group). This shows that the patient characteristics between the two groups are almost the same.

In this study, there were significant differences in respiratory rate, pulse rate, oxygen saturation, PaO_2/FiO_2, SpO_2/FiO_2, and ROX index measured 24 hours after using HFNC. In the group with successful outcomes, there was an improvement in vital sign parameters and respiratory index compared to the failed outcome group, which showed worsening or no improvement in vital signs and respiratory index parameters 24 hours after using HFNC. Wang et al. reported a significant difference in PaO_2/FiO_2 values between successful patients. They assessed patients after using HFNC for 2 hours, while Calligaro et al. reported significant differences in the respiratory rate, pulse rate, SpO_2, and ROX index, assessed 6 hours after HFNC.[7,14] Patel et al. reported that the changes in SpO_2/FiO_2 measured on day 7 were significantly different in the non-intubated HFNC group compared to the intubated group (141.4 vs. 40.5).[9]

The use of HFNC has a positive effect in the form of decreasing the workload of breathing and increasing patient comfort and compliance so that clinical improvements appear in the form of decreased respiratory rate and improved oxygenation (PaO_2 and SpO_2). This can be seen from the results of this study which illustrates that the group with successful outcomes will experience improvements in respiratory rate, pulse rate, O_2 saturation, PaO_2/FiO_2 ratio, SpO_2/FiO_2 ratio, and ROX index. In contrast, the failed group will experience worsening or no improvement in these parameters compared with the initial value.[16]

Data from patients using HFNC, Wang et al. obtained the median results of peripheral blood tests, respectively, hemoglobin (12.8 g/dL), leukocytes (5400/µL), platelets (154000/µL), and lymphocyte count 700/L.[7] Patel et al. found a lymphocyte count of 1020/µL while Calligaro et al. of 1180/µL.[9,14] In this study, the average hemoglobin was almost the same (13.2 mg/dL) but with the higher value of leukocytes (9315/µL) and platelets (259000/µL). The lymphocyte count (1113/µL) was almost the same as in other studies.

In severe and critical cases, viral replication

occurs rapidly and causes inhibition of interferon production, which causes T cell apoptosis so that the virus cannot be removed quickly. This leads to activation and excessive recruitment of neutrophils and monocytes to the site of infection. The mechanisms thought to cause the decrease in lymphocyte count are the cytopathic effect of SARS-CoV-2 on lymphocytes, myelosuppression due to excessive inflammation, activation of lymphocyte apoptosis, and redistribution of lymphocytes to tissues due to high levels of proinflammatory cytokines (IL-2, IL-6, TNF).[17,18] Wang et al. found that a neutrophil/lymphocyte ratio (NLR) 2.14 is associated with more severe clinical severity and mortality.[18]

The value of inflammatory markers in several studies gave varying results. In patients using HFNC, Wang et al. had a lower median CRP value of 39 mg/L and a PCT value of 0.07 ng/ml, while Patel et al. and Calligaro et al. reported higher results of 117.7 mg/L and 118 mg/L.[1,9,14] The median lactate value in Demoule et al.'s study was 1.5 mmol/L, while Chen et al. reported a mean of 2.4 mmol/L.[8,19] In this study, the average CRP value was 146.8 mg/L, the median PCT value was 0.175 ng/ml, and the median lactate value was 2.5 mmol/L.

This study obtained a median value of D-dimer of 1500 g/L. There are variations in the study D-dimer value in patients using HFNC. Patel et al. reported a much higher value of 5659.6 g/L, while Calligaro et al. reported a lower value of 830 g/L.[9,14] PaO_2/FiO_2 values in Calligaro's study were reported as 68, which is almost the same as that obtained in this study.[14]

Severe and critical COVID-19 patients have a hyperinflammatory state with the occurrence of cytokine storms due to dysregulation of the immune system. It is also associated with cardiopulmonary collapse and multiple organ failure. Clinically, an increase in pro-inflammatory cytokines and biomarkers such as IL-1, Il-6, IL-7, granulocyte-colony stimulating factor, macrophage inflammatory protein 1-α, tumor necrosis factor-α (TNF-α), CRP, PCT can be found. D-dimer and ferritin are associated with poor outcomes of increased mortality, more severe clinical course, the occurrence of ARDS, and the need for intensive care. Huang et al. concluded in their meta-analysis that cut-off values of increased PCT (≥0.5 mg/L), CRP (≥10 mg/L), and D-dimer (>0.5 mg/L) were associated with poor outcomes in COVID-19.[20]

This study found that the median values for urea, creatinine, aspartate transferase, alanine transferase, total bilirubin, and troponin I were in the normal range. Research on patients using HFNC by Wang et al. obtained a median creatinine value of 0.678 mg/dL and a total bilirubin value of 0.124 mg/dL.[7] Patel reported a higher mean creatinine of 2.61 mg/dL and a mean of aspartate and alanine transferase values of 56.8 U/L and 38.6 U/L. In comparison, Calligaro et al. reported a median creatinine value of 0.905 mg/dL.[9,14]

Abnormal values of blood chemistry parameters can indicate the severity of organ dysfunction. COVID-19 can cause damage to other organs outside the lungs due to the systemic inflammatory response.[21] Meta-analysis by Deng et al. found that 20% of COVID-19 patients had elevated transaminases, 8% had elevated total bilirubin, 34% had lower albumin values, and 8 % experienced an increase in creatinine values. Changes in these parameters are more clearly seen in patients who experience worsening clinical symptoms.[22]

This study showed significant differences in procalcitonin values between the groups with successful and failed outcomes at 24 hours, 7, 14, and 21 days. The troponin I and lactate values were also significantly different in the two groups at 24 hours and 7 days but were not significantly different at 14 days and 21 days of observation. Until now, there is no data comparing procalcitonin, troponin I, and lactate values in COVID-19 patients using HFNC, but it is known that increased PCT and troponin in COVID-19 patients can increase the risk of poor outcomes and death.[20,23]

The meta-analysis by Huang et al. found that an increase in PCT value of 0.5 mg/L in COVID-19 patients had consequences in the form of increased mortality, more severe clinical degrees, the

occurrence of ARDS, and the need for intensive care. In this study, the PCT values were relatively low (<0.5 mg/L) in both groups. In viral infections, the antiviral activity of interferon-γ will reduce PCT production. This explains why in uncomplicated COVID-19 patients, the PCT value is still within the reference value limit. Increased PCT on serial measurements may indicate the deteriorating clinical status of COVID-19 patients.[20]

In this study, the troponin values in the two groups were significantly different in the 24 hour and 7-day outcomes. However, they were still within the reference range, so the detected troponin levels may not reflect myocardial injury in most study subjects. Loss of significance at the 14 day and 21 day outcomes may have occurred due to failed outcomes in subjects with extreme troponin values. A meta-analysis by Zhao et al. found that 20.8% of COVID-19 patients had elevated troponin values above the reference value at the time of admission and described myocardial injury. An increase in troponin values at the beginning of hospitalization that exceeds the reference value can predict mortality risk.[23]

The CRP value in this study did not significantly differ in the outcome of 24 hours, 7, 14, and 21 days. Both groups had a mean CRP above 100 mg/L at the start of treatment, although the group with the failed outcome had a higher mean CRP value than the group with the successful outcome. Calligaro et al. found significantly different CRP values in patients who succeeded and failed after using HFNC for 6 hours. However, the CRP value gave significance as a predictor of HFNC failure at values > 500 mg/L. The CRP value of the failed group was also higher than that of the successful group (235 mg/L vs. 173 mg/L).[14]

This study found that D-dimer values were not significantly different for outcome of 24 hours, 7, 14, and 21 days. The median value of D-dimer in the group with successful outcomes was higher than in the failed group. Calligaro et al. reported significantly different D-dimer values between the successful and failed groups after 6 hours of HFNC; the successful group had a lower median D-dimer value (560 g/L vs. 1030 g/L) but only D-dimer value >5000 g/L, can be used as a predictor of HFNC failure.[14]

This study did not find significant differences in hemoglobin, leukocyte, neutrophil count, lymphocyte count, NLR, and platelet count. Both groups had almost the exact characteristics of hematological parameters. However, the group with failed outcomes had a median leukocyte, neutrophil count, higher NLR, and lower lymphocyte count than the group with a successful outcome. Although not statistically significant, Patel et al. and Calligaro et al. also found lower lymphocyte count values in patients who failed with HFNC.[9,14]

The characteristics of blood chemistry parameters often used as organ damage markers did not show significant differences in the group with successful and failed outcomes. However, the urea, creatinine, and transaminase values in the group with failed outcomes were higher than those with successful outcomes. Patel et al. and Calligaro et al. also reported similar results in baseline blood chemistry values of patients with HFNC.[9,14] The course of COVID-19 disease is dynamic and clinical deterioration may occur as the length of stay increases. It is possible that the values of blood chemistry parameters in the patients in this study would be different between the two outcome groups if serial examinations were performed.

The success of using HFNC on this study's 21st day of observation was 45.2%. Calligaro et al. reported successful use of HFNC (defined as patients who were not intubated and did not die) of 47%, while Patel et al. reported a 64.42% intubation prevention rate (requiring NIV or intubation). Moreover, Demoule et al. reported that 56% of patients with HFNC required intubation at 28 day follow-up.[8,9,14]

LIMITATIONS

This study was conducted retrospectively so that the quality of the data depends on the completeness of the medical record. Laboratory data also cannot be analyzed serially because examination intervals are not uniform. Prospective studies and serial laboratory studies are needed to

confirm the findings.

CONCLUSION

There were significant differences between the success and failure outcomes in patient COVID-19 using HFNC. Improvement of parameters such as respiratory rate, pulse rate, oxygen saturation, PaO2/Fio2, SpO2/FiO2, and ROX index indicated successful treatment of COVID-19 using HFNC.

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CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest.

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Original Article

Surfactant Protein D Levels in Cement Workers

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Abstract

Background: Pneumoconiosis occurs almost all over the world. Pneumoconiosis is a threat to cement workers. Serological abnormalities are observed in pneumoconiosis. Surfactant protein D (SP-D) levels were increased in workers exposed to silica. SP-D may be useful as a biomarker for the early diagnosis of pneumoconiosis but it has not been studied in Indonesia.

Methods: This cross-sectional study was conducted with consecutive sampling technique. The number of subjects was 61 people, consisting of 44 workers exposed to cement and 17 controls from September 2017 to March 2018. Serum level of SP-D was measured using ELISA method. Cement exposed workers were workers in the production area and workers in quarry areas.

Results: All of the study subjects were male (100%) with mean age of 42.5 years old. The youngest and oldest subjects were 21 and 55 years old, respectively. Majority of the subjects was in the normal weight group (47.7%). Based on smoking history, there were 26 subjects (59.1%) had never smoked, 12 subjects (27.3%) as smokers, and 6 subjects (13.6%) as former smokers. Duration of exposure <10 years was found in 9 subjects (20.5%) while exposure ≥10 years was observed in 35 subjects (79.5%). Good category of using self-respiratory safety instrument was observed in 5 subjects (11.4%), moderate category in 36 subjects (81.8%) and poor category in 3 subjects (6.8%). Mean serum SP-D levels in the exposed group was 111.027 ng/ml and in control group was 67.648 ng/ml. Serum SP-D levels were significantly higher in the exposed group than control group (*P*=0.014).

Conclusion: Serum SP-D levels was statistically higher in the exposed group than in control group.

Keywords: biomarker, cement worker, serum SP-D levels

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INTRODUCTION

The cement industry in Indonesia displays encouraging developments with increasing production output. This development will certainly be beneficial from an economic point of view, but the negative effects arose from these industrial developments will also have an impact on health.[1] The cement industry causes air pollution both inside and outside the work environment which has an influence on the respiratory system. Work environment factors are defined as potential sources of hazard that may occur in the work environment due to a work process.[2]

Air quality conditions in the work environment can play a role in occupational health. Several studies in cement factories that measured dust exposure, including a study in Tanzania, pointed out high levels of dust exposure in several work areas.[2] Study in Indonesia on 2006 obtained the highest dust levels in mining areas (20.23 mg/m^3), packing (18.47mg/m^3), and limestone crusher (14.98 mg/m^3). The results of this study indicated that there were several working areas in the cement factory with dust levels which did not meet the standard limit compared to the threshold value issued by the Minister of Manpower.[3]

Pneumoconiosis is an occupational lung disease caused by deposition of dust in the lungs and the reaction of lung tissue due to dust exposure.[4] Pneumoconiosis occurs almost all over the world and is a problem that threatens the workers. Data on the prevalence of pneumoconiosis, including silicosis, vary from country to country in the world. The Pathology Automation System (PATHAUT) database, a record of data from pathologists in South Africa, reported autopsy results on the deaths of mining workers with occupational lung disease. In 2014 there were 206 cases of silicosis (19.3% of all autopsy cases).[5] Data from World Health Organization (WHO)

in 2002 reported that 1.288.000 cases of pneumoconiosis occur every year.[6]

In Indonesia, various studies on the effect of dust on workers' health have been carried out, but national data on the prevalence of pneumoconiosis in Indonesia are currently not available. Reports of the effects of cement dust vary. Research on residents living near cement factories by Setiawan and Musawaris mentioned a significantly higher prevalence of impaired lung function and chronic bronchitis in exposed areas than in unexposed areas.[7,8]

Fordiastiko in 2001 revealed that about 9.4% of the chest x-rays (CXR) of cement workers were suspected of having pneumoconiosis with also pulmonary function abnormalities in the form of restriction (7.3%) and obstruction (19.4%).[9] Wihastuti did not find pneumoconiosis in their study.[10] Yunus et al. in 2007 obtained radiological suspicion of pneumoconiosis in 0.5% of cement factory workers.[11]

Efforts to look for the possibility of finding silicosis earlier have begun to be developed. Several serological abnormalities can be found in patients with silicosis, but none can diagnose this disease, and tests performed to detect abnormalities are not routinely carried out.[12] Study by Wang et al. in 2007 found that serum level of Clara cell protein (CC16) was decreased in workers exposed to silica, while the serum level of surfactant protein D (SP-D) was increased. Serum CC16 and SP-D levels could be used as biomarkers for the early diagnosis of silicosis.[13] Study on differences in serum surfactant levels of workers exposed to industrial dust and those who are not exposed is still not widely known even in Indonesia; therefore, this study was proposed and aimed to determine the difference in serum SP-D levels of cement factory workers and the normal population.

METHODS

This was a cross-sectional study. The sampling consecutive of study subjects was conducted at PT. Semen Tonasa Pangkep, South Sulawesi from September 2017 to March 2018. Study subjects were cement workers of PT. Semen Tonasa who worked in the raw material and production areas. Inclusion criteria for study case were those who worked in the raw material and production work areas, have worked for at least 5 years, male, were willing to participate in the study and signed a letter of consent, were willing to have their blood samples taken and followed the research procedures.

Inclusion criteria for control subjects were not working as cement workers, not living in the surrounding area near the factory, willing to participate in the study and signed the consent letter, willing to have their blood samples taken and followed the research procedures. Exclusion criteria were having a history of pulmonary TB, bronchiectasis, pneumonia, asthma, COPD, lung tumors, and corticosteroid treatment.

RESULTS

The number of subjects in this study was 94 subjects. There were 2 study subjects who were dropped out, 21 study subjects excluded due to incomplete CXR data (20 subjects) and a suspicion of pulmonary TB on CXR (1 subject).

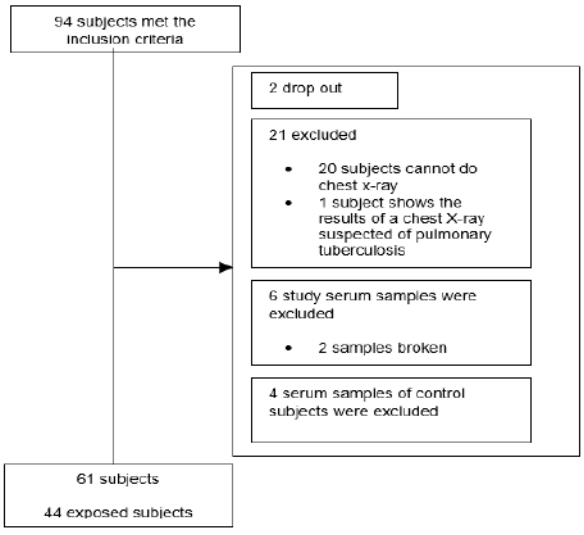

Figure 1. Subject flow that meets the research criteria

About 6 samples of study subjects were excluded because damaged samples (2 samples) and damaged labels (4 samples). There were 4 excluded samples of control subjects due to damaged labels. The total study subjects who met the

criteria were 44 people, while the control subjects were 17 people, as seen in the following (Figure 1).

Table 1. Subjects characteristics

Variable	Exposed (n=44) n (%)	Control (n=17) n (%)	Total (n=61) n (%)
Gender			
Male	44 (100)	17 (100)	61 (100)
Female	0 (0.0)	0 (0.0)	0 (0.0)
Age			
<40 years	11 (25)	15 (88.2)	26 (42.6)
≥40 years	33 (75)	2 (11.8)	17 (57.37)
Education			
Low	5 (11.4)	0 (0.0)	5 (8.2)
Moderate	29 (65.9)	0 (0.0)	29 (47.5)
High	10 (22.7)	17 (100)	27 (44.3)
BMI			
Less	1 (2.3)	0 (0.0)	1 (1.63)
Normal	21 (47.7)	9 (52.9)	30 (49.2)
Overweight	14 (31.8)	3 (17.6)	17 (27.9)
Obesity	8 (18.2)	5 (29.4)	13 (21.3)
Smoking History			
Non-smokers	26 (59.1)	17 (100)	43 (70.5)
Ex-smokers	6 (13.6).	0 (0.0)	6 (9.8)
Smokers	12 (27.3)	0 (0.0)	12 (19.7)
IB			
Mild	10 (22.7)	0 (0.0)	10 (16.4)
Moderate	8 (18.2)	0 (0.0)	8 (13.1)
Heavy	0 (0.0)	0 (0.0)	0 (0.0)
PPE			
Good	5 (11.4)	0 (0.0)	5 (8.1)
Moderate	36 (81.8)	0 (0.0)	36 (59)
Bad	3 (6.8)	0 (0.0)	3 (5)
Length of Work			
<10 years	9 (20.5)	0 (0.0)	9 (14.7)
≥10 years	35 (79.5)	0 (0.0)	35 (57.37)
Respiratory Complaints			
Existed	2 (4.5)	0 (0.0)	2 (3.27)
None	42 (95.5)	0 (0.0)	42 (68.8)
Working Areas			
Cement Packer	6 (13.6)	0 (0.0)	6 (14.8)
Kiln	4 (9.1)	0 (0.0)	4 (6.6)
Crusher	10 (22.7)	0 (0.0)	10 (16.4)
Finish mill	6 (13.6)	0 (0.0)	6 (9.8)
Quarry	5 (11.4)	0 (0.0)	5 (8.1)
Raw mill	2 (4.5)	0 (0.0)	2 (3.27)
Silica crusher	6 (13.6)	0 (0.0)	6 (9.8)
Others	5 (11.4)	0 (0.0)	5 (8.2)

All subjects were male (100%). The mean age of the study subjects was 42.5 years, with the youngest subject being 21 years old and the oldest being 55 years old. Subjects in the age group <40 years were 11 subjects (25%), while in the age group >40 years were 33 subjects (75%). Most of the subjects were at moderate education (65.9%), followed by high education level in 10 subjects (22.7%) and low education level in 5 subjects (11.4%).

In general, almost all study subjects had no respiratory complaints (95.5%). In this study, the study subjects worked in 8 areas, namely the cement packing area for as many as 6 subjects (13.6%), the kiln area (an installation that produces cement which has areas such as calcination area, transition area, combustion area and cooling area) for as many as 4 subjects (9.1%), the crusher area for as many as 10 subjects (22.7%), the finishing mill area for as many as 6 subjects (13.6%), the quarry area for 5 subjects (11.4%), the raw mill area for 2 subjects (4.5%), the silica crusher area for 6 subjects (13.6%), and other areas for 5 subjects (11.4%). Table 1 shows the characteristics of the subjects in this study.

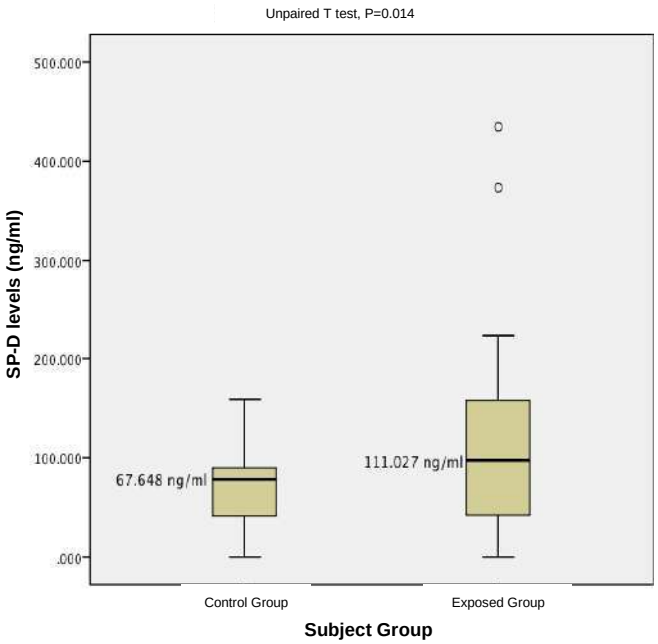

Figure 2. Box plot graph of SP-D levels in the exposed and control groups

In this study, the mean SP-D levels in the exposed group and in the control group were 111.027 ng/ml and 67.648 ng/ml, respectively. Figure 2 is a box plot graph which describes the levels of SP-D in the exposed group and the control group. The difference in SP-D levels between the exposed group and control group was statistically significant with *P*=0.014, as observed in Table 2.

Table 2. Serum SP-D levels based on the exposed group and the control group

	Research Group	n	Mean	SD	*P**
SP-D (ng/ml)	Exposed	44	111.027	91.654	0.014
	Control	17	67.648	41.092	

Note= *Unpaired T-test

This study obtained that the mean serum SP-D level in the <40 years age group was lower (87.624 ng/ml) compared the age 40 years (118.827 ng/ml). The correlation between serum SP-D levels and the age group of the study subjects was not statistically significant (*P*=0.241), which can be seen in Table 3.

From table 3, the serum SP-D levels in low BMI group, normoweight, overweight and obese groups were 434.693 ng/ml, 122.357 ng/ml, 94.183 ng/ml, and 70.300 ng/ml, respectively. The correlation between serum SP-D levels and the BMI group of study subjects was statistically significant (*P*=0.001).

The mean results of serum SP-D levels in the mild IB group and the moderate IB group were 74.947 ng/ml and 106.264 ng/ml. The association between SP-D levels and IB was not statistically significant (*P*=0.324). In this study, the mean serum SP-D levels were 126.368 ng/ml in the non-smoker group, 51.584 ng/ml in the ex-smoker group, and 107.506 ng/ml in the smoker group. The correlation between serum SP-D levels and smoking history was not statistically significant (*P*=0.198).

In this study, the mean SP-D levels among subjects with good PPE use, moderate PPE use and bad PPE use were 66.782 ng/ml, 105.702 ng/ml, and 248.656 ng/ml, respectively. The correlation between SP-D levels and PPE use was statistically significant (*P*=0.016). Based on the post hoc analysis, it was found that the association between good PPE use and moderate PPE use was not significantly different with *P*=1.000, but the association between good PPE use and bad PPE use was significantly different with *P*= 0.016.

Mean SP-D level for subjects with <10 years length of work was 65.425 ng/ml, while those with ≥10 years length of work group was 112.753 ng/ml. The correlation between SP-D levels and the duration of the workgroup was statistically significant with *P*=0.015, and it can be observed in Table 3.

Table 3. Correlation of Serum SP-D Levels with Age, BMI, Smoking History, IB, PPE and Length of Work

Variable	SP-D levels (ng/ml)				
	n	Mean	SD	Post Hoc	*P*
Age					
<40 years	11	87.624	64.904	----	0.241*
≥40 years	33	118.827	98.594	----	
BMI					
Low	1	434.693	----		
Normoweight	21	122.357	83.099	----	0.001**
Overweight	14	94.183	58.176	----	
Obese	8	70.300	88.172	----	
Smoking History					
Non-smoker	26	126.368	108.552	----	
Ex-smoker	6	51.584	61.327	----	0.198**
Smoker	12	107.506	43.021	----	
IB					
Mild	26	126.368	108.552	----	
Moderate	10	74.947	46.018	----	0.324**
Heavy	8	106.264	63.532	----	
PPE					
Good	5	66.782	56.977	Ref***	
Moderate	36	105.702	105.702	1.000***	0.014**
Bad	3	248.656	248.665	0.016***	
Length of Work					
<10 years	9	65.425	44.589	----	0.015*
≥10 years	35	112.753	97.285	----	

Note = *Unpaired T-test; **One-way anova test; ****Post hoc*

Table 4. Description of SP-D Serum Levels by Work Area

Work Area	SP-D levels (ng/ml)					
	N	Mean	Med	SD	Min	Max
Cement packer	6	130.7	129.347	18.077	108.8	158.12
Kiln	6	74.48	80.284	24.791	40.1	97.260
Crusher	12	108.7	127.484	89.05	0.000	223.12
Finishing mill	10	118.5	109.059	63.443	26.4	199.93
Quarry	5	115.1	45.092	180.66	4.10	434.69
Silica crusher	9	128.1	74.695	140.03	6.17	373.41
Raw mill	8	45.7	45.713	2.634	43.85	47.576
Others	7	113.4	111.337	69.192	43.85	210.28

DISCUSSION

This was the first study in Indonesia regarding serum SP-D level as a biomarker of occupational lung disease in cement workers. Previous studies have investigated serum SP-D level as a biomarker for various lung diseases, including ARDS, pulmonary fibrosis, alveolar proteinosis, pulmonary tuberculosis, sarcoidosis, asthma, pneumonia, COPD, bronchiectasis, panbronchiolitis, and silicosis.[14]

All subjects (100%) in this study were male. This was because there were no female workers in the affordable population. In this study, the highest mean serum SP-D level was obtained in subjects working in cement packer area, namely 130.796 ng/ml. The difference in surfactant levels by gender was not fully understood, but the study from Sorensen GL et al. reported that SP-D levels were increased in males.[15]

The mean age of the study subjects was 42.5 years, there were more study subjects in the age group ≥40 years (75%). The mean serum SP-D level was higher in the ≥40 years age group (118.827 ng/ml) than in the <40 years age group. In these two age groups, there were differences in SP-D levels although statistically, it was not significant (*P*=0.241). Study subjects in the age group ≥40 years had longer working hours than those <40 years, this could possibly be the cause of differences in SP-D levels. Sorensen GL et al. mentioned that SP-D levels escalated with increasing age.[15]

Majority of the study subjects had no respiratory complaints (95.5%). Only 2 subjects had respiratory complaints. These subjects obtained SP-D levels of 149.013 ng/ml and 15.696 ng/ml. Both had normal chest X-rays, so they were not excluded from the study. One subject had cough for 2 weeks, while the other had cough for 5 days.

About 26 subjects (59.1%) were non-smokers, followed by 12 active smokers (27.3%) and 6 ex-smokers (13.6%). The highest mean serum SP-D level was observed in the non-smoker group (126.368 ng/ml), while the lowest was in the ex-smoker group (51.584 ng/ml). The relationship between serum SP-D levels and smoking history was not statistically significant (*P*=0.198). The mean level of SP-D in the former smokers was lower than in other groups. This result might be influenced by nutritional status because most former smokers had nutritional status in the obesity category. The SP-D levels among obese subjects were found to be lower than other categories. The results obtained in the smoking and non-smoking groups were also likely to be influenced by nutritional status because most subjects of the smoking and non-smoking groups had good nutrition.

Injury to AT-II epithelial cells will lead hyperpermeability of the epithelial-endothelial barrier, leading to an increase in blood surfactant levels. Cigarette smoke can cause injury to AT-II epithelial cells so that low molecular weight surfactant proteins such as SP-A will escape into the blood vessels before SP-D, which has a larger molecular weight. This result is in line with the study of Kobayashi et al. which showed that it was statistically significant for serum SP-A levels but not significant for SP-D levels.[16]

Among the smokers and ex-smokers, mild IB was found in 10 subjects (22.7%), moderate IB in 8 subjects (18.2%), however, severe IB was not obtained in study subjects (0.00%). The mean level of SP-D in the moderate IB group (106.264 ng/ml)

was higher than in the mild IB (74.947 ng/ml). Nevertheless, the correlation between SP-D levels and IB was not statistically significant (*P*=0.324). This was in line with the study of Zaky et al. Higher mean SP-D level was observed in subjects with moderate IB.[17] Kobayashi explained that surfactant protein levels could predict AT-II cell epithelial cell injury induced by cigarette smoke.[16]

Moderate (fair) category of adherence in PPE use was found most in 36 subjects (81.8%), followed by 5 subjects in the good category (11.4%) and the bad category in 3 subjects (6.8%). The highest mean SP-D level was obtained in bad PPE use (248.656 ng/ml), followed by moderate (105.702 ng/ml) and good PPE use (66.782 ng/ml). The correlation between SP-D levels and PPE use was statistically significant (*P*=0.016), however, the post hoc analysis mentioned that good PPE use and moderate PPE use were not significantly different (*P*=1.000). Nonetheless, good PPE use and bad PPE use were significantly different (*P*=0.016). The use of masks is one of the efforts to prevent occupational diseases in the work environment which protects workers from the hazard of exposure to cement dust. According to PPE use in the form of masks, good adherence showed lower results than poor adherence.[18]

Most of the subjects had length of work ≥10 years (79.5%). The correlation between SP-D levels and length of work was not statistically significant, (*P*=0.292). Mean SP-D level in subjects with working duration ≥10 years was higher (112.753 ng/ml) than those <10 years (65.426 ng/ml). Although not statistically significant, the increase in SP-D levels was parallel with the increase in length of work over 10 years. The longer the exposure lasts, the number of particles which settle in the lungs also elevates. Every inhalation of 500 particles per cubic millimeter of air induces the alveoli to receive at least 1% of the particles.[27]

If the concentration reaches 1000 particles per cubic millimeter, 10% of that amount will be deposited in the lungs. Concentrations exceeding 5000 particles per cubic millimeter are often associated with pneumoconiosis. Pneumoconiosis due to dust will occur after the patient has been in contact with dust for a long time.[19] Abnormalities are rare when exposure is still less than 10 years.[20] In this study, all subjects were not proven to have pneumoconiosis because it might be related to the concentration of inhaled dust exposure, and there was still an effect of medium category of mask adherence. Although the study subjects did not have pneumoconiosis, SP-D levels pointed out an increase in the results with the escalating duration of exposure.

The work area was one of the factors which could affect the occurrence of occupational lung disease. Portland cement will not cause silicosis because it does not contain free silica, but the manufacture of cement uses a mixture of silica sand containing free silica with varying levels so that silicosis can occur in workers in the raw material area, cleaners, workers in closed rooms and slag milling.[16,21] Although all subjects did not exhibit silicosis, the SP-D levels in the cement packer, finish mill, silica crusher, crusher areas were quite high compared to subjects in the control group.

The difference in SP-D levels in the exposed and control groups was statistically significant with a *P*-value of 0.014. This could be influenced by adherence to PPE, nutritional status, and the length of work. Studies on differences in SP-D levels in lung disease with control groups have been carried out in various diseases. Study on subjects with fibrotic lung disease obtained a mean SP-D level of 339 ng/ml while the control group had 66 ng/ml.[14]

Subjects with alveolar proteinosis, pulmonary TB, sarcoidosis had mean SP-D levels of 461 ng/ml, 119 ng/ml, and 104 ng/ml, respectively, while it was 66 ng/ml in the control group.[14] A study from Wang et al. of factory workers exposed to silica, factory workers with suspected silicosis, and factory workers diagnosed with silicosis mentioned that the SP-D results were significantly different on the suspected silicosis group and the silicosis group compared to controls.[13]

The difference of SP-D levels in the control group and the group exposed to cement dust that was not diagnosed with pneumoconiosis were found to be statistically significant. The mechanism by which SP-D is present in serum is stated by several hypotheses,

namely: elevated apoprotein concentration gradient between the alveoli and the circulation, increased pulmonary capillary permeability, destruction of the barrier between the alveolar epithelium and the endothelium epithelium, i.e injury to the basement membrane and escalated clearance of surfactant from the circulation. The detectable level of SP-D in serum can be used as a non-invasive diagnostic tool in several lung diseases.[21]

The highest dust content was observed in the cement packer area of 31.45 mg/m^3, followed by the crusher area of 9.78 mg/m^3, the finishing mill area of 4.41 mg/m^3, and the raw mill area of 0.52 mg/m^3. Previous study in Indonesia revelaed that the dust content in cement packer area was 18.47 mg/m^3, in mining area was 20.23 mg/m^3, and in crusher area was 14.98 mg/m^3, while the raw mill and finishing mill areas were both <10 mg/m^3.

In cement packer area, there was an increase in dust content. Elevated levels of dust which exceed the NAV can be a risk factor for pneumoconiosis in cement workers. Tungu mentioned that with a decrease in total dust content, there was also an increase in lung function among cement workers.[22]

LIMITATION

This study employed limited population for control subjects even though it was in accordance with the operational definition. All research subjects were listed as workers working in the production and raw material areas, but there were still cement workers who were not registered as employees of PT Tonasa in the work area, so that researchers could not enroll them as study samples. Researchers could not select the location of work areas to evaluate the dust content.

CONCLUSION

Most subjects aged ≥40 years with good nutritional status, were non-smokers, had medium category of PPE use and mostly had length of work ≥10 years. The difference of SP-D levels in the exposed group compared to the control group was statistically significant. The correlations of serum SP-D levels to age, smoking history, IB, length of work were not statistically significant among the study subjects.

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CONFLICT OF INTEREST

None.

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Original Article

The Effect of N-Acetylcysteine as Adjuvant Therapy of Hypoxemia in COVID-19 Patients, Assessed by Interleukin-6 Level and PaO_2/FiO_2 Ratio

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Abstract

Background: Interleukin 6 (IL-6) is a cytokine that plays an essential role in lung damage and mortality. Arterial-to-inspired oxygen (PaO_2/FiO_2) ratio, also known as the Horowitz index, is a measure of hypoxemia in respiratory failure. N-Acetylcysteine (NAC) might be helpful in managing coronavirus disease 2019 (COVID-19) patients by decreasing the cytokine storm, which will lead to a decrease in disease severity. This study aims to analyze the effect of NAC as adjuvant therapy on IL-6 level and PaO_2/FiO_2 ratio in COVID-19 patients.

Methods: This is a quasi-experimental, non-equivalent control group designed study of confirmed COVID-19 patients moderate to critical in Saiful Anwar Hospital Malang. Seventy-five patients received NAC intravenously 5000mg/72 hours as adjuvant therapy for seven days, and 16 subjects in the control group. IL-6 level and PaO_2/FiO_2 ratio were measured on day one and day 8 in both groups from blood samples. Wilcoxon, Mann-Whitney U Test, and Pearson correlation were conducted for statistical analysis.

Results: The decrease in IL-6 level on days 1 to 8 in the NAC group is significantly lower (94.49±253.51) than in the control group (P=0.002). The increase in PaO_2/FiO_2 ratio from day 1 to day 8 in the NAC group is significantly improving (126.94±76.05), the same as the control group (P<0.001). There is a weak correlation between IL-6 level and PaO_2/FiO_2 ratio after administration of NAC (r=0.154, P=0.186).

Conclusion: There is a significant decrease in IL-6 level after administration of NAC. NAC has no significant effect on hypoxemia in COVID-19 patients.

Keywords: IL-6, N-acetylcysteine, PaO_2/FiO_2 ratio

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INTRODUCTION

On December 31, 2019, China reported a mysterious case of pneumonia of unknown origin. Samples isolates were studied, and the results showed the presence of coronavirus infection, a new type of beta-coronavirus named 2019 novel Coronavirus (2019-nCoV). On February 11, 2020, World Health Organization named the new virus Severa Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), and the disease was named Coronavirus disease 2019 (COVID-19).[1–3]

The total global confirmed cases of COVID-19 as of March 10, 2021, were 117,424,768 cases, with 2,608,231 deaths (CFR 2.2%) in 222 infected countries and 187 local transmission countries. The list of countries affected by COVID-19 is growing every day. In Indonesia alone, until March 10, 2021, there were 1,398,578 confirmed cases and 37,932 deaths due to COVID-19.[4]

In COVID-19 patients, IL-6 levels increase sharply, and this cytokine plays a role in the induction of B lymphocyte differentiation and antibody production, as well as the proliferation and differentiation of T lymphocytes. Cytokine storms in COVID-19 can increase vascular permeability. Fluid and blood cell movement in the alveoli will thus result in acute respiratory distress syndrome (ARDS), which can lead to death. The PaO_2/FiO_2 ratio assesses hypoxemia at different FiO_2 levels. The average ratio varies from 300 to 500 mmHg. Shock and organ

failures—such as the kidneys, heart, lungs, and liver, severely damaged due to a cytokine storm—are caused by an increase in inflammatory cytokines, including IL-6, IL-1β, TNF-, IL-8, IL -2, IL-17, G-CSF, GMCSF, CXCL10, CCL2, CCL3.[5,6]

IL-6 (Interleukin-6) is a pleiotropic cytokine with a wide range of biological activity, which affects immune regulation, hematopoiesis, inflammation, and oncogenesis. IL-6 levels increase rapidly in severe and critical COVID-19 patients. Coomes' systematic review and meta-analysis showed that IL-6 levels were significantly elevated in COVID-19 patients and were associated with poor clinical outcomes.[7–9]

There is currently no definitive therapy for COVID-19. The primary strategy for treating COVID-19 is symptomatic and supportive care by monitoring vital signs, maintaining oxygen saturation, and treating complications (e.g., secondary infections and organ failure).[10] At present, there is yet a specific antiviral targeting the virus.[11]

N-acetylcysteine (NAC) is an antidote drug against paracetamol poisoning, first discovered in 1960. It has been widely used since the 1970s as a phlegm-thinning drug. N-acetylcysteine is also a precursor of Glutathione — an excellent antioxidant and free radical scavenger in the body. Therefore, NAC has as potential as COVID-19 therapy through several possible mechanisms viz; increasing Glutathione, increasing T-cell response, and modulating inflammation. In an in-vitro study by Guo et al., NAC was proven to reduce IL-6 levels. Another study by Suter et al. proved that administration of NAC could improve the PaO_2/FiO_2 ratio in ARDS patients.[12–14]

Based on the theory and several supporting journals, the author was interested in the effect of giving NAC as adjuvant therapy on IL-6 levels and the PaO_2/FiO_2 ratio in COVID-19 patients at RSSA.

METHODS

This quantitative research was conducted using a quasi-experimental non-equivalent control group design. The study was conducted from June 2020 to July 2021 on confirmed COVID-19 subjects treated in the INCOVIT room of Dr. Saiful Anwar Regional General Hospital. The inclusion criteria in this study were patients who were: confirmed to have COVID-19 based on PCR, within moderate to critical stages, aged more than 14 years old, and were willing to participate in the study by signing an informed consent form. Subjects who were not treated or died before being treated in the INCOVIT room of dr. Saiful Anwar's hospital and were pregnant, asymptomatic, or confirmed with a mild case of COVID-19 were not included in this study.

The minimum number of samples is 16 for each dependent variable. The number of samples in the non-NAC group was less due to the difficulty of the study in obtaining the number of populations that agreed not to be given NAC because, as the guidelines developed, NAC has been included in the clinical practice guideline.

Samples were obtained by consecutive sampling that met the inclusion and exclusion criteria. Standard therapy provided according to clinical practice guidelines of dr. Saiful Anwar Hospital Malang refers to the Indonesia's local guideline and the decree of the minister of health, which develops dynamically in the research process: 1) Chloroquine phosphate, 500 mg oral/12 hours (days 1-3) followed by 250 mg/12 hours (days 4-10) OR Hydroxychloroquine dose 400 mg oral/ 24 hours (for five days); 2) Azithromycin 500 mg oral/ 24 hours (for five days) or levofloxacin 750 mg intravenous/24 hours (5 days); 3) Hydrocortisone 100 mg intravenous/24 hours (first three days); 4) Treatment of comorbidities and existing complications. Ninety-one subjects were measured for the PaO_2/FiO_2 ratio and the level of IL-6 on the 0th and eighth days after receiving NAC 5000mg/72 hours.

Data processing and analysis are carried out using IBM SPSS software version 16.0. Differences in IL-6 on D1 and D8 were analyzed by paired T-test or Wilcoxon. Comparison of IL-6 levels at D1 and D8 between the group given NAC and the group not was analyzed by independent T-test or Mann Whitney. The PaO_2/FiO_2 ratio comparison after given NAC between D1 and D8 was analyzed using paired T-test

or Wilcoxon. The comparison of PaO_2/FiO_2 at D1 and D8 between the group given NAC and the group was not analyzed using the independent T-test or Mann Whitney. The relationship between changes in IL-6 levels and the PaO_2/FiO_2 ratio was analyzed using the Pearson correlation test.

RESULTS

This study was carried out from June 2020 to July 2021 in the INCOVIT room of dr. Saiful Anwar hospital, Malang. Ninety-one subjects who met the inclusion and exclusion criteria and were willing to participate in the study by signing an informed consent were found.

There was a total of 91 subjects —16 in the group not given with NAC and 75 in the group given with NAC. The demographic characteristics of the two groups can be seen in Table 1. The median age of patients in the NAC group was 53.12 years, and this was not much different from the median in the group without NAC, which was 52.31 (*P*>0.05) years. Males dominated both groups — 58.7% in the NAC group and 75% in the non-NAC group, with *P*=0.225, and thus, it could be concluded that both groups had no significant difference.

The highest proportion of disease severity in the NAC group was moderate (58.7%), while in the non-NAC group was severe (68.8%). However, with *P*=0.526, the degree of severity between the NAC group and the group without NAC was not significantly different. Only 81.3% of patients in the NAC group experienced shortness of breath, while those in the non-NAC group all experienced shortness of breath (100%).

The test results obtained *P*=0.062, thus, indicating that there was no significant difference in the complaints of shortness of breath between both groups. As much as 80% of the subjects in the NAC group showed a symptom of cough, while in non-NAC, 100% of the subjects did. The test results obtained *P*=0.052, indicating that the cough symptom does not significantly differ between both groups. As much as 70.6% of the subjects in the NAC group showed a symptom of fever, and in non-NAC, all the subjects did (100%).

Table 1. Demographic Profile of Research Subjects

Variable and Category	NAC group (n=75)	non-NAC group (n=16)	*P*
Age (mean±SD), normally distributed	52.31±11.52	53.12±11.18	0.795
Age [median (min-max)]	56,00 (24–76)	52,50 (25–69)	
Sex			
Male	44 (58,7%)	12 (75%)	0.225
Female	31 (41,2%)	4 (25%)	
Severity			
Mild	33 (44,0%)	3 (18,8%)	
Severe	21 (28,0%)	11 (68,8%)	0.526
Critically ill	21 (28,0%)	2 (12,5%)	
Symptoms			
Shortness of breath	61 (81,3%)	16 (100%)	0.062
Cough	60 (80%)	16 (100%)	0.052
Fever	53 (70,6%)	16 (100%)	0.013
Anosmia/Ageusia	15 (20%)	10 (62,5%)	0.001
Indigestion	42 (56%)	10 (62,5%)	0.635
Smoking/History of smoking			
Yes	35 (46,67%)	10 (62,5%)	0.253
No	41 (54,67%)	6 (37,5%)	
Comorbid			
Yes	35 (46,67%)	7 (43,75%)	0.833
No	41 (54,67%)	9 (56,25%)	
Outcome			
Recovered	64 (85,3%)	15 (93,8%)	0.369
Dead	11 (14,7%)	1 (6,3%)	

The test results obtained *P*=0.013, thus, indicating that complaints of fever between both groups have a significant difference. As much as 20% of patients in the NAC experienced symptoms of anosmia/ageusia, and in the group, without NAC, there were 62.5% did. The test results obtained *P*=0.001, thus, indicating a significant difference between the symptoms of anosmia/ageusia in both groups. 56% of patients in the NAC group experienced indigestion, and in the group, without NAC there were 62.5% did. The test results obtained *P*=0.635, thus, indicating no significant difference between the complaints of indigestion in both groups.

There are 46.67% of the subjects in the NAC group had a smoking history. The test results obtained *P*=0.253, thus, indicating no significant difference in the smoking history between the group given with NAC and the group not.

The distribution of subjects with comorbidities in the two groups was similar and could be called balanced (46.67% in the NAC group and 43.75% in the non-NAC group). The test results obtained *P*=0.833, thus, indicating that the history of comorbidity between the NAC group and the group without NAC did not differ significantly. The most remarkable outcome in both groups was the proportion of patients who recovered (85.3% in the NAC group and 93.8% in the non-NAC group). The test results obtained *P*=0.369, thus, indicating no significant difference between the outcome of both groups.

Table 2. Comparison of TNF-α levels between D1 and D8

Variable	D1 Median (min-max)	D8 Median (min-max)	*P*
IL-6 with NAC (pg/ml)	121.62 (7.09–1058.32)	18.91 (1.12–970.15)	0.001
IL-6 without NAC (pg/ml)	41.33 (2.72–524.76)	34.68 (3.36–515.74)	0.408

As seen in Table 2, of 75 patients who were given adjuvant NAC therapy, the IL-6 levels on the first day had a median value of 121.62 pg/ml, and on the eighth day, the median value was 18.91 pg/ml. The p-value was 0.001, thus, indicating a significant difference in the levels of IL-6 in the group given adjuvant NAC therapy between D1 and D8, where on the eighth day after adjuvant NAC therapy, the levels of IL-6 had a median decrease of 102.71 pg/ml.

From the 16 patients in the group without NAC, the median value of IL-6 on the first day they had IL-6 was 41.33 pg/ml, and on the eighth day, the median value was 34.68 pg/ml. The Wilcoxon test resulted in *P*=0.408, thus, indicating no significant difference in the IL-6 levels between D1 and D8 in the group not given NAC. Although, on the eighth day after adjuvant NAC therapy, IL-6 decreased in value with a difference of 6.65 pg/ml in the median, the median value of IL-6 on D1 and D8 did not differ too much; thus, the test results showed no significant difference.

Table 3. Comparison of IL-6 levels on D1 and D8 between the group given NAC and the group not

Variable	Non-NAC group Median (min-max)	NAC group Median (min-max)	*P*
IL6 (pg/ml) on D1	41.33 (2.72–524.76)	121.62 (7.09–1058.32)	0.015
IL-6 (pg/ml) on D8	34.68 (3.36–515.74)	18.91 (1.12–970.15)	0.654

As seen in Table 3, the IL-6 levels on the first day of the 91 subjects showed *P*=0.015, thus, indicating a significant difference in IL-6 levels on the first day between NAC and non-NAC groups, with a median difference of IL-6 between the two groups on D1 of 80.28 pg/ml. This result concludes that the levels of IL-6 on the first day in the NAC group were higher than in the non-NAC.

As for testing IL-6 levels on day 8, of 91 samples, *P*=0.654 was obtained, thus, indicating no significant difference in IL-6 levels on the eighth day between the groups given NAC and the groups not. The median difference in IL-6 between the two groups on the first day was not too vast; thus, the difference was not statistically significant.

Table 4. Comparison of PaO2/FiO2 between D1 and D8

Variable	D1	D8	*P*
PaO_2/FiO_2 with NAC (mmHg)	182.18±78.28	309.12±68.42	<0.001
PaO_2/FiO_2 without NAC (mmHg)	171.46±67.89	296.26±74.97	<0.001

As seen in Table 4, from 75 samples of patients who were administered with NAC, the PF ratio on the first day had an average of 181.18 mmHg, and on the eighth day, the average ratio was 309.12 mmHg. The paired T-test resulted with *P*<0.001, thus, indicating a

significant difference in the PF ratio of the group given NAC between D1 and D8, where on the eighth day after adjuvant NAC therapy, the PF ratio increased by 136.94 mmHg.

Sixteen patients in the group without NAC had a PaO_2/FiO_2 ratio with an average value of 171.46 mmHg on the first day, and on day eight, the average value became 296.26 mmHg. The Wilcoxon test resulted with $P<0.001$, thus, indicating a significant difference in the PaO_2/FiO_2 NAC group between D1 and D8. For the eighth day after adjuvant therapy, the NAC PaO_2/FiO_2 increased in value with an average of 124.79 mmHg.

Table 5. Comparison of PF ratio between D1 and D8 between the group given NAC and the group not

Variable	Non-NAC group	NAC group	*P*
PF ratio (mmHg) on D1	171.46±67.89	182.18±78.28	0.613
PF ratio (mmHg) on D8	296.26±74.97	309.12±68.42	0.504

As seen in Table 5, the PF ratio on the first day of the 91 subjects had $P=0.613$, thus, indicating no significant difference in the PF ratio on the first day between the group given NAC and the group not. Although the median difference in the PF ratio between the two groups on the first day was 11.76 units, this difference is not too vast; thus, the test results showed no significant difference.

As for the PF ratio on day 8, of 91 subjects, $P=0.504$ was obtained, thus, indicating no significant difference in the PF ratio on the eighth day between the group given NAC and the group not. Although the median difference in the PF ratio between the two groups on the eighth day was 19.67 mmHg, this difference is not too vast; thus, the test results show no significant difference.

As for the relationship between changes in IL-6 levels and changes in the PF ratio of COVID-19 patients after administration of adjuvant NAC therapy, the correlation coefficient value is 0.154 with a significance value $P=0.186$, thus, indicating no positive and significant correlation between changes in IL-6 levels and changes in the PF ratio of COVID-19 patients after administration of adjuvant NAC therapy. In other words, the changes in IL-6 levels in COVID-19 patients in the group receiving adjuvant NAC therapy did not affect the changes in the PF ratio.

The effects of changes in IL-6 levels and changes in the PF ratio of COVID-19 patients after administration of adjuvant NAC therapy, in accordance to the results of this study, could be depicted in the form of a linearity graph as shown in Figure 1.

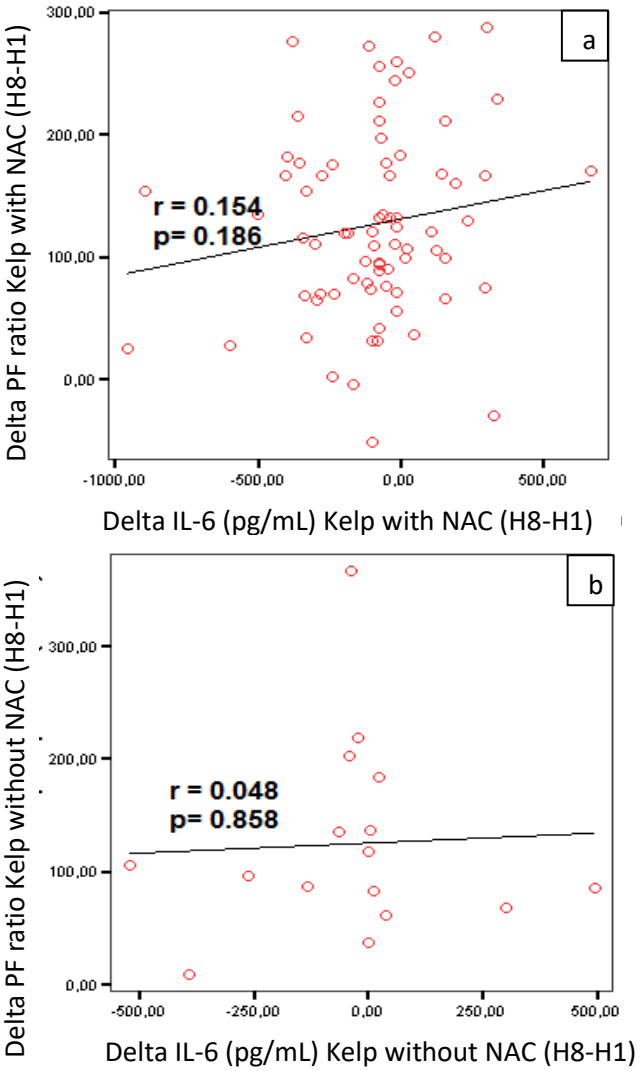

Figure 1. Linearity graph between changes in IL-6 levels and changes in the PF ratio of COVID-19 patients in a) the group with adjuvant NAC therapy; b) the group without adjuvant NAC therapy

Based on the linearity graph above, it can be seen that the regression line between changes in IL-6 levels and changes in the PF ratio of COVID-19 patients after administration of NAC adjuvant therapy points to the top right. These findings prove the linearity of IL-6 levels with changes in the PF ratio of COVID-19 patients after administration of adjuvant NAC therapy. However, because the test results

obtained insignificant results, it can be concluded that the high and low changes in IL-6 levels in COVID-19 patients in the group with NAC adjuvant therapy did not affect the high or low changes in the PF ratio.

These results prove the hypothesis—that the correlation test between changes in IL-6 levels (delta IL-6) and changes in the PF ratio (delta PF ratio) of COVID-19 patients in the group administered with adjuvant NAC therapy has a positive correlation. However, the correlation between the two variables is not significant.

The correlation test between changes in IL-6 levels (Delta IL-6) and changes in the PF ratio (Delta PF ratio) of COVID-19 patients in the group not administered with adjuvant NAC therapy resulted in a correlation coefficient value of 0.048 with a significance value *P*=0.858, thus, indicating no positive and significant correlation between changes in IL-6 levels and changes in the PF ratio of COVID-19 patients in the group without adjuvant NAC therapy. In other words, changes in IL-6 levels in COVID-19 patients not administered with adjuvant NAC therapy did not affect the level of change in the PF ratio.

The effect of changes in IL-6 levels and changes in the PF ratio of COVID-19 patients not administered with NAC therapy, based on the results of this study, is shown in the form of a linearity graph (Figure 1). The regression line between changes in IL-6 levels and changes in the PF ratio of COVID-19 patients in the group not given NAC adjuvant therapy tends to be horizontal but slightly points to the upper right. However, because the test result was not significant, it can be concluded that changes in IL-6 levels in COVID-19 patients in the group without adjuvant NAC therapy did not affect the level of change in the PF ratio.

These results prove the hypothesis — that the correlation test between changes in IL-6 levels (delta IL-6) and changes in the PF ratio (delta PF ratio) of COVID-19 patients in the group not administered with adjuvant NAC therapy has a positive correlation — to be true. However, the correlation between the two variables is not significant.

DISCUSSION

In the group administered with NAC, the mean age value was 53.12 years old, the youngest was 24 years, and the oldest was 76 years. This result does not differ much from the average age in the group not administered with NAC, which is 52.31 years old, where the youngest age was 25 years and the oldest was 69 years (*P*=0.795). Qiu et al. performed a systematic review and meta-analysis of 2,401 COVID-19 patients and found an average age of 69.9.[15] the result was comparable to the systematic review study and meta-analysis conducted by Baradaran et al., which showed that the average age was 51.[16]

Both groups were dominated by the male sex — 58.7% in the group NAC and 75% in the group not — with *P*=0.225, thus, indicating no significant difference in the gender of respondents of the two groups. Qiu et al., through a systematic review and meta-analysis, suggested that of the total 2,401 COVID-19 patients, 66.6% of the population was male. Females generally have more robust innate and adaptive immune responses than males, possibly due to X-chromosome and hormonal protection. For this reason, women are less likely to become infected with bacteria and viruses. On the other hand, males tend to have more bad habits than females (such as smoking, drinking, and more underlying illnesses), which may also be the reason why men infected with COVID-19 are more likely to die than women.[15]

The highest proportion of disease severity in the group given NAC was moderate (44.0%), while in the group not given NAC, the most significant proportion was severe (68.8%). They were not significantly different, with *P*=0.526. The degree of COVID-19 disease correlates with the course of the disease and levels of pro-inflammatory cytokines. The finding is evident from the study conducted by Han et al., where there is a significant difference in the levels of IL-6 and IL-10 in critically ill COVID-19 patients compared to severe, moderate, and mild COVID-19 patients.[17]

In the group of subjects administered with NAC, only 81.3% showed a symptom of shortness of breath,

while in the group not given NAC, all subjects showed said symptom (100%). This result had *P*=0.062, thus, indicating no significant difference in the symptom of shortness of breath between the two groups. 80% of the subjects administered with NAC had a cough, while all the subjects in the other group did (100%). This result had *P*=0.052, thus, indicating that the symptoms of cough between the group given NAC and the group were not significantly different.

As much as 70.6% of the subjects in the group given NAC had a fever, and in the group not given NAC, all subjects had a fever (100%). This result had *P*=0.013, thus, indicating a significant difference in fever symptoms between the two groups. 20% of the subjects in the NAC group experienced symptoms of anosmia/ageusia, and in the other group, 62.5% did. This result had *P*=0.001, thus, indicating a significant difference between the symptoms of anosmia/ageusia between the group given NAC and the group not. 56% of the subjects in the NAC group experienced digestive disorders, and in the other group, 62.5% did. This result had *P*=.635, thus, indicating that the symptoms of digestive disorders were not significantly different between the two groups.

For smoking history, there was 46.67% of the subjects in the group administered with NAC had a history of smoking; from the test results obtained *P*=0.253, thus, indicating that smoking history between the group given NAC and the group was not significantly different. A meta-analysis study with a total sample of 11,590 COVID-19 patients by Patanavanich showed a significant relationship between smoking and COVID-19 progression (OR=1.91; 95% confidence interval [CI]=1.42-2.59; *P*=0.001).[18] The same result was also proven by Reddy et al. through a meta-analysis study of 32,849 COVID-19 patients, of which there were 8,417 patients with a smoking history. Patients with a history of smoking have a significantly increased risk of COVID-19.[3]

The distribution of patients with comorbidities in the two groups is similar and could be considered balanced (46.67% in the group given NAC and 43.75% in the group not). The test results obtained *P*=0.833, thus indicating that the history of comorbidity between the NAC and non-NAC groups was not significantly different. Baradaran explained that the most common finding in confirmed COVID-19 patients was hypertension, which was found in 1/5 patients (21%). Comorbidities were also associated with a significantly increased risk of death, kidney disease (RR=4.90; 95% CI=3.04–7.88; *P*<0.00001), cerebrovascular disease (RR=4.78; 95% CI=3.39–6.76; *P*<0.00001), cardiovascular disease (RR=3.05; 95% CI=2.20–4.25; *P*<0.00001), respiratory disease (RR=2.74: 95% CI=2.04–3.67; *P*<0.00001), diabetes (RR=1.97; 95% CI=1.48–2.64; *P*<0.00001), hypertension (RR=1.95: 95% CI=1.58–2.40; *P*<0.00001), and cancer (RR=1.89; 95% CI=1.25-2.84; *P*=0.002), as suggested through a systematic review and meta-analysis conducted by Biswas et al..[19]

The most considerable outcome in both groups was the proportion of patients who recovered (85.3% in the group given NAC and 93.8% in the group not). This result had *P*=0.369, thus, indicating that the patient outcome between both groups was not significantly different.

Interleukin-6 (IL-6) is a cytokine that plays a central role in acute inflammation. IL-6 was first discovered by Weissenbach et al. in 1980. IL-6 is a multifunctional cytokine that plays a vital role in human metabolism, autoimmune cell differentiation, disease treatment, and others. This cytokine is tightly regulated, and the level is primarily low in healthy individuals. During infection, trauma, or other stress, IL-6 is expressed in much higher concentrations and has been implicated in the pathogenesis of several chronic disease conditions—including cardiovascular disease, atherosclerosis, and obesity.[20,21] In this study, 46.67% in the NAC group and 43.75% in the no-NAC group had comorbidities, where comorbidity could affect IL-6 levels.

N-acetylcysteine has been suggested as an adjunct therapy as standard treatment for SARS-CoV-2 infection. NAC is beneficial in its effect — increasing glutathione synthesis, enhancing immune function, and modulating the inflammatory response. Various studies have described the benefits and

effects of giving NAC on IL-6 levels, but more data are still needed for cases of COVID-19. The effect of NAC on IL-6 is through the inhibition of NFKB and ROS, as well as glutathione metabolism.[22]

IL-6 levels in the group administered with NAC decreased significantly with a median value of 102.71 pg/mL on day 8 (*P*=0.001), with an average decrease in IL-6 levels of 94.49 pg/mL (*P*=0.002). In the group not administered with NAC, the IL-6 levels also decreased with a median value of 6.65 pg/mL, and the value was lower on the eighth day compared to the first day (*P*=0.408), with an average decrease in IL-6 levels experienced by individuals of 37.5 pg/mL (*P*=0.539). This result, however, was not significant. These data indicate that using NAC as adjuvant therapy significantly reduces IL-6 levels — as IL-6 levels are associated with a poor prognosis in COVID-19 cases through various studies.

Saddadi et al. conducted a study to see the effectiveness of NAC on IL-6 and CRP levels in subjects undergoing hemodialysis. Twenty-four patients (nine males and fifteen females) on maintenance HD with an average age of 55.3 years were given oral NAC (600mg twice daily) for three months. Serum levels of biomedical parameters and IL-6 and hs-CRP were measured prior to and three months after initiation of treatment. There was a significant decrease in serum levels of CRP (22.4 vs. 5.2) and IL-6 (8.1 vs. 3.6).[23]

Paterson et al. conducted a study to see the effect of NAC on IL-6 and IL-8 levels in septic subjects. Twenty sepsis patients were divided into two groups of 10 people each. The first group was given a bolus of 150 mg/kg N-acetylcysteine in 100 mL 0.9% saline for 15 minutes, then 50 mg/kg in 100 mL 0.9% saline for 4 hours as a loading dose, and then a maintenance dose of 50 mg/kg in 200 mL of 0.9% normal saline over any 24 hours for a total of 72 hours. The second group was given a placebo. The result showed a decrease in IL-6 levels in both groups. However, the result was not significant.[24] This result was in contrast to our study, where there was a decrease in IL-6 levels in the group given NAC and without NAC on the eighth day, and the decrease of IL-6 levels in the group given NAC was significant.

Gosset et al. conducted a study to see NAC's effect on TNF-α, IL-6, and IL-8. There is a significant decrease in TNF-α, IL-6, and IL-8 in BAL fluid samples after administration of NAC for 48 hours. In our study, IL-6 levels decreased significantly after administration of adjuvant NAC therapy at a dose of 5gram/72 hours for eight days.

N-acetylcysteine has been shown to inhibit NF-κB and the replication of the human influenza virus (H5N1 strain, Vietnam/VN1203) in human lung epithelial cells. NAC also reduces the production of pro-inflammatory cytokines (IL-8, CXCL10, CCL5, and IL-6), thereby reducing monocyte chemotactic migration. It has been shown to have a protective effect against ARDS. N-acetylcysteine can also inhibit viral replication and the expression of pro-inflammatory molecules. This drug can inhibit pulmonary inflammation, myeloperoxidase (MPO) activity, neutrophil macrophages, IL-6, IL-1β, CXCL-10, and TNF-α.[25] It was proven in this study as there was a significant decrease in IL-6 levels after administration of adjuvant NAC therapy of 5 grams/72 hours for eight days.

There was a significant difference in the PF ratio of the group given NAC between D1 and D8; on the eighth day after administration of adjuvant NAC therapy, the PF ratio increased by an average value of 126.94 mmHg (*P*≤0.001). However, it turns out that the same result was also found in the group not given NAC, where there was a significant difference in PaO_2/FiO_2 between D1 and D8, and on the eighth day after administration of adjuvant NAC therapy, PaO_2/FiO_2 showed an increased average value of 124.79 mmHg (*P*≤0.001).

Moradi et al. conducted a study to see the effect of giving NAC on 27 ARDS patients treated in the ICU. The subjects were divided into two groups — 14 patients were administered with NAC, and 13 control patients were given a placebo. NAC was administered intravenously at a dose of 150 mg/kg on the first day, followed by 50 mg/kg/day for three days of administration. The ARDS criteria were following the American European Consensus Conference on ARDS. The study's results showed a significant increase in the PF ratio in the group of patients given

NAC compared to the group given placebo (*P*≤0.001).[21]

Similarly, in a previous study about the effect of administering NAC on ARDS patients admitted to the ICU, the subjects were divided into two groups; those who were given NAC intravenously at 40 mg/kg/day for three days (32 subjects) and those who were given a placebo (29 subjects). There was a significant increase in the PF ratio in patients given NAC, while in the placebo group, there was no significant increase in the PF ratio. In our study, there was no difference between the group given NAC and the group not; as in both groups, there was a significant improvement in PF ratio values on the eighth day.

The relationship between changes in IL-6 levels and changes in PF ratio of COVID-19 patients after administration of adjuvant NAC therapy shows correlation coefficient of 0.154 with *P*=0.186, thus, indicating a weak, positive, but not statistically significant correlation. In other words, the changes in IL-6 levels in COVID-19 patients receiving NAC adjuvant therapy had a weak influence on the change in PF ratio.

The correlation test between changes in IL-6 level (Delta IL-6) and changes in PF ratio (Delta PF ratio) of COVID-19 patients in the group without adjuvant NAC therapy showed correlation coefficient value of 0.048, with *P*=0.858, thus, indicating neither positive nor significant correlation. In other words, the change in IL-6 levels in COVID-19 patients not administered with adjuvant NAC therapy did not affect the change in PF ratio.

There are not many studies on the correlation between IL-6 and PF ratio. Hagau et al. studied the correlation between several cytokines — such as IL-6, IL-15, IL-8, and TNFα — and PF ratio in 31 patients infected with the severe H1N1 virus. The study showed a negative correlation between IL-6 levels and the PF ratio (r = -0.556, *P*=0.001).[26] In the study of Benucci et al., lung improvement estimated through the SpO_2/FiO_2 ratio was observed in 7 of 8 patients with COVID-19 pneumonia who received tocilizumab treatment. Clinical recovery is associated with increased lymphocyte counts, decreased levels of IL-6, and CRP.[27]

NAC decreased IL1β, IL18, IL6, and TNF-α in vitro. It inhibits downstream activity post TNF- α receptor activation, while NAC inhibits TNF- α and IL-6 gene expression under oxidative stress.[13] The effect of NAC on IL-6 is through the inhibition of NFkB and ROS, as well as glutathione metabolism. It is known that ROS plays an essential role in the pathogenesis of lung injury and that the alveolar epithelial lining of ARDS patients is deficient in Glutathione.[22] In this study, changes in IL-6 have a weak effect on changes in PF ratio; this is because IL-6 is not the only factor that affects PF ratio, as what could affect it is multifactorial.

LIMITATION

The control group was not comparative, with only 16 subjects due to obtaining more samples in the non-NAC population because it was difficult to get samples that agreed not to be given NAC, especially when NAC was included in the treatment guidelines.

CONCLUSION

There was a significant decrease in IL-6 levels in COVID-19 patients who were given NAC as adjuvant therapy compared to COVID-19 patients who did not receive adjuvant NAC therapy. There was a significant decrease in PaO_2/FiO_2 ratio in both COVID-19 patients who were given NAC as adjuvant therapy and COVID-19 patients who did not. There is no positive and significant correlation between decreased IL-6 levels and increased PaO_2/FiO_2 ratio in COVID-19 patients receiving adjuvant NAC therapy; neither is there in COVID-19 patients who did not receive adjuvant NAC therapy.

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CONFLICT OF INTEREST

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Original Article

Association Between Ferritin Levels and Severity of COVID-19 in RSUP Dr. M. Djamil Padang

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Abstract

Background: Ferritin is one of the inflammatory markers used to predict the severity of COVID-19. Early assessment of severity is expected to be a priority in disease management. This study aims to determine the association between ferritin levels and the severity of confirmed COVID-19 patients at dr. M. Djamil Hospital Padang.

Methods: This study is a retrospective cohort study on confirmed COVID-19 patients from January to May 2021. Chi-square analysis was calculated to assess the association between ferritin levels and clinical grade, the severity of the chest X-ray, and the level of need for oxygen therapy. To assess the risk opportunities for ferritin levels on each dependent variable, an association analysis was performed by calculating the Odds Ratio.

Results: Characteristics of the patients were mainly female (54.25%), aged more than 50 years (59,00%), a clinical grade above category 4 (54,75%), required oxygen therapy (74,75%), the severity of chest X-ray was mild (75.50%), ferritin level <500 ng/ml (52.75%) and had no comorbidities (51.25%). This study found that ferritin levels correlated with a clinical grade, severity of chest X-ray, and level of need for oxygen therapy with HFNC and ventilator (*P*<0.001). Ferritin levels >1000 ng/mL have a risk opportunity for clinical grade category 7 OR=8.28 (95% CI=2.69-25.41), severe chest X-ray severity OR=5.52 (95% CI=2.55-11.97), and need for oxygen therapy with HFNC and ventilator, OR=4.76 (95% CI=2.70-8.39) vs. OR=7.69 (95% CI=3.97-14.92).

Conclusion: High ferritin levels significantly increase the risk of severe clinical severity, severe chest X-ray, and the level of need for oxygen therapy using HFNC and a ventilator in COVID-19 patients.

Keywords: COVID-19, ferritin levels, severity

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INTRODUCTION

Coronavirus Disease 2019 (COVID -19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV2). Indonesia is a country with confirmed COVID-19 cases and the highest death rate in Southeast Asia and occupies the second position in Asia after India. Since Indonesia first reported cases of COVID-19 on March 2, 2020, Indonesia has received 1,012,350 confirmed cases of COVID-19 and 24,468 cases of death (2.8% confirmed cases fatality rate) until January 26, 2021.[1] The number of confirmed cases of COVID-19 that occurred in West Sumatra until August 15, 2021, was 81,886 out of 639,348 tested people. The positive rate is 12.81%. There were 11,447 patients (13.98%), who died 1,794 (2.19%) and 68,645 (83.83%) patients who were treated.[2]

Medical Research subjects in COVID-19, including epidemiology, clinical presentation, laboratory tests, diagnosis, and disease therapy, are still undergoing. Several inflammatory markers have been shown to correlate with the COVID-19 severity, such as lymphopenia, high D-dimer, T lymphocytes, IL-1 and IL-6, and high ferritin values.[3]

The mechanism of hyperferritinemia in COVID-19 patients is explained based on three theories. First, ferritin synthesis increased due to increased proinflammatory cytokines such as IL-1β, TNF-, and IL-6. Second, cellular damage due to the inflammatory process can lead to leakage of intracellular ferritin, thereby increasing serum ferritin. Third, acidotic conditions and increased Reactive Oxygen Species (ROS) in COVID patients with ARDS can liberate ferritin from the cell. Ferritin, as a

marker of the inflammatory response, is expected to be a predictor factor in assessing the severity of the disease at the beginning of treatment and determining priorities in patient management. Early and rapid assessment supports the provision of more optimal therapy.[4]

Cheng et al. found that the median value of ferritin levels in the heavy group was 4.7 times higher than the non-heavy group (*P*=0.049).[5] The COVID-19 severity patients can also be assessed based on the chest X-ray and the level of need for oxygen therapy. Eroglu et al.'s study in Turkey obtained a chest X-ray score <5, which had a lower median ferritin level (92.1) than the median ferritin level in the group with a score of 5 (286.0) with *P*<0.001. A study by Barciela et al. in Spain found an association of higher ferritin levels with the use of a high flow nasal cannula (HFNC) with *P*=0037.[6]

This study aims to determine the association between ferritin levels and the severity of confirmed COVID-19 patients at RSUP dr. M. Djamil Padang.

METHODS

This retrospective cohort study was conducted from January 1, 2021, to November 30, 2021, at RSUP Dr. M. Djamil Padang. The entire study population was confirmed COVID-19 patients who were treated at RSUP Dr. M. Djamil Padang from January 1 to May 31, 2021. The convenience technique with inclusion criteria confirmed COVID-19 patients from the results of RT PCR/TCM SARS-CoV-2 taken from a nasal/nasopharyngeal swab and aged >18 years. Exclusion criteria were COVID-19 patients with incomplete medical record data, including demographic data, description of clinical severity, ferritin levels, chest X-ray, oxygen therapy, and comorbidities.

Clinical severity is the patient's most severe condition in the first 24 hours based on The WHO ordinal scale modified by Beigel et al.[7] consists of Category 3: hospitalized, not requiring oxygen therapy; Category 4: hospitalized, does not require oxygen therapy, needs medical treatment; Category 5: hospitalized, requires oxygen therapy; Category 6: hospitalized, requiring HFNC or NIV; Category 7: hospitalized, requiring mechanical ventilation or ECMO.

The baseline characteristic data is presented as a frequency distribution table. The analysis was performed using the SPSS version 21 program. The chi-square was done in the bivariate analysis to see the significance of the independent and dependent variables and the chance for each variable to continue the analysis using the test binary logistic regression on the dependent variable, which has two categories. Meanwhile, analysis was performed by multinomial logistic regression for the dependent variable with more than two categories. The final result can be interpreted if *P*<0.05, significant if the value of OR>1 is a risk factor, OR<1 is a preventive risk factor/protective factor, and OR=1 is not a risk/reference.

RESULTS

The baseline characteristics are described in Table 1. This study's patients were aged 50 years, with 236 people (59.00%) and 217 women (54.25%). The most clinical severity of COVID-19 patients were patients who needed oxygen therapy, as many as 219 patients (54.75%), consisting of category 5 is 95 people (23.75%), category 6 is 89 (22.25%), and category 7 is 35 people (8.75%). The results of this study obtained the most characteristics were ferritin levels <500 ng/mL in as many as 211 people (52.75%), mild chest X-ray severity in 302 people (75.50%), and 299 people requiring oxygen therapy (74.75%). Most patients in this study had no comorbidities (51.25%).

The association between ferritin levels and the clinical severity of confirmed COVID-19 patients can be seen in Table 2 and displays a significant analysis result (*P*<0.001). Ferritin levels >1000 ng/mL provide an opportunity for the severity of category 3 (OR=3.45, 95% CI=1.89–6.27), category 4 (OR=14.17, 95% CI=3.36–59.67), category 5 (OR=2.82, 95% CI=1.62–4.92), category 6 (OR=6.97, 95% CI=3.75–12.99), and category 7 (OR=8.28; 95% CI=2.69–25.41).

Table 1. The Baseline characteristics of Confirmed COVID-19 Patients Treated at RSUP Dr. M. Djamil Padang

Patient Characteristics	Total (n= 227)	%
Aged		
<50 years	164	41,00
≥50 years	236	59,00
Gender		
Female	217	54.25
Male	183	45,75
Clinical Severity		
Category 3	119	29,75
Category 4	62	15,50
Category 5	95	23,75
Category 6	89	22,25
Category 7	35	8,75
Ferritin Levels		
<500 ng/mL	211	52,75
500–1000 ng/mL	73	18,25
>1000 ng/mL	116	29,00
Chest X-ray Severity		
Mild	302	75,50
Moderate	59	14,75
Severe	39	9,75
Need for Oxygen Therapy		
Free air	101	25,25
Oxygen Therapy	299	74,75
Nasal Cannulae	52	13,00
NRM	70	17,50
HFNC	95	23,75
Ventilator	82	20,50
Number of Comorbidities		
No Comorbid	205	51,25
1 Comorbid	110	27,50
>1 Comorbid	85	21,25
Comorbid Type		
Hypertension	107	26,75
Diabetes Mellitus	69	17,25
Cardiovascular Disease	39	9,75
Chronic Kidney Disease	30	7,50
Obesity	28	7,00
Malignancy	17	4,25
Chronic Lung Disease	9	2,25
Cerebrovascular Disease	8	2,00
Chronic Liver Disease	6	1,50
Immunodeficiency	2	0,50

The association between ferritin levels and risk opportunities in the chest X-ray severity can be seen in Table 3, and the analysis results obtained a significant association (*P*<0.001). Most patients were patients who had ferritin levels <500 ng/mL, as many as 211 people (52.75%), and most (61.26%) had a mild severity of chest X-rays. While patients with ferritin levels >1000 ng/mL, 116 patients (29%) had the highest severity of chest X-ray, which was the heavy group (25 patients (64%)).

The results of the statistical test showed the probability of the risk of ferritin levels on the severity of the chest X-ray at a ferritin level of 500-1000 ng/mL associated with moderate severity (OR=2.64, 95% CI=1.20–5.80) and mild (OR=2.16, 95% CI=1.09–4.27). Meanwhile, ferritin levels >1000 ng/mL were associated with severe severity (OR=5.52, 95% CI=2.55–11.97), moderate (OR=4.25, 95% CI=2.20–8.21) and mild (OR=2.42, 95% CI=3.71–11.11).

In Table 4, the statistical tests showed a significant association between ferritin levels and the need for oxygen therapy, HFNC, and ventilators (*P*<0.001). However, there was no correlation between ferritin levels and the need for nasal cannula oxygen therapy and NRM (*P*=0.120 and *P*=0.172, respectively). Ferritin levels >1000 ng/mL have the opportunity to need oxygen therapy with a ventilator (OR=7.69, 95% CI=3.97–14.92) and HFNC (OR=4.76, 95% CI=2.70–8.39).

Table 2. Association between ferritin levels and risk opportunities on the clinical degree of COVID-19 patients

Clinical Severity		Ferritin Levels			Total	*P*
		<500 ng/mL	500–1000 ng/mL	>1000 ng/mL		
Cat 3	**(N/%)**	86 (72.27%)	19 (15.97%)	14 (11.76%)	119 (100%)	<0.001
	OR (95% CI)	Ref	1.69 (0.92–3.08)	3.45 (1.89–6.27) *	---	
Cat 4	**(N/%)**	51 (82.25%)	9 (14.52%)	2 (3.23%)	62 (100%)	<0.001
	OR (95% CI)	Ref	2.34 (1.00–5.48) *	14.17 (3.36–59.67) *	---	
Cat 5	**(N/%)**	43 (45.26%)	21 (22.11%)	31 (32.63%)	95 (100%)	<0.001
	OR (95% CI)	Ref	2.21(1.15-4.24) *	2.82 (1.62–4.92)	---	
Cat 6	**(N/%)**	25 (28.09%)	18 (20.22%)	46 (51.69%)	89 (100%)	<0.001
	OR (95% CI)	Ref	3.46 (1.66–7.23) *	6,97 (3.75–12.99)	---	
Cat 7	**(N/%)**	6 (17.14%)	6 (17.14%)	23 (65.72%)	35 (100%)	<0.001
	OR (95% CI)	Ref	3.00 (0.73–12.32)	8,28 (2.69–25.41) *	---	

Table 3. Association between ferritin levels and risk opportunities on the severity of chest X-rays of COVID-19 patients

The Chest X-ray Severity		Ferritin Levels			Total	*P*
		<500 ng/mL	500–1000 ng/mL	>1000 ng/mL		
Mild	(N/%)	185 (61.26%)	56 (18.54%)	61 (20.20%)	302 (100%)	<0.001
	OR (95% CI)	Ref	2.16 (1.09–4,27) *	2.42 (3.71–11.11) *	---	
Moderate	(N/%)	16 (27.12%)	13 (22.03%)	30 (50.85%)	59 (100%)	<0.001
	OR (95% CI)	Ref	2.64 (1.20–5.80) *	4.25 (2.20–8.21) *	---	
Severe	(N/%)	10 (25.64%)	4 (10.26%)	25 (64.10%)	39 (100%)	<0.001
	OR (95% CI)	Ref	1.17 (0.35–3.84)	5.52 (2.55–11.97) *	---	

Note=*P<0.05 significance; *Pearson chi-square test*; *multinomial logistic regression*; Ref:Reference

Table 4. Association between ferritin levels and risk opportunities on the oxygen therapy needs of COVID-19 patients

Need for Oxygen Therapy		Ferritin Levels			Total	*P*
		<500 ng/mL	500–1000 ng/mL	>1000 ng/mL		
Free air	(N/%)	87 (86.14%)	13 (12.88%)	1 (0.99%)	101 (100%)	<0.001
	OR (95% CI)	Ref	1.17 (1.17–2.39) *	1.74 (1.66–1.87) *	---	
Nasal cannula	(N/%)	40 (76.92%)	10 (19.23%)	2 (3.85%)	52 (100)	0.120
	OR (95% CI)	Ref	1.05 (0.46–2.36)	0.41 (0.16–1.02)	---	
NRM	(N/%)	40 (57.14%)	13 (18.57%)	17 (24.29%)	70 (100%)	0.172
	OR (95% CI)	Ref	1.69 (0.81–3.52)	1.72 (0.91–3.25)	---	
HFNC	(N/%)	28 (29.47%)	19 (20%)	48 (50.53%)	95 (100%)	<0.001
	OR (95% CI)	Ref	2.02 (0.99–4.09)	4.76 (2.70–8.39) *	---	
Ventilator	(N/%)	16 (19.51%)	18 (21.95%)	48 (58.54%)	82 (100%)	<0.001
	OR (95% CI)	Ref	3.64 (1.66–7.98*)	7.69 (3.97–14.92) *	---	

Note=*P<0.05 significance; *chi –square test*; *binary logistic regression*; Ref:reference

DISCUSSION

The baseline characteristics showed that most COVID-19 patients were treated at RSUP dr. M. Djamil Padang is mainly 50 years (59.00%). Perrotta et al. found that age is related to the severity of COVID-19 disease. Age causes significant changes in the immune response and chronic inflammatory processes.[6] One of the main signs of aging in the immune system is a reduction in the number of lymphocytes associated with the involution of the thymus, a reduction in hematopoietic cells, and inadequate peripheral regulation.[8]

Most gender displayed in this study is female (54.3%) and male (45.8%). This study's results align with the results of Sensusiati et al. in Surabaya (51.4%) and Ni et al. in China (52%).[8,9] Chen et al. showed that ACE2 expression increased up to 100% in Asian women in the adrenal glands, adipose tissue, esophagus, and heart. ACE2 expression also increases in the lungs, blood vessels, colon, and adrenal glands.[10]

The most severe COVID-19 patients in this study are categories above category 4 with a total of 219 (54.75%), consisting of category 5 (23.75%), category 6 (22.25%), and category 7 (8.75%). Beigel et al. found that the highest number was above category 4, with category 5 being the most (41%).[7] The highest need for oxygen therapy was 299 (74.75%) patients requiring oxygen therapy, consisting HFNC (23.75%), ventilator (20.50%), NRM (17.50%), and nasal cannula (13,5%). While patients who do not need oxygen therapy (free air) as much as 25.25%. The most commonly used oxygen therapy is HFNC. The number of COVID-19 patients increased rapidly in a short time during the COVID-19 outbreak, and many experienced a sudden worsening. This condition increases the need for intensive care facilities, and HFNC becomes essential. HFNC is considered easier to operate, not limited to pulmonology or intensive care specialists.[11]

Most of the patients' radiological features were mild (75.50%). Sathi's study in India also used the RALE score in his study and obtained the same results, namely the distribution of severity of chest X-rays in the mild group (45%).[11] The highest ferritin level in this study was <500 ng/mL (52.75%). This study's results align with the research of Ghwell et al.,

who found the highest ferritin levels <350 ng/mL (51.51%).[12]

This study found that more than 50% of patients did not have comorbid diseases (51.25%), comparable to Surendra et al. in Jakarta, which found that most patients did not have comorbidities (69%).[1] Patient with one or more comorbidities is associated with a poor outcome. Khedr et al concluded that the number of comorbidities was a risk factor for death. Patients with 3 or more comorbidities had an HR of 2.9 (95% CI=1.5-5.6).[13] The three most comorbid patients in this study were hypertension (26.75%), diabetes mellitus (17.25%), and cardiovascular disease (9.75%).

In this study, there was a significant association between ferritin levels and the clinical severity of patients (*P*<0.001), as presented in Table 5.2. Ferritin levels more than 1000 ng/mL risk 8.28 times higher for the occurrence of severity category 7 (95% CI=2.69-25.41). High ferritin levels significantly increase the risk of a more severe clinical severity in the patient. Ghweil et al. found an association between ferritin and patient severity (95% CI=1.01-1.03) with *P*<0.001.[12.] Dahan et al. found that the mean ferritin level in the severe patient group (2817.6 ng/mL) was higher than the non-severe group (708.6 ng/mL).[14]

Ferritin acts as an iron binder and plays a role in inflammatory processes and the immune system.[5] The mechanism of hyperferritinemia in COVID-19 patients can be explained based on three emerging theories. First, increased ferritin synthesis caused increased proinflammatory cytokines such as IL-1β, TNF-, and IL-6. Second, cellular damage due to the inflammatory process can lead to leakage of intracellular ferritin, thereby increasing serum ferritin. Third, acidotic conditions and increased ROS in COVID patients with ARDS can liberate ferritin from the cell.[15]

Research on clinical features and laboratory biomarkers shows COVID-19 as part of the hyperferritinemia syndrome.[16] Hyperferritinemia syndrome is a collection of several diseases that exhibit hyper inflammation and hyperferritinemia, some of which are life-threatening. Hyperferritinemia is a body condition characterized by more than 500 g/ml serum levels. Four clinical groups of diseases have been classified as hyperferritinemia syndrome: macrophage activation syndrome (MAS), adult-onset Still's a disease (AOSD), catastrophic APS (CAPS), and septic shock.[17] In addition to the process of infection and inflammation, the levels of ferritin in the body are influenced by gender, age, hypoxic conditions, the amount of iron intake, chronic liver disease, kidney disease, and malignancy.[18] These conditions can act as a confounding factor in this study.

This study found a correlation between ferritin levels and chest X-ray severity (*P*<0.001). Ferritin levels >1000 ng/mL, 5.52 times higher risk for the occurrence of severe chest X-ray findings. High ferritin levels significantly increase the risk of severe chest radiographic severity in COVID-19 patients. The study's finding comparable with Eroglu et al. in Turkey, which found that the group with a chest X-ray score <5 had a lower median ferritin level (92.1) than the median ferritin level in the group with a score of 5 (286.0) with *P*<0.001.[18]

Kaleemi et al received a chest x-ray severity score (CXR-SS) of 5-8 at the time of the patient's initial admission to the hospital, which was associated with a predictable ICU stay (*P*<0.001) and mortality (*P*<0.001).[19] This study is in line with that of Borghesi et al., who found that patients with high Brixia scores on chest X-rays were associated with a higher risk of death in the hospital (*P*<0.0001).[20] In addition, Sensusiati et al. in Surabaya found a RALE score >2 increased patient mortality up to 7 times. [9] Rapid chest X-ray examination can be an initial reference when providing therapy to patients. The limitations of CT scans and radiologists, especially in Indonesia, make chest X-rays an essential examination in establishing a diagnosis and determining the severity of COVID-19 patients.[21]

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This study has resulted in line with the study of Eroglu et al. in Turkey, which found that the group with a chest X-ray score <5 had a lower median ferritin level (92.1) than the median ferritin level in the group with a score of 5 (286.0) with *P*<0.001.[18]

LIMITATION

This research has the limitation is that the sampling technique is carried out without selection of factors confounders that affect the ferritin content and composition of the sample size as well not equal so that it could lead to bias in this study.

CONCLUSION

Characteristics of COVID-19 patients treated at RSUP dr. M. Djamil Padang were primarily women aged more than 50 years, with a clinical grade above category 4, requiring oxygen therapy, mild radiological features, and almost half ferritin levels of 500 ng/mL, and had no comorbidities. High ferritin levels significantly increase the risk of severe clinical severity, severe chest X-ray, and the level of need for oxygen therapy using HFNC and a ventilator in COVID-19 patients.

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CONFLICT OF INTEREST

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Literature Review

The Effect of Shisha on Respiratory Health

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Abstract

In the Middle East, smoking shisha is considered a more socially acceptable activity. The prevalence of shisha smoking among Middle Eastern adolescents varies. Smoking shisha requires burning tobacco with a distinct aroma, commonly referred to as molasses, over coals. Some people believe that shisha is a safer alternative to cigarettes, but evidence suggests that shisha use is associated with harmful and detrimental respiratory health effects.

Keywords: Respiratory health, Shisha, smoking

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INTRODUCTION

Smoking is a serious health problem and the most important avoidable cause of death globally.[1] An estimated 1.3 billion people worldwide smoke, and 80% live in developing countries. Cigarettes occupy the second position as the leading cause of death globally and are estimated to be the cause of death of 1 in 10 adults in the world.[2] The number of smoking-related deaths is expected to reach 8.3 million by 2030.[1,3] Smoking, regardless of the method, can cause health hazards. There are various smoking methods available in different parts of the world, including cigarettes, e-cigarettes, or the form of shisha/hookah.[4] Geographic areas, such as the Middle East, where tobacco use has become part of the culture, have a very high prevalence of shisha use, especially among young people[5]

The prevalence of shisha smokers varies between 6–34% among adolescents in the Middle East.[6] The number of shisha smokers has also increased in recent years in the United Arab Emirates and has caused particular concern in the society.[7] The number of adolescents who use tobacco in the form of shisha, Dokha, and cigarettes are very high in the United Arab Emirates/Saudi Arabia. Although the legal age for smoking is 18 years, recent statistics show that in the 13–15 year age group, 19% of men and 10% of women used shisha.[5] Study in the UAE pointed out that Shisha users in Emirati were 26.8%, lower than Arab Non-Emirati for as much as 42.6% with the most age group 18–29 years old of 41.6% compared to ages 30–39 years of as much as 37.6%.[7] Moreover, in one study, it was found that nearly 15% of students at the University of Sharjah, Saudi Arabia reported that they had smoked either regular cigarettes or shisha. Furthermore, 18% of students in Dammam, Saudi Arabia, also smoked.[4]

Shisha goes by various names, including hookah, narghile, water-pipe, argils, etc.[1,2,6,8] A smoking session of shisha usually lasts 20–80 minutes. Thus, smokers are exposed to so much smoke for a long time. Shisha smokers inhale 50–200 puffs in one session, inhaling 0.15–1 L of smoke in one session, the equivalent of smoking 100

cigarettes. Shisha was also associated with a higher effect on passive smokers than regular smokers.[6]

Smoking shisha is considered a more socially acceptable activity because it is often considered harmless.[3,5,9,10] A study in Saudi Arabia found that 50% of students considered shisha to be less harmful than cigarettes, and 61% of them thought that the harmful substances in shisha were purified.[11] Broadly, shisha is presumed a safer alternative to cigarettes because, with shisha devices, the smoke is passed through the water first in an attempt to “filter/purify” the smoke and filter out all harmful chemicals such as tar, CO, and nicotine.[1,4,7-10] Some people believe that there is a little or no nicotine in shisha.[10] In addition, people also think that shisha smoke is more environmentally friendly.[3]

Despite these misconceptions, various studies have indicated that smoking shisha actively might be the same or even more dangerous than smoking and was associated with various diseases and adverse health effects such as cardiovascular and respiratory complications, cancer, infections, infertility, and others.[1,4,7-9,11] Shisha smoke also contains the same toxins as regular cigarette smoke, even though it has been passed through the water before.[4] Compared to cigarettes, shisha has high levels of nicotine, arsenic, chromium, and lead. In addition, CO exhaled by shisha smokers is twice as high as that of regular cigarettes.[7] Another thing that attracts people to use shisha is the trend of smoking shisha among young people and the availability of various shisha aromas such as chocolate, mint, grape, cherry, apple, and others.[6,11] Shisha smoke leaves a pleasant smell, unlike cigarette smoke in general.[1,10,11]

Lately, shisha is also assumed normal or even ordinary and has been assimilated into popular culture, marked by the many pop-up “hookah bars” or “shisha cafés” that are found in many big cities around the world.[6,10] The existing misunderstanding is also further strengthened by the fact that people regard smoking shisha is a social and popular/famous activity at family gatherings or other social events.[4,7,10,11] Many shisha smokers believe that smoking shisha provides pleasure, strengthens intimacy in social gatherings, and relaxes the mind. However, they do not realize that smoking shisha indirectly causes addiction both physically and mentally and can be harmful to health.[4,10]

SHISA COMPONENT

There are three types of commonly used shisha/hookah, namely Mouassal or "Muessel," Jurak, and Tumbak. The three types of shisha have different contents. In short, Mouassal in Arabic means "honey" contains 30% tobacco and about 70% honey/sugar cane as well as glycerol and flavorings. Moussal is the most common type of shisha used in the Kuwaiti population. Meanwhile, Jurak contains tobacco, sugar cane, and about 20% of other spices and dried fruits. Jurak is commonly used in the Middle East and the Gulf region. Lastly, tumbak, which is mainly used in Asia, is a pure form of unflavored tobacco leaf that is burnt over charcoal.[12,13]

Basically, smoking shisha involves burning tobacco with a certain aroma, generally referred to as molasses, and burning it using coal. [10,11] When a person inhales smoke from a smoking pipe, the air is drawn through the tobacco and heated with coal to produce cigarette smoke. As a result, smoke contains components of tobacco and coal.[11]

Tobacco is the main source of smoke in both hookah/shisha and cigarettes. Hookah users are exposed to the same toxic compounds or toxic byproducts as cigarette users but at much higher levels and with a worse impact on shisha users.[12] This tobacco contains high levels of PAH (polycyclic aromatic hydrocarbon) and carcinogenic compounds. These high levels compounds are also largely due to the burning of coal. Significant PAH exposure can establish various types of cancer in shisha smokers, including lung cancer.[11,12]

Other toxic compounds obtained in shisha smoke include nicotine, carbon monoxide, aromatic amines, aldehydes, furanic and phenolic compounds, TAR, heavy metals, and ammonia.[2,6,11-14] The amount of these toxins may be higher or lower in

shisha compared to cigarette smoke (per stick/and per pack/day) depending on the heating process as well as different charcoal burning process.[12]

Nicotine, the main source of this tobacco addiction, has several ingredients in shisha that vary greatly depending on the type of tobacco used. Similar to smokers, plasma nicotine levels were also elevated in shisha users. However, the amount of plasma nicotine in shisha smokers is much higher than that of regular smokers. This phenomenon can be explained by longer sessions of using shisha with a higher number/volume of puffs. After using shisha for 5 minutes, nicotine levels increased significantly from 2–6 ng/ml. Increased nicotine levels have been shown to significantly trigger an increase in heart rate. Serum HDL levels, apolipoprotein A-1, total antioxidant capacity and vitamin C were significantly lower in Shisha users compared to non-smokers thereby increasing the risk of cardiovascular disease.[11,12]

Carbon monoxide (CO) levels also significantly increased after smoking shisha. The plasma carboxyhemoglobin concentration in shisha users is higher than in regular smokers, indicating that carbon monoxide is also inhaled during shisha use. CO displaces oxygen (O_2) bound to hemoglobin to form carboxyhemoglobin (the affinity of CO for hemoglobin is 200 times that of O_2) and shifts the oxygen dissociation curve to the left, causing hypoxia and impaired cellular respiration. Carbon monoxide is also known to induce various cardiovascular diseases.[12]

The concentration of carboxyhemoglobin in shisha smokers was more than 10%, while the carboxyhemoglobin concentration in regular cigarette users was 6.5%, and in non-smokers was 1.6%. One study also stated that acutely elevated levels of CO can contribute to CO poisoning. In such cases, the carboxyhemoglobin level could reach between 20-30%, and the patient might lose consciousness as well as experience headaches and shortness of breath.[11,12]

Furthermore, after using shisha, another carcinogenic compound, nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), was also found to increase levels in the urine. This indicates the presence of TSNA (tobacco-specific nitrosamines) in shisha smoke. NNAL itself is a metabolite that is formed after 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) enters the body.[12]

In addition, TAR (nicotine-free dry particulate matter) in 1 session of shisha for 45 minutes can reach 802 mg, which is 36.5 times higher than smoking 1 cigarette. This TAR level varies depending on the length of the session; the level can be up to 100 times higher if the use of shisha lasts longer.[12]

The volatile aldehydes in shisha include acrolein, formaldehyde, acetaldehyde, propionaldehyde, and methacrolein. These components are associated with respiratory diseases, airway irritation, COPD, and lung cancer. Acrolein can also generate cardiopulmonary toxicity, potentially induce leukemia, and be prothrombotic. Formaldehyde is also a strong carcinogen that can trigger leukemia. The average level of volatile aldehydes in shisha was significantly higher than in cigarettes. Therefore, shisha smoke might cause a higher incidence of aldehyde-related diseases.[11,12]

EFFECTS OF SHISHA ON RESPIRATORY HEALTH

Taufik FF et al. in their study observed that respiratory symptoms and other symptoms that were most often experienced after using shisha were cough (29.2%), shortness of breath (12.5%), dizziness (8.3%). Two people complained shortness of breath and dizziness (4.2%), and two people complained cough and dizziness (4.2%) Martinasek et al. in their study found that shisha smokers reported experiencing respiratory symptoms and other symptoms such as dizziness (66%), fatigue (57.4%), headache (46.8%), palpitations (21.3%), nausea (17%), dry throat (17%), and shortness of breath (7%).[15]

Raad et al. in their systematic review and meta-analysis conducted a separate literature search comparing shisha users with non-smokers

and shisha users with smokers, then performed a spirometry examination to obtain FEV_1 (forced expiratory volume in 1 second), FVC (forced vital capacity), and the FEV_1/FVC ratio. In 6 studies with a total of 1,156 patients, shisha users were found to have significant reduction in FEV_1 and FEV_1/FVC compared with non-smokers but not significantly different compared to smokers.[6] In a population-based study comparing spirometry data of 245 non-smokers with 245 shisha users, Bathouee et al. pointed out that 10.2% of shisha users had an obstructive pattern on spirometry compared to 0% of the non-smokers control group.[16] Saad et al. also found that in an analysis of 110 shisha users, 36% were proven to have static hyperinflation on lung function tests.[10] From these three data, it could be concluded that, like smokers, shisha smokers also experienced negative effects on lung function and were at risk for COPD.[3,6,10,16]

The content contained in shisha, such as tar, PAH, and carbonic content such as formaldehyde and acetaldehyde, elevated the risk of developing lung cancer. Carbonic content also increased a person's risk of promoting laryngeal cancer.[10,17] In a meta-analysis by Mamtani et al. regarding risk estimates from Middle Eastern countries, researchers compared daily hookah/shisha users with a control group. Data were compiled and adjusted for other forms of tobacco use. The study noted that for lung cancer, six studies had an OR of 3.18 (95% CI, 1.87–5.42).[10]

In addition, the use of shisha was associated with an increased risk of lung infection as various devices used, especially the mouthpiece, could act as a reservoir of pathogens.[3,7,14,17] Alaidarous et al. obtained cultures from water reservoirs and mouth pipes from 10 different shisha cafes and found a high frequency of bacterial contamination with resistant bacteria. A recent study showed an increased risk of inhaling spore-producing mold, which was isolated from the inside of shisha. Aspergillus was isolated from shisha water in a leukemia patient with invasive pulmonary aspergillosis. Mycobacterium tuberculosis was also found to grow and survive inside shisha pipe.[11] The potential for transmission has been demonstrated in a cluster of pulmonary tuberculosis cases associated with shisha sharing in Queensland.[17] In the Middle East on 2010, an outbreak of tuberculosis cases associated with shisha sharing was reported.[11]

In addition, there are many case reports of acute eosinophilic pneumonia in shisha smokers. Dial et al. reported that a 26-year-old woman who had recently started smoking shisha was admitted with complaints of cough, dyspnea, and pleuritic chest pain. Initial chest CT showed a small nodular opacification in the right lower lobe. However, the patient's condition worsened, so she had to be admitted to the ICU. Repeated chest X-rays revealed extensive bilateral lung opacities. Bronchoalveolar rinses indicated 61% eosinophils. She was diagnosed with acute eosinophilic pneumonia and improved with prednisone.[17] Several other cases following a similar clinical course have been reported, affecting young adult patients.[17] It progressed rapidly to diffuse pulmonary infiltration in all reported cases and was diagnosed by bronchoalveolar lavage with >50% eosinophils. There was a progressive respiratory failure in two cases leading to intubation and in one requiring extracorporeal membrane oxygenation (ECMO). None of these patients had a lung biopsy and histological assessment of the lung lesions. In addition, two case reports informed cases of necrotizing granulomatous lung disease associated with the habit of using shisha.[15]

LIMITATIONS

None

CONCLUSION

Hookah smoking has become a worldwide phenomenon, including in Saudi Arabia, with an alarming increase in its use in the adolescent population to young adults. There is a growing misconception in society about shisha, which is considered safer, and less harmful than ordinary

cigarettes, a culture in society that considers shisha a social activity. However, there were more and more evidences that consistently showed the harmful and detrimental health effects associated with the use of shisha. It is clear that, like smoking, hookah use also poses significant public health risks, including the risk of developing pulmonary complications such as decreased lung function, COPD, lung infections such as pneumonia, tuberculosis, lung cancer, as well as laryngeal cancer. Armed with knowledge about hookah use and its dangers, health care providers can more effectively educate and correct public misperceptions about the dangers of shisha

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Literature Review

Long COVID: Diagnosis and Treatment of Respiratory Syndrome in Post COVID-19 Conditions

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Abstract

The ongoing COVID-19 pandemic has given rise to another medical burden that came from the symptoms experienced by patients after acute infection with SARS-CoV-2, a condition often called as Long COVID. As the number of COVID-19 cases remain rising, various studies and scientific researches are being conducted to understand more about Long COVID, and findings have consistently shown increased burden due to Long COVID that needs more attention from the clinical world. This article review collects various sources regarding the diagnosis and management of respiratory syndrome in post-COVID-19 conditions. Long COVID, currently referred to as a post-COVID-19 condition, consists of symptom(s) that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, with symptoms lasting at least two months and cannot be explained by any alternative diagnosis. Symptoms that occur are very diverse from various organ systems, including the respiratory system. Knowledge regarding the possible symptoms as well as a thorough evaluation is needed to identify and diagnose post-COVID-19 conditions, and multidisciplinary management through a tiered system may help reach more cases of post-COVID-19 conditions. The treatment for post-COVID-19 conditions needs to be adjusted to the patient's condition, and the administration of pharmacological therapy such as steroids, bronchodilators, and mucolytics/antioxidants has to be based on clinical symptoms and radiological abnormalities.

Keywords: Long COVID, post-COVID-19 conditions

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INTRODUCTION

The term Long COVID first appeared and was highlighted on social media in May 2020 by Perego to refer to the condition of persistent symptoms after acute SARS-CoV-2 infection. The symptoms experienced can be the same as the acute condition of COVID-19 and new symptoms. The spectrum of symptoms experienced is also very wide, ranging from cardiorespiratory, digestive, neuro-musculoskeletal to psychiatric symptoms.[1–4]

There is no agreement on the definition and terminology for this condition, with several other names such as long haulers, post-COVID syndrome, post-acute COVID-19, sequalae post-acute COVID-19, and chronic COVID syndrome referring to the same condition.[5]

In October 2021, World Health Organization (WHO) released special case definitions for post-COVID-19 conditions from studies using the Delphi consensus method. This consensus involved clinicians and expert researchers, and patients with post-COVID-19 conditions.[5]

This study defines post-COVID-19 conditions as:

1. Conditions in individuals with a history of confirmed or probable COVID-19 infection usually occur within three months after COVID-19, and symptoms persist for at least two months. Another diagnosis cannot explain them.
2. Common symptoms include fatigue, shortness of breath, cognitive dysfunction, and other symptoms that generally affect daily living functioning.
3. No minimum of symptoms required for diagnosis.
4. Symptoms can be new-onset after recovering from acute COVID-19 infection, or symptoms persist since acute COVID-19 and may fluctuate or relapse over time.

5. Different definitions can be found in children.

The Indonesian Society of Respirology or Persatuan Dokter Paru Indonesia (PDPI) Clinical Practice Guideline on COVID-19 also adopted the definition from the study and defined Long COVID as: A post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset of COVID-19, with symptoms lasting at least two months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, and cognitive dysfunction that impact daily functioning. Symptoms may develop after recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms can also fluctuate or recur from time to time.[6]

The increase in COVID-19 cases due to Omicron variants currently raises a new question: Can infection with Omicron variants also cause post-COVID-19 conditions? Scientists' opinions are currently divided, and further studies are needed regarding the incidence of post-COVID-19 conditions in cases of Omicron infection, considering that this variant was newly discovered in November 2021, so there are no studies that can show its effect on the incidence of post-Covid-19 conditions. Dr. Anthony Fauci believes that post-COVID-19 conditions can occur due to any infection variant, with a history of mild or severe symptoms. Meanwhile, other scientists predict that Omicron will not increase the incidence of post-COVID-19 conditions because its infection does not cause a persistent increase in inflammatory markers in the body.[7]

OVERVIEW

A. Diagnostic Approach

History and Physical Examination

At the first visit of a patient suspected of having a post-Covid-19 conditions, a complete history and physical examination is required to obtain all the symptoms and complaints of a post-COVID-19 conditions covering various systems. Although clinical manifestations can be categorized based on the system with predominant complaints, it does not mean that complaints in other systems can be immediately ruled out.[8,9] Some important points in the history of post-COVID-19 conditions that need to be considered are:

1. History of acute COVID-19 infection, both confirmed and suspect.
2. Complaints during acute infections and current complaints.
3. Onset and duration of complaints after COVID-19 infection compared to the beginning of acute infection.
4. Comorbid history and other diseases.[1,8]

Guideline or *Panduan Praktik Klinik* (PPK) PDPI said the history that can be explored in suspicion of post-COVID-19 conditions is as following:[10]

1. Patient history of possible or confirmed COVID-19.
2. There are symptoms/lung and breathing disorders that are permanent > 4 weeks of the onset of COVID-19 symptoms.
3. There are one or more of the following symptoms and signs:
    a) Non-productive or productive cough
    b) Shortness of breath/heavy breathing/ breathing panting/easily tired
    c) Limited activity
    d) Chest pain
    e) Throat pain or itchy throat.

Possible other etiologies besides post-COVID-19 conditions in each complaint need to be studied thoroughly in patients to eliminate the differential diagnosis. On a general examination, it is also necessary to give attention to danger signs such as hypoxemia or desaturation, cardiac chest pain, and Multisystem Inflammatory Syndrome in Children (MIS-C) that need immediate treatment. The physical examination can shows normal findings or abnormalities, thus the findings of routine physical examination do not rule out the possibility of diagnosis.[6,9]

Supporting Examination

The minimum essential supporting examination that can be done on examination of post-

COVID-19 conditions is a complete blood test, kidney function, liver function, electrolytes, inflammatory markers, ECG, and plain chest x-ray.[2] PDPI demonstrates complete supporting examinations for diagnosis and management of respiratory syndrome on post-Covid-19 conditions, including:

1. Laboratory tests in the form of complete blood tests, CRP, ferritin, SGOT, SGPT, ureum, creatinine, blood sugar, HbA1c, blood gas analysis, electrolyte, D-dimer, PT, APTT, Fibrinogen, IgM and IgG antibodies of SARS-CoV-2, and PCR SARS-CoV-2 (according to indications).
2. Measurement of peripheral oxygen saturation (SpO_2).
3. Radiological examination in the form of AP/PA chest x-ray, thoracic ultrasound, chest CT scan, and lung perfusion scan (according to indications).
4. Lung function examination in the form of a 6-minute walking test, diffusion capacity, and cardiopulmonary exercise test.
5. ECG examination.
6. Bronchial provocation test (according to indications).
7. Assessment of quality of life through questionnaires, such as the World Health Organisation Quality of Life assessment (WHOQOL) questionnaire instrument.[6]

In addition, the supporting examination needed to rule out the differential diagnosis also needs to be done according to patient complaints, as listed in Table 1.[2,8]

In addition to laboratory supporting examinations, the use of tools for diagnosis and scoring can help assess patient complaints and see the effects of post-COVID-19 conditions on daily life. Table 2 shows the types of examination tools used in the post-COVID-19 diagnosis approach.[8] Some diagnosis of differential respiratory complaints in post-COVID-19 conditions are as follows:[6]

1. Nasopharyngitis or pharyngitis
2. Acute bronchitis
3. Bacterial pneumonia
4. Pulmonary tuberculosis
5. Interstitial pulmonary disease
6. Lung embolism
7. Heart failure
8. Kidney failure
9. Chronic obstructive pulmonary disease (COPD)
10. Asthma
11. Bronchiectasis
12. Obstructive Sleep Apnea Syndrome (OSAS)
13. Mycosis

Table 1. Additional supporting examination according to complaints for differential diagnosis[2,8]

Category	Laboratory Test
Rheumatologic condition	Antibody antinuclear, rheumatoid factor, anti-cyclic citrullinated peptide, anti-cardiolipin, and creatine phosphokinase
Coagulase disturbance	D-dimer, fibrinogen
Myocardial injury	Troponin
Distinguishes pulmonary cardiac symptoms	*B-type natriuretic peptide*

Table 2. Inspection tools according to complaints for post-COVID-19 conditions[8]

Category	*Inspection Tools*
Functional/*quality of life status*	Patient-Reported Outcomes Measurement Information System (PROMIS) (e.g., Cognitive Function 4a); Post-COVID-19 Functional Status Scale (PCFS); EuroQol-5D (EQ-5D)
Respiratory Conditions	Modified Medical Research Council Dyspnea Scale (mMRC)
Neurology Conditions	Montreal Cognitive Assessment (MoCA); Mini Mental Status Examination (MMSE); Compass 31 (for dysautonomia); Neurobehavioral Symptom Inventory
Psychiatrist condition	General Anxiety Disorder-7 (GAD-7); Patient Health Questionnaire-9 (PHQ-9); PTSD Symptom Scale (PSS); Screen for Posttraumatic Stress Symptoms (SPTSS); PTSD Checklist for DSM-5 (PCL-5); Impact of Event Scale-Revised (IESR); Hospital Anxiety and Depression Scale (HADS)
Physical activity capacity	1-minute sit-to-stand test; 2-minute step test; 10 meter walk test (10MWT); 6-minute walk test
Balance and risk of falling	BERG Balance Scale; Tinetti Gait and Balance Assessment Tool
Other	Wood Mental Fatigue Inventory (WMFI); Fatigue Severity Scale; Insomnia Severity Index (ISI); Connective Tissue Disease Screening Questionnaire; Tilt-table testing (e.g., for POTS); Orthostatic HR assessment

B. Management

Management of post-COVID-19 conditions need to be done in a planned program because it requires a multidisciplinary evaluation and periodic evaluation approach. Patient visits to management of post-COVID-19 conditions are recommended to be done at least three times, including:

1. The first visit as an initial assessment, to plan further examination and management by working diagnosis. This examination can be carried out in the 4th week after the COVID-19 infection, with the condition of the PCR swab of the patient has been negative.
2. The second visit to evaluate the findings of the first examination and adjust the diagnosis and management with the results of new examinations. This examination is carried out in weeks 8-10 after the COVID-19 infection.
3. The third visit was conducted for the evaluation of complaints and evaluation of the long-term complaints experienced by patients.[2,8]

Multidisciplinary Management

In post-COVID-19 conditions management, especially in cases that experience multiorgan symptoms, a multidisciplinary approach and referral to related specialists are needed, especially for further complaints of pulmonology, cardiology, and psychiatry.[2,8,9]

For this reason, NHS suggested that there are three levels of team handling teams after Covid-19, namely:[10]

1. Level 1, Covid Multidisciplinary Team (MDT), which handles post-COVID-19 patients with prolonged symptoms (>3 months) or multidisciplinary cases, with complaints that interfere with the independence of patients in daily activities and require input from ≥2 professionals. This team can include pulmonologist, cardiologist, medical rehabilitation, nurses, physiotherapists, occupational therapists, dietitians, coordinators, researchers, team managers, and administrative support officers.
2. Level 2, the Community Therapy Team, which handles post COVID-19 patients with mild/medium complexity, requires input from 1 professional discipline.
3. Level 3, primary service, which handles post COVID-19 patients with mild symptoms that last for 1–2 months, can recover with independent management.

Noteworthy for multidisciplinary management is the need for a system of recognition of cases of post-COVID-19 conditions, a multidisciplinary team that is pursued, and a referral system between service levels.

Some management that can be given to patients in primary services are:[2,9,11]

1. Medical management such as antibiotics if secondary infections are found and symptomatic such as paracetamol and NSAIDs.
2. Self Management Guidance Complaints, including determining realistic targets for the development of complaints, connecting with support groups, and contacting for further consultation.
3. Optimal management for accompanying diseases.
4. Rehabilitation guidance and planning for complaints

Post-COVID-19 Respiratory Syndrome Management

In general, patients with the post-COVID-19 respiratory syndrome can be given non-pharmacological therapy in the form of:[6]

1. Maintain a healthy lifestyle
2. Eat balanced nutrition
3. Get enough rest and meditation
4. Do the exercise gradually if it can be done
5. Breathing exercises for patients with shortness of breath
6. Olfactory exercises for patients with complaints of anosmia
7. Quit smoking
8. Keep applying the health protocols (wearing masks, washing hands, maintaining distance, avoiding crowds, limiting mobility)

9. SARS-COV-2 vaccination one month after recovery in patients with mild-moderate symptoms and three months later in patients with severe-critical symptoms.

For pharmacological therapy, management of the syndrome is adjusted to the patient's condition, including: (a) clinical symptoms are absent, radiological abnormalities are present; (b) clinical symptoms are present, radiological abnormalities are not present; and (c) clinical symptoms are present, radiological abnormalities are present. The treatments given are pharmacological therapy, pulmonary rehabilitation, oxygen therapy, nutritional therapy, and psychotherapy.[6] The management algorithm for each patient condition recommended by PDPI can be seen in Figure 1.

Supportive examinations for evaluation that can be carried out are laboratory, radiology, and lung function tests, and the need for additional examinations based on complaints and the results of these supporting examinations. This is necessary to monitor the repair of lung parenchymal damage due to SARS-CoV-2 infection. In patients with post-COVID inflammatory lung disease, corticosteroids can be given, while other treatments such as preventing pulmonary fibrosis after acute infection using antifibrotic therapy are still in the research stage.[1]

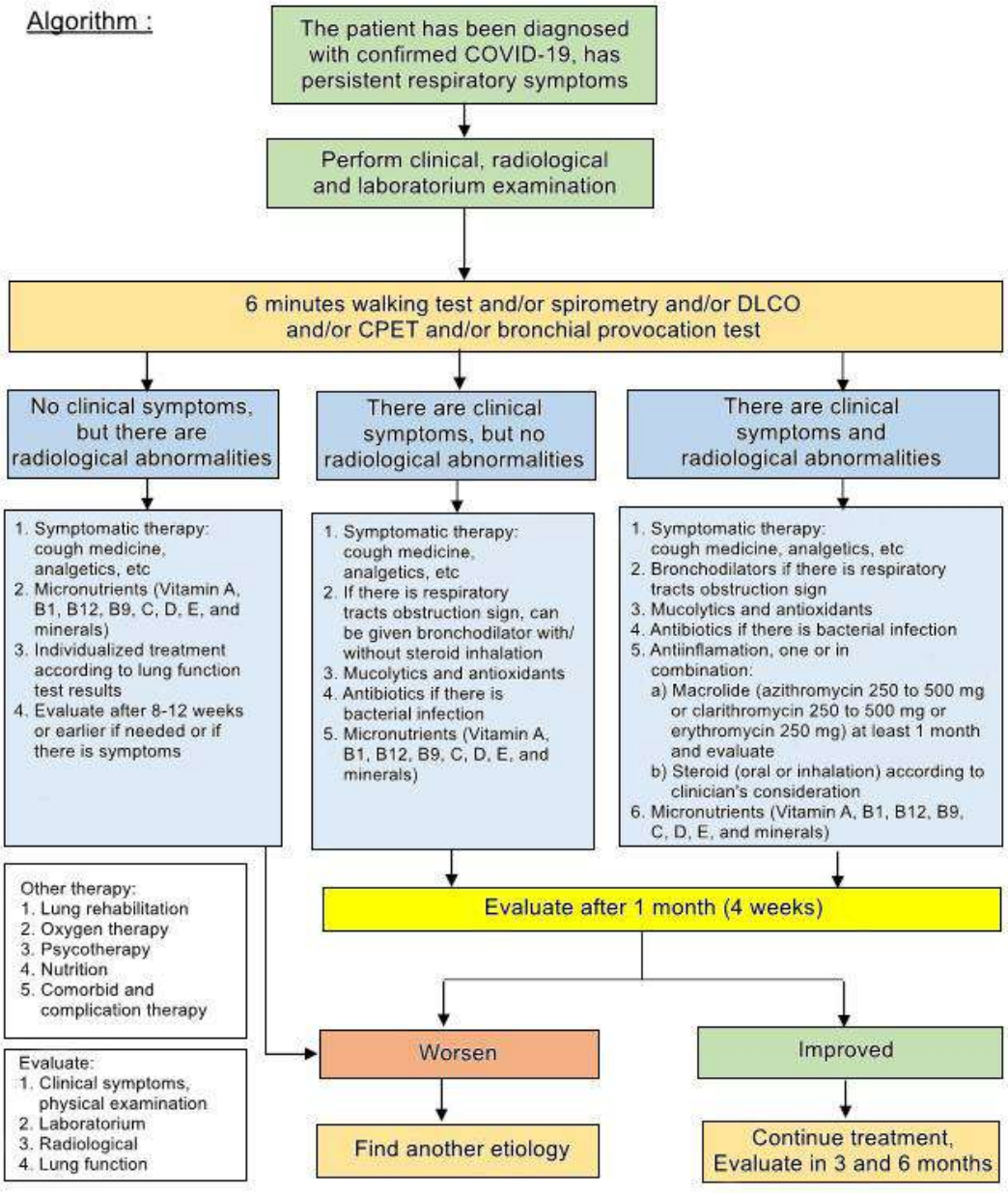

Figure 1. Post-COVID-19 respiratory syndrome management algorithm from PDPI[12]

Steroid Use

A cohort study conducted by Myall KJ et al.[12] in post-COVID-19 patients with evidence of interstitial lung disease (ILD) at 4 weeks post-discharge from treatment for acute infections demonstrated a benefit of steroid use on ILD improvement in patients assessed based on patient complaints, lung function (FEV_1 and FVC), and chest CT scan imaging. In this study, patients were given a maximum initial dose of 0.5 mg/kg prednisolone and then tapered off for up to 3 weeks.

The key to giving steroids to improve ILD in post-COVID-19 patients is the early recognition of ILD cases by a multidisciplinary team so that patients can be given immediate intervention.[12]

Use of Bronchodilators

A study by Maniscalco M et al.[13] evaluated the effect of administering a bronchodilator of 400 g salbutamol to post-COVID-19 patients with a maximum time of 2 months from the onset of acute infection. This study shows an increase in FEV_1 and FVC in post-COVID-19 patients, both those with COPD and concomitant asthma, so bronchodilators should be considered for patients with obstructive symptoms.

It should be noted that this improvement in lung function, when compared with similar studies before the pandemic, showed a lower increase in FEV_1 and FVC, i.e., a 41.8 mL increase in FEV_1 in the post-COVID-19 study compared to 77.2 mL in the pre-pandemic healthy study population. This is suspected as a result of persistent lung damage in post-COVID-19 patients.

Mucolytic/Antioxidant Use

The use of mucolytics/antioxidants is recommended in patients with obstructive disorders such as COPD, and in post-COVID-19 patients with multiple obstructive disorders, these drugs may be considered. The comparative analysis study of Rogliani P et al.[14] showed that erdosteine, carboxysteine, and N-acetylcysteine significantly reduced the risk of acute exacerbations of COPD. Among the three types of mucolytics/antioxidants, erdosteine showed the highest efficacy and the most minor side effects.

Evaluation of Post-COVID-19 Condition Management

The evaluation was carried out at 1 month, 3 months, and 6 months post-therapy by monitoring:

1. Clinical symptoms
   a) Cough (evaluate changes in cough symptoms)
   b) Shortness of breath (evaluate changes in breathlessness)
   c) Chest pain (evaluate changes in chest pain)
2. Recovery from illness (COVID-19)
3. Physical examination of the lungs, including assessment of oxygen saturation (SpO_2)
4. Laboratory examination (as needed)
5. Radiological (evaluate residual lung lesions radiologically)
6. Examination of lung function (evaluation of improvement in lung function)

CONCLUSION

Post-COVID-19 conditions occur in individuals with a history of possible or confirmed SARS-CoV-2 infection with symptoms that last at least two months and cannot be explained by an alternative diagnosis. Symptoms are very diverse from various organ systems, including the respiratory system. Knowledge of the complaints that can be experienced, as well as a thorough evaluation to identify and diagnose post-COVID-19 conditions, and multidisciplinary management through a tiered system can help reach cases of post-COVID-19 conditions. The treatment given needs to be adjusted to the patient's condition, and the administration of pharmacological therapy such as steroids, bronchodilators, and mucolytics/antioxidants needs to be based on clinical symptoms and radiological abnormalities.

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