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Original Article

Inflammatory Markers of ARDS Events among Patients with Severe and Critical COVID-19 Infection at Adam Malik General Hospital, Medan, North Sumatera

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Abstract

Background: COVID-19 can cause fatal outcomes, especially acute respiratory distress syndrome (ARDS). It manifests as organ dysfunction during COVID-19's hyperinflammatory phase, which is associated with a high mortality rate. Data on the clinical characteristics and inflammation markers of patients with severe and critical degrees of COVID-19 with ARDS events are limited.

Method: This study is carried out at the Haji Adam Malik General Hospital in Medan. We grouped 204 medical records from February to July 2022 of hospitalized patients with severe and critical COVID-19 cases into two groups, ARDS and non-ARDS. Characteristics of demographic and laboratory inflammatory markers upon admission between each group were collected. After collecting data and serving as categorical data in the frequency distribution table by SPSS ver 25.0.

Results: We identified 116 patients (56.9%) who had ARDS event upon hospital admission. ARDS event are most commonly found in the elderly group and the median age of ARDS group patients was 59.5 years higher than the non-ARDS group. Male patients were more likely to have ARDS than female patients. Compared with the non-ARDS group, ARDS group patients had lymphocytopenia, neutrophilia, increased neutrophil-to-lymphocyte ratio (NLR), Procalcitonin and C-Reactive Protein levels.

Conclusion: Lymphocytopenia, neutrophilia, increased NLR, procalcitonin and CRP levels upon admission revealed that they were higher in ARDS patients compared to non-ARDS patients. It is critical to identify high-risk groups, such as male sex, the elderly, those with comorbidities, and patients with impaired inflammatory markers to prevent severe complications from COVID-19.

Keywords: ARDS, COVID-19, Indonesia, inflammatory markers, severe COVID-19

INTRODUCTION

In December 2019, the 2019 Coronavirus disease epidemic, also known as COVID-19, was first discovered in China, Wuhan Province. Coronavirus 2019 (COVID-19), caused by the SARS-COV-2 virus globally, hit the world, so the World Health Organization (WHO) declared this plague a significant threat to international health. COVID-19 is contagious and can cause fatal outcomes, especially acute respiratory distress syndrome (ARDS). COVID-19's disease progression may be divided into three stages: early infection, pulmonary phase, and hyperinflammation phase, each of which has a distinct alteration in particular biochemical markers.[1]

Virus infiltration into the lung parenchyma marks the beginning of the first phase, where SARS-CoV-2 infects ciliated bronchial epithelial cells through interaction with ACE2. This stage may be recognized by the presence of lymphopenia. During the pulmonary phase, the pneumonia virus causes localized inflammation of the lungs. Lymphopenia, elevated transaminase enzymes, and systemic inflammatory markers such as C-Reactive Protein are some of the biochemical parameters (CRP). At this stage, most patients need hospitalization. The last stage is the hyperinflammation phase, which is characterized by systemic inflammation or cytokine storm, which could also progress to ARDS and MOF (multiple organ failure). Some inflammatory markers increase significantly.[1]

Most patients with COVID-19 infections have mild flu symptoms, including fever, coughing, and myalgia. However, Acute Respiratory Distress Syndrome (ARDS) is one of the most frequent COVID-19 complications with a high enough mortality rate. ARDS appears as an organ dysfunction in the hyperinflammatory phase of COVID-19. COVID-19 patients who have ARDS have a mortality rate of 50% - 94%.[2–5]

Patients with severe COVID-19 infection exhibit a hyperinflammation state and markers related to inflammation that will be helpful for disease risk stratification. Many studies found that in patients with severe and critical degrees, a picture of hyperinflammation characteristics consisting of decreased lymphocyte levels, an increase in NLR (Neutrophil Lymphocyte Ratio), C-Reactive protein (CRP), which increased and increased procalcitonin. These findings show an essential role of cytokine storms in the pathophysiology of COVID-19.[6,7]

The disease progression begins with a time of incubation of about 3-14 days (an average of five days). Leukocyte and lymphocyte counts are still slightly decreased or normal level and patients are not symptomatic. The next stage in symptoms started to initiate, and the virus spreads hematogenously, majorly in the tissue expressing ACE-2, such as the lungs, digestive tract, and heart. Clinical symptoms in this stage are commonly mild. The second attack occurs 4-7 days after the

early symptoms arise. The patient still has a fever; the lung lesions worsen, and lymphocytes decrease. Inflammatory markers begin to rise in number, and hyperactivity of blood coagulation begins. If the problem is not handled, the following stage of inflammation will be uncontrolled, and a cytokine storm will occur, which will result in ARDS, sepsis, and other form of complications.[8]

Acute Respiratory Distress Syndrome is one of the emergencies in the field of pulmonology, characterized by alveolar-capillary membrane disruption, causing pulmonary edema and severe hypoxemia accompanied by diffuse infiltrate in both lung fields and without clinical signs or objective evidence of left heart failure, and as a one of the leading cause of death in COVID-19, with one of the main features of ARDS is cytokine storm, an inflammatory response systemically caused by the release of cytokines and pro-inflammatory chemical substances.[9,10] In 2008, Raghavendran et al. reported that the average mortality of ARDS was 40-70%. Hartini et al. at Cipto Mangunkusumo General Hospital in 2014 reported an incident of mortality of 75.3%.[11]

This study aims to identify the characteristics of neutrophils, lymphocytes, NLR, procalcitonin and C-Reactive Protein in severe and critical degree COVID-19 patients. However, still few studies have revealed that these inflammatory markers characteristics in severe and critical degree of COVID-19 patients and the correlation in ARDS event.

METHOD

This was a retrospective study from 204 medical records of hospitalized patients with severe and critical COVID-19 cases from February to July 2022 that was conducted at the Haji Adam Malik General Hospital in Medan, Indonesia with a total sampling method. Patients aged 18 years and older with confirmed COVID-19 with severe and critical disease from February to July 2022 that hospitalized were included in this study. COVID-19 diagnosis was made according to the guidelines released by the Ministry of Health and complied with WHO interim guidelines.[12]

When patients presented with one of the following symptoms, they were considered severe cases: 1) respiratory distress with a rate of respiration ≥30 breaths/min; 2) peripheral oxygen saturation ≤93% at resting state; 3) fraction of the oxygen tension in the arterial blood with inspiratory oxygen less than 300 mmHg. Critical cases were defined when patients presented with one of the following: 1) ARDS; 2) sepsis; 3) further organ failures that need critical care unit. [12]

Demographic data (age, age category, sex, comorbidities, onset of symptom to hospital admission and phase of disease) collected as well as laboratory inflammatory markers (neutrophils, lymphocytes, calculated neutrophil-to-lymphocyte ratio (NLR), C-Reactive Protein and procalcitonin). ARDS events defined using Berlin Criteria.[13]

All statistical analyses were carried out using the SPSS version 25.0 software (SPSS Inc). For categorical data, frequencies and percentages were used for descriptive analysis, whereas the median (minimum–maximum) was for quantitative variables.

RESULTS

Between February 2021 and July 2021, 204 COVID-19 confirmed cases' medical records with severe and critical cases were collected at Haji Adam Malik General Hospital.

Acute respiratory distress syndrome event are most commonly found in the elderly group, as shown in Table 1. We categorized the subjects into three following age groups. The median age of ARDS group patients was 59.5 years higher than the non-ARDS group, 57.50 years. Male patients were more likely to have ARDS than females (32.8% vs 24.1%).

We categorized the course of the symptoms into three groups, phase 1 (0-4 days), phase 2 (4-10 days), and phase 3 (≥11 days), more patients in the ARDS group were on phase 2 and 3 than in phase 1 (30.4% vs 18.6% vs 7.8%).

Table 1. Demographic characteristics of the samples

Variable	ARDS	Non-ARDS	Total
Sex			
Male	67 (32.8%)	52 (25.5%)	119 (58.3%)
Female	49 (24.1%)	36 (17.6%)	85 (41.2%)
Age [Median (min-max)] (years)	59.50 (21-84)	57.50 (21-81)	58.50 (21-84)
Young Adult (20-39)	11 (5.4%)	10 (4.9%)	21 (10.3%)
Adult (40-59)	47 (23.0%)	40 (19.6%)	87 (42.6%)
Elderly (≥60)	58 (28.4%)	38 (18.6%)	96 (47.1%)
Diabetes Comorbid			
Yes	40 (19.6%)	28 (13.7%)	68 (33.3%)
Hypertension Comorbid			
Yes	71 (34.8%)	38 (18.6%)	109 (53.4%)
Heart Disease Comorbid			
Yes	30 (14.7%)	20 (9.8%)	50 (24.5%)
Kidney Disease Comorbid			
Yes	13 (6.4%)	13 (6.4%)	26 (12.7%)
Malignancy Comorbid			
Yes	0 (0%)	6 (2.9%)	6 (2.9%)
Others			
Yes	9 (4.4%)	107 (52.5%)	116 (56.9%)
Comorbidities			
No comorbid	29 (14.2%)	22 (10.8%)	51 (25.0%)
1 comorbid	33 (16.2%)	32 (15.7%)	65 (31.9%)
>1 comorbid	54 (33.9%)	34 (16.7%)	88 (50.6%)
Symptom to admission [Median (min-max)] (days)	8 (2-20)	7 (2-15)	7.5 (2-20)
Phase			
Phase 1 (day 0-4)	16 (7.8%)	23 (11.3%)	39 (19.1%)
Phase 2 (day 5-10)	62 (30.4%)	62 (25.5%)	114 (55.9%)
Phase 3 (day ke ≥11)	38 (18.6%)	13 (6.4%)	51 (25.0%)

Table 2. Characteristics of inflammatory markers in ARDS and non-ARDS groups

Variable	ARDS	Non-ARDS	Total
Neutrophil [Median (min-max)]	9.76 (1.89-31.34)	7.57 (0.16-21.90)	8.39 (0.16-32.34)
Neutrophilia	89 (43.6%)	46 (22.5%)	135 (66.2%)
Lymphocyte [Median (min-max)]	0.91 (0.25-3.98)	0.92 (0.14-3.48)	0.92 (0.14-3.98
Lymphocytopenia	96 (47.1%)	74 (36.3%)	170 (83.3%)
NLR [Median (min-max)]	11.02 (1.72-50.14)	6.97 (0.47-71.43)	0.92 (0.14-3.98)
Increased NLR	86 (42.2%)	43 (21.1%)	129 (63.2%)
Procalcitonin [Median (min-max)]	0.40 (0.02-373)	0.14 (0.03-58.50)	0.24 (0.02-373)
Increased Procalcitonin	88 (43.1%)	44 (21.6%)	132 (64.7%)
C-Reactive Protein			
Increased CRP	68 (33.3%)	38 (18.6%)	106 (52.0%)

The median time from the beginning of the first symptom to hospital admission was 7.5 days. In ARDS patients, the median duration from the first onset of symptom to hospital admission was 8.05 days, longer than the non-ARDS group, 6.96 days.

We noted that more patients in the ARDS group had comorbid hypertension (34.8% vs 18.6%), diabetes (19.6% vs 13.7%), heart disease (14.7% vs 9.8%), and more than one comorbid (33.9% vs 16.7%).

Laboratory findings (Table 2) on admission showed that the inflammatory markers were increased in patients in the ARDS group. Neutrophilia was found in 43.6% of patients in the ARDS group, with a median value higher than the non-ARDS group (9.76 x 10^3/µL vs 7.57 x 10^3/µL). On admission, lymphocytopenia was present in 83.3% and more frequent in the ARDS group compared to the non-ARDS group (47.1% vs 36.3%). Using this data, we calculated the NLR and found a higher NLR in ARDS patients compared to the non-ARDS patients (42.2% vs 21.1%) with a higher median value (11.02 vs 6.97).

DISCUSSION

Despite significant control measures, the global COVID-19 epidemic is damaging, with high morbidity and fatality. We need accessible, cost-effective markers to simplify diagnostics and assess disease severity. In severe COVID-19, ARDS can arise from a dysregulated host response to SARS-CoV-2.

In this study, we revealed that male, elder patients, or patients with comorbidities, were more likely to develop ARDS. In healthy individuals, innate immunity neutralizes the virus early on, preventing it from infiltrating the alveoli. In older people, when innate immunity is compromised, the virus can get into the alveoli and replicate in large numbers. This causes macrophages and lymphocytes to initiate a robust reaction to eliminate virally infected cells. Enhanced levels of cytokines are related to this reaction. It can explain why the elderly are more prone to severe COVID-19 infections.[14,15]

It was hypothesized that the increased of neutrophils and decreased of lymphocytes were triggered by a cytokine storm in the body that triggers a series of

immunological reactions. In severe instances, the levels of inflammatory markers were found to be greater than in less severe cases. It indicates that a hyperinflammatory response could play an important role in the development of COVID-19. NLR is a simple inflammatory parameter that may be assessed in routine hematological examinations. Previous research has shown that increased NLR to clinical progressivity and fatality in COVID-19 cases.[15,16]

Furthermore, our present study showed that elevated procalcitonin and CRP were detected more in patients with ARDS compared with those without ARDS. It is attracting increased attention, as many COVID-19 patients with ARDS present with a dysregulated immune state. In addition, activated immune cells drive additional infiltration and increase the generation of reactive oxygen species and nitric oxide, which damages the epithelial-endothelial barrier and causes an imbalance in the ventilation/blood flow ratio, hence promoting the progression of ARDS.[17]

CONCLUSION

Placing high-risk patients in monitored isolation is crucial for tracking the fatal case of COVID-19. Identifying high-risk groups, such as elderly persons and those with comorbidities, and placing them in appropriate care is important. Neutrophilia, lymphocytopenia, increased NLR, and increased procalcitonin occurred in most patients in the ARDS group compared to the non-ARDS group. Consideration of inflammatory markers would help an early prediction for COVID-19 patients with ARDS event. These markers may be useful in determining how to allocate respiration equipment amongst patients in the intensive care unit. Nonetheless, further clinical research is required to determine the advantages of these inflammatory markers in anticipating ARDS.

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Original Article

Analysis of C-Reactive Protein, Neutrophil-to-Lymphocyte Ratio, PaO_2/FiO_2 Ratio on the Success of High Flow Nasal Cannula Usage in Hospitalized COVID-19 Patients

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Abstract

Background: Several studies had shown High Flow Nasal Cannula (HFNC) is effective in treating hypoxemic COVID-19 patients. The C-Reactive Protein and Neutrophil-to-Lymphocyte Ratio is an inflammatory marker that could predict the severity of COVID-19, where the P/F ratio infers oxygenation status. Since COVID-19-related ARDS is closely related to a hyper-inflammatory state and HFNC becomes widely utilized for hypoxemic patients, it has become important to discover reliable inflammatory biomarkers related to therapeutic HFNC success. This study aims to assess the factors that influence the success of HNFC therapy, in terms of demographic and laboratory profiles of CRP, NLR, and P/F ratio.

Method: A retrospective, single-center cohort study was conducted in a tertiary care hospital in Malang, East Java from January to March 2022. Subjects of 31 PCR-confirmed, hospitalized COVID-19 patients who were treated with HFNC were included.

Results: This study involved 2 groups comprised of 19 subjects with successful HFNC and 12 patients who failed. Significant demographic factors affecting successful HFNC were female gender (OR=1.46 95% CI=1.08-1.99; P=0.037) and occupation type (P=0.023). Whereas, biomarkers of CRP (8.90±6.8 mg/L vs 12.39±11.7 mg/L; P=0.656), NLR (7.24±4.66 vs 12.85±12.9; P=0.243) and P/F ratio (171.40±54 vs 148.00±40; P=0.219) were found to be non-significant between successful and failed HFNC cohorts, respectively.

Conclusion: HFNC could provide a specific positive end-expiratory pressure in COVID-19 patients with contributing factors of successful HFNC being female and occupational type. However, CRP, NLR, and P/F did not contribute significantly to HFNC's success.

Keywords: COVID-19, CRP, HFNC, P/F ratio

INTRODUCTION

The coronavirus disease 2019 (COVID–19) pandemic is a major global health problem. The disease was first reported in Wuhan City, Hubei Province, China, on December 31st, 2019, and was later identified as a new type of

coronavirus, i.e. SARS-CoV-2.[1] Until June 2022, there were more than 500 million cumulative cases with a total of more than 6 million deaths due to COVID-19.[2]

Although the incidence of COVID-19 in Indonesia experienced a significant decrease, the coverage of vaccination in Indonesia is still low, where only 17% of the population had received a booster, i.e. the third dose of the COVID-19 vaccine.[3] Therefore, the possibility of an increase in COVID-19 cases would still likely happen.

Approximately, 14% of patients with COVID-19 would be at risk of developing hypoxemic respiratory failure, and 5% would require advanced oxygen therapy, including mechanical ventilation, and therefore respiratory support therapy is very crucial for these patients. Although the mechanism is still unclear and yet to be elucidated, patients with COVID-19 might develop pneumonia characterized by bilateral interstitial infiltrates, which could lead to acute respiratory distress syndrome (ARDS) and respiratory failure due to ventilation-perfusion mismatch and shunt effects.[4]

Several studies had mentioned the advantages of using HFNC over non-invasive ventilation (NIV) and continuous positive airway pressure (CPAP) in acute hypoxemic respiratory failure due to COVID-19.[5] However, based on our recent study, there were currently no clear evidence-based guidelines in this regard.

High Flow Nasal Cannula for oxygen therapy is a new technology for respiratory support that is gaining attention. In recent years, it had attracted lots of attention for medical applications due to its advantages of stable oxygen performance and constant oxygen output.[6]

The utilization of HFNC in the management of COVID-19 was still controversial, mainly due to concerns regarding aerosol-generating effects, thus predisposing medical personnel to the risk of transmission. However, the evidence from recent studies further confirmed minimal effect of aerosolization and the risk of transmission to medical personnel with the use of HFNC.[7]

A report from two hospitals in Chongqing, China stated 63% of patients with acute respiratory failure due to COVID-19 were treated with HFNC as the first line; among these patients, 59% had a successful recovery, whereas 41% had a failure. However, the failure rate in patients with a PaO_2/FiO_2 (P/F) ratio >200, i.e., mild ARDS, was 0%. Several studies from China also found that early use of HFNC and NIV resulted in a lower mortality rate from COVID-19 with <1% requiring intubation, as compared to their national average mortality rate of 2.3%.[8]

The previous study noted that the severity of inflammation had been well correlated with the success rate of HFNC. Adult patients with acute hypoxemic respiratory failure from sepsis showed a higher P/F ratio and lower lactate contributed to successful HFNC. Another finding from this study also noted that lower SOFA scores were significantly correlated with successful HFNC.[9]

Several inflammatory biomarkers had been investigated for their correlation to

predict the severity of pulmonary disease. C-reactive protein (CRP) is an acute-phase protein synthesized primarily by the liver in response to interleukin 6 (IL-6), a pro-inflammatory cytokine.[10] These properties made CRP an inflammatory marker and could assist in predicting the severity of community-acquired pneumonia (CAP).

As previously stated, COVID-19 pathophysiology is based on a cytokine-mediated hyper-inflammatory process that evolved into a cytokine storm. Hyper-inflammation biomarkers include CRP, IL-6, ferritin, D-dimers, lactate dehydrogenase (LDH), procalcitonin, lymphopenia, and thrombocytopenia.[11] Since COVID-19-related ARDS is closely related to a hyper-inflammatory state and HFNC becomes widely utilized for hypoxemic patients, it has become important to discover reliable biomarkers related to inflammation as an indicator of therapeutic HFNC success.

This study investigated factors related to a successful HFNC therapy in adult hypoxemic COVID-19 subjects in regards to mortality rate and the need for intubation, as well as linked it to inflammatory markers of CRP and NLR, s as well as oxygenation status of P/F ratio.

METHOD

This study was designed as a retrospective cohort, single-centered at Saiful Anwar General Hospital's integrated airborne-isolation ward, consecutively from January to March 2022. Subjects included in this study were hospitalized COVID-19 patients confirmed by reverse-transcriptase polymerase chain reaction (rt-PCR) or GeneXpert® SARS-CoV-2 rapid molecular testing method and treated with HFNC.

Demographic data were obtained. Further laboratory testing results were collected when the patient was first admitted. Nominal variables were expressed in frequency and percentage (%) and numeric parameters were noted at means±standard deviation (SD). Further bivariate analysis with T-test, Mann-Whitney, and Chi-square was conducted. All statistical analyses were performed with SPSS 25.0 to determine significant factors contributing to the success of HFNC. Consequently, the use of HFNC may improve the prognosis for COVID-19 patients. This study aims to assess the factors that influence the success of HNFC therapy in the management of severe COVID-19 patients.

RESULTS

Thirty-one subjects, consisted of 25 males and 6 females rt-PCR confirmed hospitalized COVID-19 patients requiring HFNC, were included in this present study. Most of the patients were between the ages of 50 and 64 years old. Chi-square test were conducted between categorical variables to yield odds ratio (OR). From demographic profiles, Fischer exact test showed that gender was statistically significant with P=0.037 and OR=1.46 (1.08-1.98), indicating that there was a correlation between gender and the success of HFNC, where males were more

vulnerable to HFNC failure. Chi-square analysis showed a significant difference between occupation type and the success of HFNC with value of P=0.023, where laborers and unemployed people had a high risk of failing HFNC therapy.

Table 1. Distribution data according to age, between subjects

Age (years)	Frequency	P
15-49	11 (35.5%)	
50-64	17 (54.8%)	0.578%
>64	3 (9.7%)	

Note: *Statistical analysis with Chi-square test

Table 2. Distribution data according to gender and occupation between subjects

Parameter	HFNC Outcome (frequency, %)		P
	Success (n=19)	Failure (n=12)	
Gender			
Male	13 (41.9)	12 (38.7)	0.037*[b]
Female	6 (19.4)	0	1.46 (1.08-1.99)[c]
Occupation type			
Shopkeeper	5 (16.1)	1 (3.2)	
Civil servant	7 (22.6)	0 (0)	
Housewife	1 (3.2)	0 (0)	0.023*[a]
Nurse	1 (3.2)	0 (0)	
Laborers	2 (6.5)	5 (16.1)	
Unemployed	3 (9.7)	6 (19.4)	

Note: [a]Statistical analysis with Chi-square test; [b]Analysis with Fischer exact test; [c]Odds ratio (OR) with 95% confidence interval; *P<0.05 is considered statistically significant

Table 2. Laboratory differences between cohorts of COVID-19 inpatients who received successful and unsuccessful HFNC therapy

Parameter	HFNC Outcome (mean±SD)		P
	Success (n=19)	Failure (n=12)	
Leukocyte count (cell/mm^3)	7932.10 ± 2771.33	10270.83 ± 7740.25	0.715[a]
Lymphocyte (cell/mm^3)	1070 ± 380.37	988.88 ± 945.62	0.553[b]
Monocyte (cell/mm^3)	502.85 ± 177.40	610.07 ± 298.3	0.215[b]
Neutrophil (cell/mm^3)	6324.68 ± 2675.89	8524.64 ± 7797.31	0.746[a]
Platelets count (cell/mm^3)	253284.21 ± 106009	248916.66 ± 104936.74	0.911[a]
Haemoglobin (g/dL)	14.50 ± 1.39	13.65 ± 2.20	0.133[a]
C-reactive protein (mg/L)	8.9 ± 6.8	12.39 ± 11.7	0.656[a]
Procalcitonin (ng/mL)	0.298 ± 0.345	0.79 ± 0.87	0.109[a]
Serum ferritin (µg/L)	1223.93 ± 1415.71	1867.8 ± 1995.06	0.522[a]
Fibrinogen	497.85 ± 83.56	550.47 ± 103.79	0.460[b]
LDH	435.0 ± 77.06	502.0 ± 261.62	1.000[a]
AST	76.94 ± 47	51.83 ± 29.1	0.118[a]
ALT	69.68 ± 56.5	48.08 ± 34.65	0.133[a]
Random blood glucose (mg/dl)	147.05 ± 58.7	156.83 ± 45.21	0.453[a]
Ureum	37.82 ± 57.57	59.45 ± 57.57	0.465[a]
Serum Creatinine	10.90 ± 0.39	1.37 ± 1.12	0.951[a]
PaO_2/FiO_2 Ratio	171.40 ± 54	148 ± 40	0.219[b]
D-dimer	3.25 ± 6.3	1.75 ± 1.7	0.500[a]
NLR	7.24 ± 4.66	12.85 ± 12.9	0.243[b]
Lactate	2.78 ± 0.88	3.30 ± 1.4	0.242[b]
SP-D	6.94 ± 7.8	1.54 ± 1.19	0.052[a]

Note: [a]Statistical analysis with Mann-Whitney test; [b]Analysis with independent t-test; LDH=lactate dehydrogenase; AST=aspartate transaminase; ALT=alanine transaminase; NLR=neutrophil-to-lymphocyte ratio; SP-D=surfactant protein-D.

The average CRP value in our cohorts who failed HFNC therapy was 12.39±11.7 mg/L. This finding was higher than patients who were successfully treated with an average of 8.9±6.8 mg/L. Through the Mann-Whitney test, the value of P=0.656, a non-significant difference between the two groups. The average NLR value in patients who failed therapy was 12.85±12.9, while in patients who were successfully treated was 7.24±4.66, through the Mann-Whitney test, with P=0.243, so it can be concluded that there is no significant difference between the two groups. The P/F Ratio in patients who failed therapy was 148.40, while it was 171.40 in patients who were successful in HFNC therapy.

DISCUSSION

Currently, non-invasive mechanical ventilation has become the first-line choice in the ventilation procedure for critically ill patients. One of the non-invasive mechanical ventilations widely utilized is HFNC. HFNC is considered an alternative to CPAP for respiratory support in critically ill patients.[12] HFNC is a sophisticated and high-cost mechanical ventilation system that uses oxygen. Therefore, the use of HFNC should be considered clinically by attending physician jurisdiction.[13]

High flow nasal cannula system consisted of an oxygen or air mixer, an active hot humidifier, a single heated circuit, and a nasal cannula. In the air/oxygen mixer, the value of the inspired oxygen fraction (FiO_2) is adjusted from 0.21 to 1.0 in flows up to 60 L/min.[12] From clinical aspects, HFNC is also beneficial for patients' comfort and ease of use, as well as physiological aspects, including higher oxygenation, alveolar recruitment, humidification and heating, increased clearance of secretions, and reduction of dead space, as well as preventing damage to lung function and endotracheal intubation.[14]

The average NLR value in patients with failed HNFC therapy showed a higher value, but this was statistically non-significant. The average CRP value in our cohorts who failed HFNC therapy was higher than patients who were successfully treated, value of P=0.656, a non-significant difference between the two groups. Although non-significant, the trend of these findings were in concordance with previous studies. Based on Zablockis et al study, the NLR and CRP value showed that there was a progressively higher level of NLR and CRP among subjects who failed non-invasive oxygen therapy.[15]

However, there was a non-significant difference in NLR and CRP levels between NIV failure groups and HFNC failure groups.[15] In this regard, NLR and CRP might be reliable biomarkers for inflammatory states,[16] but could not predict the event of failed or successful HFNC treatment.

From previous studies, the uses of HFNC could improve patient's oxygenation, reduce the work of respiratory muscle and energy consumption, also accelerate the recovery of patient's physical condition. However, due to small number of cases and

poor representativeness in this study, data from a large sample is needed to verify this study. Furthermore, HFNC reduces the rate of intubation and improve clinical prognosis of patients with acute respiratory failure as stated in previous study.[17]

In this study, the P/F ratio in subjects with failed HFNC treatment was lower, but statistically non-significant. A higher P/F ratio meant a milder degree of respiratory failure, thus inferring better oxygenation, and vice versa.[18] This finding exhibited a similar trend to the previous study, i.e. higher P/F ratio in successful HFNC treatment. Eryuksel et al that stated higher PaO_2 and higher P/F ratio could predict significantly the odds of successful HFNC treatment.[9]

In this study, Eryuksel et al emphasized that HFNC was associated with a considerable risk of mortality in cases where it was not successful; therefore, identifying the factors that contribute to the prediction of unsuccessful outcomes could be valuable in reducing mortality rates of hypoxemic respiratory failure.[9]

Geng et al showed that after providing HFNC for 2 hours, the rate of oxygenation was improved. During treatment, 8 patients with COVID-19 found that HFNC could meet their oxygen requirements, characterized by increased P/F ratio and higher ROX (rate of oxygenation).[19]

In 2020, Teng et al compared HFNC oxygen therapy with conventional oxygen therapy, including nasal cannula and simple mask within severe COVID-19 cohorts. In Teng et al study, it was found that after 6 hours of use, PaO_2/FiO_2 was better in HFNC group with value of P=0.045.[6]

High-flow nasal cannula oxygen therapy is more effective in improving the P/F Ratio compared with conventional oxygen therapy. In this regard, HFNC is superior because of its ability to produce a specific positive end-expiratory pressure (PEEP), therefore it is beneficial for mild and moderate type I respiratory failure. HFNC also reduces the metabolic work associated with atmospheric gas conditioning because HFNC provides warm, humidified gas through the nasal pharynx, conducive to the recovery of airway ciliary function, promoting the discharge of secretion, and reduces the loss of heat and water in the respiratory tract.[17] After treatment HNFC, P/F Ratio had improved significantly with the prolongation of treatment time.

However, there are several factors affecting the failure of HFNC. Abboud et al, which examined HFNC in patients with bronchiolitis, stated HFNC failure was associated with low respiratory rates and high pCO_2 values.[20] Guillot et al study also stated that pCO_2 affects HFNC failure.[17] Kim et al found that HFNC failure was significantly related to the attending physician's decision to use HFNC, respiratory rate, SaO_2, SpO_2 <6 hours before HFNC insertion, and ROX index <6 hours preceding HFNC insertion.[13]

This present study showed several biomarkers that could potentially predict HFNC outcomes in COVID-19 patients admitted to the hospital. However, there

are some limitations of this study, i.e. single-centered and retrospective manner of the study. The other limitation would be the limited sample size and this study was not considering an early usage of HNFC as demonstrated by Duan et al, where sooner HFNC commencement to the patient, the more optimal the effect would be.[8] Further investigation is required to analyze potential inflammatory biomarkers in a prospective, longitudinal manner with a larger population.

CONCLUSION

HFNC could provide a specific positive end-expiratory pressure for mild and moderate type I respiratory failure in COVID-19 patients with significant contributing factors to a successful HFNC being female and occupational type, in this study. From laboratory profiles, subjects with successful HFNC treatment exhibited lower CRP, lower NLR, and higher P/F ratio. Despite being considered potential factors, CRP, NLR, and P/F were found to have no significant contribution toward the efficacy of HFNC treatment in our study. Further investigations were required to analyze biomarkers that could predict the success of HFNC usage.

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Original Article

Myocard Injury in COVID-19 Patients After Application OfUmbilical Cord Mesenchymal Stem Cell (UC-MSC) as Adjuvant Therapy in Persahabatan Hospital

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Abstract

Background: Myocardial injury was a frequent cardiovascular manifestation of COVID-19 and associated with high mortality. Cell-based approaches, primarily using mesenchymal stem cell (MSC) has demonstrated safety and possible efficacy as adjuvant therapy in COVID-19 patients. This study aims to evaluate myocardial injury in patients with moderate-severe and critically ill COVID-19 after the application of umbilical cord mesenchymal stem cell (UC-MSC) as adjuvant therapy in Persahabatan hospital.

Method: This is a retrospective and prospective cohort study. A total of 28 subjects were allocated to 13 subjects in the control and 15 subjects in the experimental group. Subjects were given the standard treatment and UC-MSC or placebo. Myocardial injury is defined by an increase of troponin I >26 pg/ml. The biomarkers of troponin I, NT-proBNP and CRP was examined periodically. Cardiac pump evaluated by EF and TAPSE from echocardiography examination before and after UC-MSC application. The evaluation of myocardial injury, biomarkers, cardiac pump and 15-day mortality were observed between the two groups.

Results: The incidence of myocardial injury was 28,6% of total subjects. Subjects with worsening myocardial injury were higher in the control group (6 subjects) than the experimental group (4 subjects) although not statistically significant. The difference in biomarkers (troponin I, NT- pro-BNP and CRP), cardiac pump function (EF and TAPSE) and 15-day mortality between two groups were not statistically significant. There was a trend of decreasing troponin I, NT-proBNP and CRP in the experimental group.

Conclusion: UC-MSC application can be an option as adjuvant therapy in improving myocardial injury of moderate-severe and critically ill COVID-19 patients.

Keywords: COVID-19, mesenchymal stem cell, myocardial injury

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) has become a pandemic, causing high and still increasing mortality and morbidity rates worldwide.[1] As of 23 July 2020, WHO reported 15,012,731 cases and 619,150 deaths (4.1% mortality rate) worldwide. Meanwhile, the Ministry of Health of the Republic of Indonesia said in July 2020 there were 95,418 cases and 4,665 deaths (mortality rate 4.9%).[2]

Myocardial injury is the most common cardiovascular manifestation of COVID-19 and is associated with a worse outcome. A meta-analysis by Zou et al reported a prevalence of myocardial injury of 24.4% in hospitalized patients with a fivefold increase in mortality compared to those without myocardial injury.[3] The Chinese Center for Disease Control and Prevention reports that cardiovascular comorbidities increase the mortality rate to 10.5% compared to the total mortality rate of 2.3%.[4]

Mesenchymal stem cell therapy (MSCs) has been reported as a new therapeutic strategy for COVID-19. Hirsch et al, through clinical trials and pilot projects, said that giving MSCs to patients with severe and critical degrees of COVID-19 pneumonia decreased intensive care rates and accelerated patient recovery.[5]

Leng et al reported that giving MSCs therapy to COVID-19 patients improved symptoms and lung function.[6] The mechanism of action of MSCs in COVID-19 is not fully known, but it is suspected to have immunomodulatory abilities so that it can suppress cytokine storms improve the microenvironment of lung tissue and capillary networks and prevent fibrosis.[7]

Therefore, researchers plan to conduct a study to evaluate myocardial injury in pneumonia patients with moderate-severe and critical COVID-19 receiving additional therapy for umbilical cord MSCs (UC-MSC) at Persahabatan Hospital.

METHOD

This retrospective and prospective cohort study was part of a multicenter, randomized controlled, and double-blind phase III clinical trial entitled "Application of UC-MSC as Adjuvant Therapy for Moderate-severe and Critical COVID-19 Pneumonia Patients". This research was conducted in the COVID-19 treatment room at Persahabatan Hospital from September 2020 to March 2021. The research sample was a reachable population that met the admission criteria.

Respondent acceptance criteria were patients aged 18-95 years, diagnosed with COVID-19 pneumonia confirmed by RT-PCR examination of throat swabs, meeting the requirements for moderate-severe and acute COVID-19 pneumonia, and willing to participate in the study by signing a consent form. While the criteria for rejection are having a history of malignancy, pregnant women, or a positive pregnancy test, or the subject has participated in other clinical trials in the last 3 months.

Samples were taken by consecutive sampling according to the acceptance criteria until the number of samples was fulfilled. Statistical tests were carried out using SPSS ver 25. The Shapiro-Wilk normality test assessed data distribution. Categorical data is assessed by the Chi-square test, while numerical data is evaluated by the unpaired T-test or the alternative test if the conditions are not fulfilled.

RESULTS

This study's sample size was 38 subjects who met the acceptance criteria. These subjects consisted of 13 subjects with a critical degree of COVID-19 pneumonia and 25 subjects with a moderate-severe degree of COVID-19 pneumonia. A total of 10 subjects in the moderate-severe degree were rejected because 7 subjects entered the critical criteria and 3 subjects underwent conversion before implantation.

Subjects were divided into 13 subjects in the treatment group and 15 in the control group. As long as post-implantation follow-up is given, no subject is lost to follow-up, so all subjects can be analyzed. The basic characteristics of the subject are shown in Table 1. There were no statistical differences in the subjects' characteristics between the two groups.

The incidence of myocardial injury in all subjects before implantation was found in 8 subjects (28.6%) consisting of 5 subjects (17.9%) from the treatment group and 3 subjects (10.7%) from the control group. Furthermore, an assessment of the characteristics of the subjects who experienced myocardial injury was carried out.

The female gender was found to be more numerous, namely 5 subjects (62.5%), and the age range in both age categories was obtained. The highest BMI was found in the obese group, namely, 4 subjects (50%), more critical level Covid-19 pneumonia, 6 subjects (75%), the number of comorbidities ≥3 and cardiovascular comorbidities found in 6 subjects (75%) and the mortality outcome were found in 6 subjects (75%). Furthermore, an assessment of myocardial injury after implantation was carried out. Changes in troponin I value were considered significant if there was an increase of >20% after implantation compared to before implantation.[8]

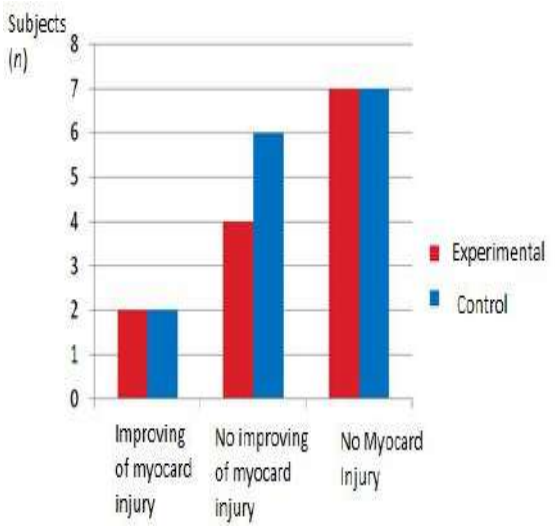

Figure 1. Evaluation of Myocardial Injury Both groups

Subjects were divided into three groups, the myocardial injury group improved, the myocardial injury group did not improve, and the myocardial injury did not.

Table 1. Basic Characteristics of Subject

Characteristic	Treatment (n=13)		Control (n=15)		P
	n	%	n	%	
Gender					
Male	8	61.5	10	66.7	1.0[f]
Female	5	38.5	5	33.3	
Age					
40-60	7	53.8	10	66.7	0.48[cs]
>60	6	46.1	5	33.3	
Body Mass Index					
Normal (18.5-25)	8	61.5	5	33.3	
Fat (25.1-27)	1	7.7	3	20	0.25[ks]
Obesity (>27)	4	30.8	7	46.7	
Number of Comorbid					
0	1	7.7	0	0	
1	3	23.1	7	46.7	0.26[ks]
2	4	30.8	6	40	
≥3	5	38.5	2	13.3	
Type of Comorbid					
Hypertension	7	25.9	9	36	
Diabetes Mellitus type II	8	29.6	7	28	
Obesity	4	14.8	7	28	
Congestive Heart Failure	4	14.8	0	0	0.77[ks]
Coronary Artery Disease	2	7.4	0	0	
Ex-Pulmonary Tuberculosis	2	7.4	1	4	
Old Cardiovascular diseases	1	3.7	1	4	
Levelst					
Critical	6	46.2	7	46.7	0.97[cs]
Moderate-Severe	7	53.8	8	53.3	
Oxygen Assistance					
Mechanical Ventilation	6	46.2	7	46.7	1.0[ks]
High Flow Nasal Cannula	6	46.2	8	53.3	
Nassal Canula	1	7.6	0	0	
Compilation					
Hospital-acquired Pneumonia	9	69.2	11	73.3	
Acute Kidney Injury	9	69.2	4	26.7	
Urinary Tract Infection	4	30.8	3	20	0.75[ks]
Systemic Candidiasis	1	7.7	0	0	
Diabetic Ketoasidosis	1	7.7	2	13.3	
Other Adjuvant Therapy					
Tocilizumab	1	7.6	0	0	0.35[cs]
Intravenous immunoglobulin (IVIG)	0	0	1	6.7	

Note: [f]Fisher's test; [cs]Chi Square Test; [ks]Kolmogorov Smirnov Test

Figure 2 shows the myocardial injury subjects improved, and no myocardial injuries were the same in both groups, namely 2 subjects and 7 subjects. While subjects with myocardial injuries did not improve, there were more in the control group, namely 6 subjects, compared to the treatment group, namely 4 subjects.

Table 2. Differences in Troponin I, NT-proBNP and CRP values of the two groups before implantation

Biomarkers/Group	Before Implementation Median (min-max)	P	After Implantation Median (min-max)	P
Troponin I				
Treatment	9.5 (0.6-179.5)	0.29[m]	10.3 (1-469.4)	0.84[m]
Control	5.6 (0.6-5.986)		16.9 (1.3-2.160.4)	
proBNP				
Treatment	336 (5-11.188)	0.7[m]	430.2 (16-10.866)	0.64[m]
Control	157.8 (38.7-10.273)		197.7 (19.2-9.287)	
CRP				
Treatment	336 (5.0-11.188)	0.66[m]	83.5 (2.8-469.4)	0.13[m]
Control	157.8 (38.7-10.273)		105 (10.3-245)	

Note: [m]Mann Whitney Test

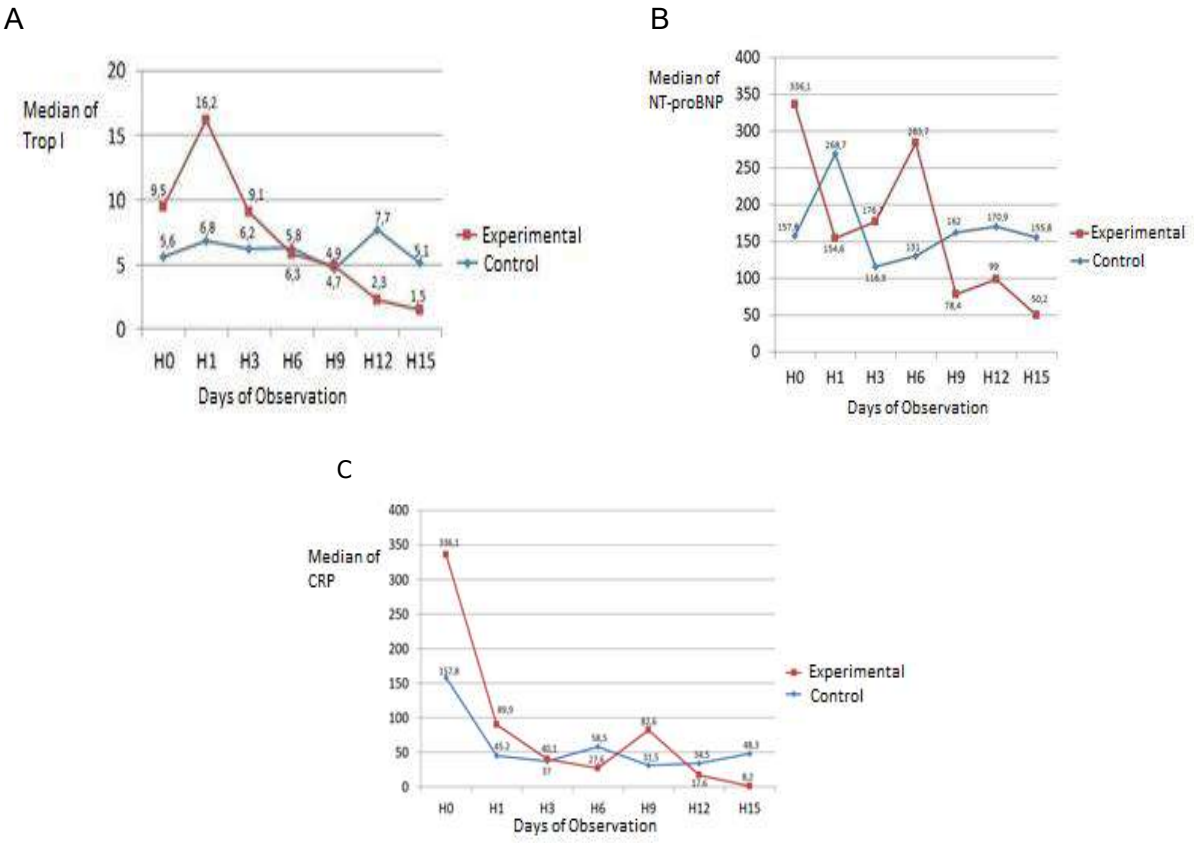

Figure 2. Graph of the trendline of the biomarker values of the two groups on each day of observation: A) Troponin I, B) NT-proBNP, and C) CRP.

In this study, three biomarkers were assessed, two markers related to cardiac pathology, namely troponin I and Nt-proBNP, and one reactive protein in acute phase inflammation, namely CRP. Measurements were taken before implantation (H0) and then periodically after implantation, namely on day 1, day 3, day 6, day 9, day 12, and day 15. The normality test of the three data shows that the data distribution is not normal. The result analysis of the values of the three biomarkers showed no statistically significant relationship between the two

groups before and after implantation (Table 2).

Figure 2A below shows the trend of changes in the median troponin I value in the two subject groups on each observation day. The graph shows that the trend of changes in the median troponin I value in the treatment group tends to decrease more compared to the control group. The median value of the treatment group started at 9.5 pg/dl, then increased on the next observation day to 16.2 pg/dl, and then decreased until the end of the observation day, which was 1.5 pg/dl. At the same time, those in the control group tended to settle down, starting from 5.6 pg/dl and decreasing slightly to 5.1 pg/dl at the end of the observation day.

Figure 2B shows the trend of changes in the median NT-proBNP values of the two groups. It can be seen that the median NT-proBNP value in both groups is still within the normal range. The treatment group started with a value of 336.1 pg/dl and tended to decrease until the end of the observation day, which reached a value of 50.2 pg/dl, although there was one more increase on the other day's 6th observation. Meanwhile, the median NT-proBNP value in the control group tended to increase, especially from the 3rd day of observation to the end of the observation.

Figure 2C below shows the difference in the trend of changes in the median CRP value in the two groups. The graph shows that the CRP value of the treatment group tended to decrease, starting from 336.1 mg/L up to 8.2 mg/L on the last day of observation. Meanwhile, the control group tended to settle down, starting from 157.8 to 48.3 mg/L on the last day of observation.

An echocardiographic examination was performed before and after implantation by assessing ejection fraction (EF), which reflects the pumping function of the left heart, and Tricuspid annular plane systolic excursion (TAPSE), which describes the pumping function of the right heart. Due to limited research resources, only 13 subjects could undergo a complete examination for EF scores (5 subjects in the treatment group and 8 subjects in the control group), and for TAPSE scores, 12 subjects (5 subjects in the treatment group and 7 subjects in the control group).

A total of 13 subjects died, 2 subjects returned from treatment before post-implantation echocardiography and 1 subject's TAPSE value could not be evaluated due to the operator's limited field of view when using level 3 PPE during the examination. The analysis results showed no significant difference in the EF and TAPSE scores in the two groups of subjects before and after implantation (Table 3).

In this study, the clinical outcomes of the subjects were assessed, namely, alive or dead. There were 15 living subjects (53.6%) of the subjects, with 6 people in the treatment group and 9 subjects in the control group. In comparison, the subjects who died were 13 subjects (46.4%) of the total subjects, with the total number of subjects in the treatment group found to be larger, namely, 7 subjects (53.8%) compared to 6 subjects (46.7%) from the control group.

Table 3. Differences in EF and TAPSE values for the two groups

Biomarkers/Group	Before Implementation Median (min-max)	P	After Implantation Median (min-max)	P
EF				
Treatment	68 (55-75)	0,67[m]	55 (50-83)	0,4[m]
Control	69.5 (64-79)		66,5 (55-80)	
TAPSE				
Treatment	2,4 (1,9-3)	0,31[m]	2,4 (1,8-3)	0,39[m]
Control	2,0 (1,8-2,5)		2,2 (1,9-2,5)	

Note: [m]Mann Whitney Test

The difference in subject outcomes between the two groups was not statistically significant, with value of P=0.74. Then, survival analysis was carried out using the Kaplan-Meier method to assess the number and time of survival of the subjects in both groups.

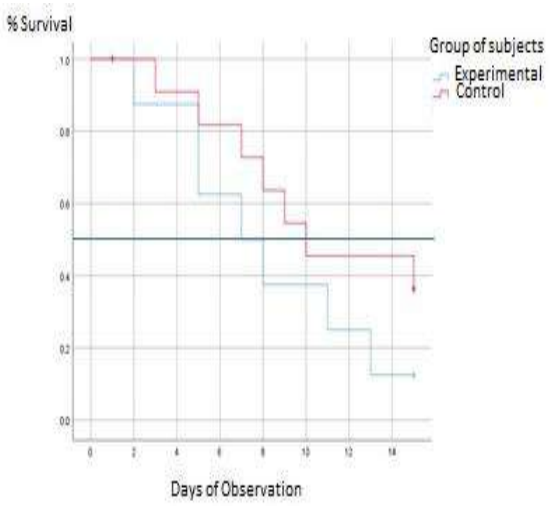

Figure 3. Kaplan Meier survival curve between treatment and control groups

In Figure 4, it can be seen that the treatment group tends to form a steeper curve than the control group. The median survival value of 50% was obtained in the shorter treatment group, which was 7 days, compared to the control group, which was 10 days. The relationship between the two was not statistically significant, with P=0.92 (log-rank) and a hazard ratio (HR)=1.05.

DISCUSSION

Myocardial injury is one of the most common cardiovascular manifestations of COVID-19 pneumonia and is associated with poor clinical outcomes. The management of COVID-19 pneumonia using a cell-based approach, particularly the UC-MSC, has been reported to show its safety and potential as an additional therapy for COVID-19 pneumonia.

In this study, the distribution of males was 18 subjects (64.3%) while females were 10 subjects (35.7%) with an age distribution in the range of 40-60 years of 17 people (60.7%) and over 60 years as many as 11 people (39.3%). The distribution of gender and age of these subjects follows the meta-analysis reported by Abate et al, who found the male prevalence of COVID-19 was higher, namely 55% compared to 45% for women.[9]

Karyono et al reported epidemiological data on COVID-19 patients in Indonesia and found that there were more males than females, namely 54.6%, with the highest age distribution in the 18-59 year range.[10] The prevalence of COVID-19, which is more in the male gender, is because men are generally more active

working outside the home than women, making it possible to interact with other people more often and for longer. Adults and the elderly are more at risk of being infected with COVID-19 due to a decrease in the body's immune system with increasing age. The CDC noted that over 40 years of age are at double the risk of infection and fifteen times the need for hospital care, while age >60 is one of the most severe clinical predictors according to WHO.[11]

The most common types of comorbidities were hypertension (57.1%), diabetes mellitus (53.6%), and obesity (39.3%). Research by Zhou et al also reported almost the same thing; namely, the most common comorbidities were hypertension, diabetes mellitus, and followed by CAD.[12] Likewise, with data in Indonesia, the most commonly found comorbidities are hypertension, diabetes mellitus, and cardiovascular disease.[10]

Kompaniyes et al reported on the American CDC page that as many as 50.7% of patients who were hospitalized from March 2020 to December 2020 were obese, and 28.3% were in the fat category.[11] In this study, the number of comorbidities in the treatment group was higher than in the control group. The number of comorbidities ≥3 was found in 5 subjects in the treatment group and 2 subjects in the control group. This difference can affect the research output.

The incidence of myocardial injury in this study was 28.5%, with 46.2% in the critical group and 13.3% in the moderate-severe group. This figure is not much different from that obtained by other studies. Based on several studies, the incidence of myocardial injury in COVID-19 generally has a fairly wide range, namely 7.2-40.9%.[13] A meta-analysis by Fu et al reported that the incidence of myocardial injury in subjects was 22%. In contrast, it was higher in subjects with severe COVID-19, namely 42%.[14]

In this study, there were more subjects with myocardial injury in women (62.7%) than in men (37.5%). These results differ from those reported by other studies in general, which found that the male sex was more numerous.[14] The mechanism of why the incidence is higher in males is still unclear. Allegedly, several genes related to the immune system located on the X chromosome cause an increase in the ability to recognize and eliminate antigens.[15] The different results in this study could be because the female subjects who experienced myocardial injury had other risk factors, namely age over 50 years (100%), number of comorbidities ≥3 (40%), critical degree of COVID-19 (60%) and have cardiovascular comorbidities (80%).

Other characteristics obtained in this study include age, BMI, number of comorbidities, and history of cardiovascular comorbidities consistent with other studies. Old age is a risk factor for myocardial injury. Fu et al reported that the group of subjects over 60 years had a significantly different prevalence of myocardial injury compared to the group aged less than 60 years.[14] Efros et al reported that subjects with myocardial injury had a history of

significant cardiovascular comorbidities, including hypertension, heart failure, ischemic heart disease, atrial fibrillation, and non-cardiovascular comorbidities, including diabetes mellitus, cerebrovascular disease, chronic kidney failure, and COPD.[16]

In this study, we found poor outcomes in patients with myocardial injury. Six subjects (75%) had critical clinical manifestations of COVID-19; the outcome was death. This is also consistent with the results of other studies, which report myocardial injury as a predictor of poor outcomes in COVID-19 patients. The results of a meta-analysis by Santoso et al showed that myocardial injury was significantly associated with higher mortality (RR=7.95), severe clinical COVID-19 (RR=13.8), and a higher need for ICU care (RR=7.94).[17] Efros et al reported significant differences in deaths and the need for mechanical ventilation in patients with myocardial injury compared to those without myocardial injury, with hazard ratios of 4.32 and 1.96.[16]

In this study, it was found that subjects with myocardial injuries did not improve; more were found in controls, namely, 6 subjects (40%), compared to the treatment group, namely 4 subjects (30.8%), although this was not statistically significant. Mesenchymal stem cells have the potential to act as immunomodulators in the inflammatory process that occurs in myocardial injury through their ability to differentiate into cardiomyocyte cells, inhibit T-cell activation, proliferation, and maturation so that they can suppress the inflammatory process and their ability to reduce ischemic processes through paracrine signaling effects.[18] There has been no previous research that specifically assessed the benefits of giving UC-MSC to myocardial injury and heart pump function in COVID-19 patients.

High troponin I, NT-proBNP, and CRP values predict poor outcomes, a higher risk of death, and ICU admission in COVID-19 pneumonia patients. CRP is a non-specific acute phase protein secreted by the liver. Clinically, CRP is used as a biomarker for inflammatory or infectious conditions. The increase in CRP is directly related to the severity of the infectious disease. Hodges et al reported that increased CRP is associated with disease progression and the extent of lung lesions in COVID-19 pneumonia.[19]

Meanwhile, troponin I and NT-proBNP are biomarkers of cardiac pathology. The inflammatory process in COVID-19 can induce cardiac injury. Respiratory disorders that occur also reduce oxygenation in the heart muscle. In addition, the binding of the SARS-Cov2 virus to the ACE2 receptor will cause the release of pro-inflammatory angiotensin, which facilitates the secretion of NT-proBNP.[8]

Mesenchymal stem cells act as immunomodulators with their ability to suppress cytokine storm processes and coagulopathy, protect alveolar epithelial cells and vascular endothelium, and are proangiogenetic and antimicrobial. Mesenchymal stem cells will suppress TNF-α and induce macrophage differentiation

into M2, which is anti-inflammatory. In the next process, it will reduce the release of pro-inflammatory proteins.[8]

This study showed a trend of decreasing troponin I, NT-proBNP, and CRP values in the treatment group compared to the control group, although this was not statistically significant. This result is consistent with several other studies. Shu et al and Guo et al reported a significant difference in CRP values in COVID-19 subjects who were given UC-MSC compared to controls.[20,21]

Liang et al reported a case report of a 75-year-old woman with COVID-19 who was given UC-SMC in addition to standard therapy with an initial proBNP value of 4,012 pg/ml, which decreased significantly to the normal range on day 12 after implantation.[22] Leng et al reported evaluating troponin I values in COVID-19 pneumonia patients who received UC-MSC starting to experience improvement on the 6th day after implantation.[6]

The median EF value of the two groups in this study was lower after implantation than before. This can illustrate decreased left heart function in patients after COVID-19 infection. Heart failure is one of the comorbidities often found in COVID-19 patients and is one of the cardiovascular manifestations of COVID-19 pneumonia. COVID-19 infection can cause an acute exacerbation in patients with a history of heart failure or the onset of new heart failure in patients without a history of heart failure.[23]

The mechanism of decreased cardiac function in COVID-19 occurs through several causes, namely (1) activation of the sympathetic nervous system in infection will cause stress cardiomyopathy, (2) an increase in the body's metabolic demand to fight infection, which is not compensated by the available supply so that it can cause ischemia cardiac muscle, (3) release of proinflammatory cytokines, which can cause acute injury to the heart muscle, (4) coagulation dysfunction, which will cause ischemia of the heart muscle, (5) the occurrence of ARDS, which will cause pulmonary hypertension to right heart failure, (6) involvement of kidney dysfunction which will cause fluid retention thereby increasing the workload of the heart, and (7) septic conditions in severe infections will cause cardiac dysfunction.[23]

There was no previous research on administering UC-MSC to COVID-19 pneumonia patients that assessed heart function parameters. Previous studies conducted before the pandemic reported the benefits of giving MSCs to improve heart function. An early study of MSCs administration in acute myocardial infarction by Chen et al reported the safety of MSCs and an increase in the left ventricle (LV) of 14% in the treatment group.[24] Another meta-analysis by Jeong et al reported an increase in LV of 3.8% and a six-minute walk test of patients after 2 years of therapy.[25]

This study showed no significant difference in EF or TAPSE scores in the two groups of subjects before and after implantation. Of the 13 subjects (5 treatment groups and 8 control groups) with complete echocardiographic data, 3

subjects (60%) were aged >60 years in the treatment group compared to 3 subjects (37.5%) in the control group, 2 subjects (40%) had comorbidities ≥3 in the treatment group compared to 1 subject (12.5%) in the control group, and 2 subjects (40%) had CHF comorbidities, whereas 8 subjects in the control group did not some have comorbid CHF.

Differences in age factors, the number of cardiovascular comorbidities, and comorbidities between the two groups can affect the study results. In addition, due to limited research resources, echocardiographic examinations could only be carried out at a different time than observation.

In this study, one subject in the treatment group had comorbid CHF with a very low pre-implantation EF value, namely 15%, which was classified as severe dysfunction. Treatment is still given according to a predetermined protocol. After implantation, this subject had an arrhythmia later resolved with medical management.

In addition, there was also one subject in the treatment group with the oldest age, namely 71 years, and with a history of comorbid CHF and arrhythmia. After the arrhythmic condition is resolved, treatment is still given according to the protocol. Evaluation of these two patients showed improvement, and no adverse events were found until the subject was discharged. So in this study, we found that administering UC-MSC was relatively safe in COVID-19 pneumonia patients who were >70 years old, had a history of arrhythmias, or had a history of CHF with severe dysfunction.

In this study, the subject outcomes at the end of the observation day (H15) were the number of deaths slightly higher in the treatment group, namely 7 subjects (53.8%) compared to the control group, namely 6 people (46.7%) with a median survival value of shorter in the treatment group, namely 7 days compared to the control group, namely 10 days, which was not statistically significant. This result differs from several other studies, which found that the mortality rate in the treatment group was lower than in the control group.

A pilot study on administering UC-MSC to COVID-19 patients was conducted by Leng et al in China. Subject criteria and the dose of UC-MSC given in this study were the same as those of Leng et al. Leng et al reported that all subjects in the treatment group (7 subjects) lived, while one in the control group died.[6]

However, Leng et al did not describe each subject's comorbid history. Meanwhile, in this study, the number of comorbidities was ≥3 in 5 subjects in the treatment group, while only 2 subjects were in the control group, although the difference was not statistically significant. Biswas et al reported that comorbidities in COVID-19 patients could increase the risk of death, namely cardiovascular disease (RR=3.05), respiratory disease (RR=2.74), diabetes mellitus (RR=1.97), and hypertension (RR=1.95).[26]

Three other studies conducted by COVID-19 patients 19 degrees severe to

critical also reported different results from this study. Sanchez-Guijo et al reported a mortality rate of 2 out of 13 subjects (15%) on the 16th post-implantation day, Guo et al reported 4 of 31 subjects who died (12.9%), and Shu et al reported no death at subjects who were given SPM while in The three studies have a protocol for administering UC-MSC that differs from this study.[21,27]

Sanchez-Guijo et al provided MSC sourced from adipose tissue at a dose of $0.98x10^6$/kg BW 2-3 times the dose with an interval of 3 days. Guo et al gave an MSC dose of 10^6 cells/kg BW with a frequency of 1-3 times the dose. These two studies did not divide subjects into two groups, namely treatment, and control, so the patient outcomes could not be compared.[21,27] Shu et al gave an MSC dose of $2x10^6$ cells/kg BW with an observation duration of 28 days, and the basic characteristics of the subjects were only 41% had comorbidities, namely hypertension and diabetes mellitus.[20]

Two other phase II clinical studies reported results that differed from this study. Lanzoni et al reported fewer deaths in the treatment group, namely 2 subjects, compared to the control group, namely 7 subjects (P=0.015). Lanzoni et al's study was conducted on mild-moderate and moderate-severe subjects, with an MSC dose of $100\pm20 \times 10^6$ cells intravenously in two doses, namely on the first day (H0) and the 3rd day of treatment (D3) which were observed up to the 30^{th} day. However, researchers only assessed the types of comorbidities, not accompanied by an assessment of the number of comorbid in each subject.[28] Shi et al conducted a study on 90 subjects with mild, moderate, to severe degrees of COVID-19 pneumonia, reporting no subject death in both groups until the 28th day of observation. The dose of UC-MSC given was $4x10^7$ cells intravenously.[29]

Differences in results between this study and other studies can be caused by factors of subject characteristics, treatment protocols and length of observation. Differences in the characteristics of the subjects in this study that could affect the outcome were fewer subjects aged 40-60 years in the treatment group, namely 7 subjects (52.8%) compared to the control group, namely 10 subjects (66.7%), the number of comorbidities ≥3 more in the treatment group, namely 5 subjects (38.5%) compared to the control group, namely 2 subjects (13.3%), comorbid CHF and CAD were only found in 6 subjects (46.1%) in the treatment group and not found in the control group. Controls and complications of AKI were more common in the treatment group with 9 subjects (69.2%) than 4 subjects (26.7%).

There are several weaknesses in this research. First, the number of subjects is limited caused of limited resources owned by researchers. Second, the assessment for evaluating myocardial injury and inflammatory markers can only be carried out at the level of biomarkers, namely Troponin I, NT-proBNP, and CRP, not yet up to the level of proinflammatory cytokines. This is also caused by the limited resources of the researcher. The

third, echocardiographic examination cannot be performed on all subjects and at the same observation time. This was due to the limited available resources and the limited field of view of the operator due to the use of level 3 PPE. Fourth, other adjuvant therapies were given to the subjects, namely tocilizumab and IVIG, which might have biased the results of this study.

CONCLUSION

There were no significant differences in troponin I, NT-proBNP, and CRP values, in COVID-19 pneumonia patients who received additional therapy for UC-MSC before and after implantation compared to controls, but there was a trend of decreasing values in the treatment group compared to controls. Besides that, there was no difference in heart pump function and the survival/death outcomes of COVID-19 pneumonia patients who received additional therapy for UC-MSC before and after implantation compared to controls. Therefore, it is necessary to carry out further research using a larger sample and administering a different treatment protocol. It is necessary to evaluate other cellular markers or proinflammatory cytokines that play a role in the pathogenesis of myocardial injury.

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Case Report

Mycobacterium tuberculosis Involvement in Tetralogy of Fallot: A Case Report of Tetralogy of Fallot Patient with Pulmonary Tuberculosis in A Tertiary Health Care in Indonesia

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Abstract

Background: Pulmonary tuberculosis in patients with congenital heart disease is a rare case and remains challenging to diagnose and treat. This study aimed to emphasize the association between pulmonary tuberculosis infection and management in patients with congenital heart disease.

Case: This case study presents 18-year-old male with Tetralogy of Fallot (ToF) who had pulmonary tuberculosis. The tuberculosis diagnosis was confirmed clinically, followed by positive IGRA. The patient underwent standard care within the hospital and upon discharge, he was prescribed with standard anti-tuberculosis regimen consisting of rifampicin, isoniazid, pyrazinamide, and ethambutol (RHZE) for a week then discontinued it. After 3 months the patient initiated intensive phase (RHZE) for 2 months and followed by 4-month maintenance phase of Isoniazid and Rifampicin. Immediate evaluation showed improved patient's chest radiography and symptoms' remission. This study presented provisioning therapy regimen and nutritional care delivery for pulmonary tuberculosis patient with ToF. Further patient's clinical evaluation suggested a substantial recovery process. The patient prescribed with infection control and dietary management upon hospital discharge. Counseling to improve patient's knowledge was performed to prevent recurrent TB. Collaborative care established between internal medicine specialists, cardiologist, pulmonologist, and clinical nutritionist appeared to be effective to promote patient's recovery and quality of life (QoL).

Conclusion: Appropriate management of cases improves patient outcomes and QoL. Early screening, diagnosis and treatment should be introduced regardless of the patient's clinical status. Adequate support from the patient's family and relatives are required to eliminate TB infection.

Keywords: collaborative care, congenital heart disease, pulmonary tuberculosis, tetralogy of Fallot

INTRODUCTION

Tuberculosis remains in the top list of common infectious diseases that pose threat to death despite advanced development of diagnosis and treatment.[1,2] Tuberculosis patients are frequently associated with congenital heart disease (CHD) due to increased pulmonary circulation compared to normal people.[3–5] Because of the nature of the disease, clinicians experienced difficulties in diagnosing tuberculosis which led to prolonged treatment or improper intervention.[6]

Patients with CHD are at higher risk for developing respiratory tract infections. Recurrent infection may occur and among frequent cases is pneumonia. Current evidence indicated that the risk for pulmonary tuberculosis remain unclear among pediatric cases as well as its associated complications.[3]

Classification of congenital heart diseases are based on the blood flow. Patients are grouped into cyanotic-CHD and acyanotic-CHD. Patients with acyanotic-CHD more susceptible to tuberculosis infection due to increased respiratory blood flow. Nevertheless, studies reported rare occurrence of pulmonary TB in patient with Tetralogy of Fallot (TOF) which categorized as a cyanotic-CHD characterized with decreased pulmonary blood flow.[2,4] Less blood volume in the lung causing delayed growth of Mycobacterium tuberculosis. Contrary, patient with normal or increased pulmonary blood flow are prone to provide suitable environment for the bacteria to replicate.

Pulmonary tuberculosis in CHD patient are rare cases, especially in the cyanotic-CHD patients. The screening, diagnosis, and treatment of these cases remain challenging. Due to the extremely rare and challenging management of this case, we presented a case of 18-year-old male patient diagnosed with TOF and pulmonary tuberculosis. Treatment regiments and intervention history were given to illustrate the day-to-day basis care. The case discovered in a tertiary care hospital in Java Island, Indonesia. Currently Indonesia is the third contributor of tuberculosis cases globally with frequent TB-HIV (human immunodeficiency virus) coinfection, and multidrug-resistant TB (MDR-TB).[7]

CASE

An eighteen-years-old male patient admitted to the hospital with TB symptoms on October 21st, 2021. The patient reported hemoptysis around 10 to 20 mL, impaired mucus excretion and breathing pattern at the time of admission. He experienced insomnia, significant weight loss and cough history in the past two months with nausea. No history of contact with positive TB cases. His past medical history indicated a delayed motoric development. Patient was able to communicate fluently in the age of 5.

During his treatment, he was not supported by his parents. The patient was living with his grandparents who actively

encouraged him to seek for medical care. He had no socioeconomical issue regarding health seeking behavior.

His body weight was 40 kg with 170 cm height, BMI 13.77 and categorized into undernourished. At the initial assessment, his respiratory rate was 26 times/minute, heart rate 130 BPM, blood pressure 130/70 mmHg and 36.9 body temperature. The patient's oxygen saturation was 84% and maintained to 92-93% with 4 lpm flow on nasal cannula.

Patient's general appearance was poor, indicated by weakness, breathlessness, and underweight. From the pulmonary examination found that fremitus tactile and the vesicular sound higher on the left lung. No abnormalities observed from the head, neck, abdominal, and extremity examination.

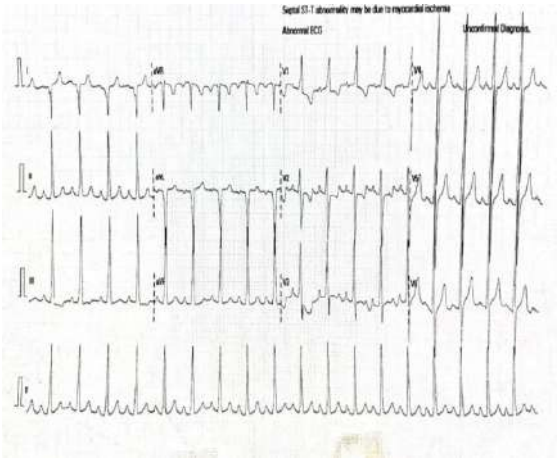

Figure 1. Patient's Electrocardiogram on Oct 2nd, 2021

From the cardiac examination found cardiomegaly. Auscultation test confirmed S1 normal, S2 single but noisy, PSM 3/6 at LPSS SIC III-IV, murmur ejection 3/6 at SIC II LPSD.

Blood examinations results indicated hemoglobin level of 14.8 gr/dL, WBC 20.72/mm3, neutrophil 85.8% and lymphocyte 7.7%. Patient's partial thromboplastin time (PTT) was 19.6 while APTT was 42.5. The INR was 1.39 and D-Dimer 715. CRP test yielded result 116 ng/ml and LDH 261 U/L.

The patient was diagnosed with tetralogy of Fallot with MAPCAS to the right lung in July 2018. Previous echocardiography examination concluded TOF with pulmonary atresia, collateral, and mild TR. The electrocardiogram indicated RAD RAE RVH with ST depressed at V1-V3.

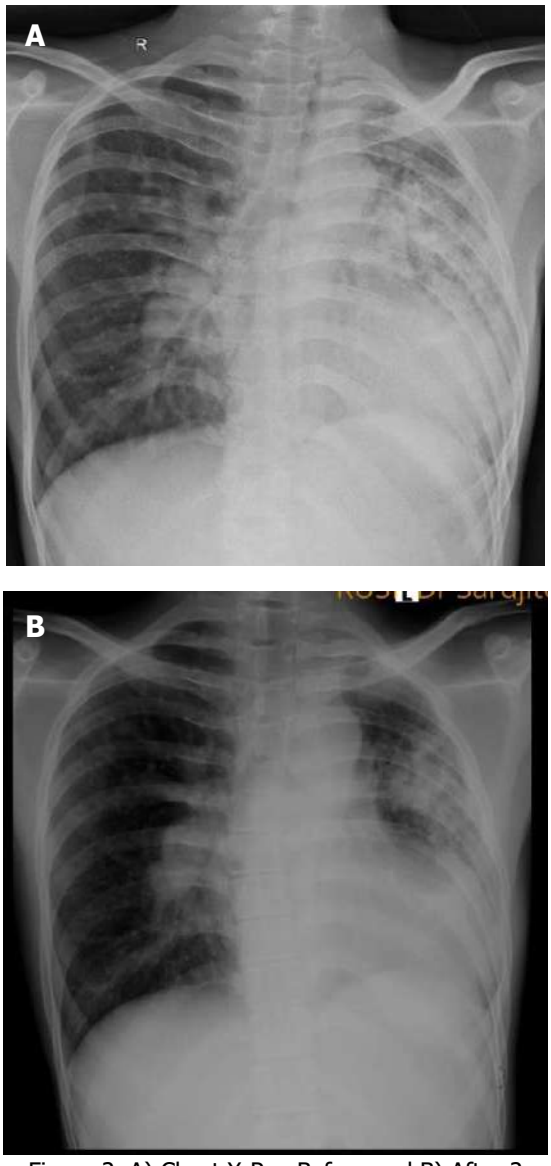

Figure 2. A) Chest X-Ray Before and B) After 2 Months TB Treatment

The Interferon Gamma Release (IGRA) tuberculosis blood test was positive, indicated the patient was infected with pulmonary TB. Neither TCM/AFB test was carried out due to difficulties in sputum sample collection. Additionally, the patient had recurrent hemoptysis, therefore IGRA test was performed as an alternative. Recurrent TB infection occurs due to lack of TB treatment adherence. On August 2021, the patient was prescribed for anti-TB regimen but didn't manage to follow the therapy. He took the medicine for a week and discontinued it. Further intervention during the hospital admission ensures the patient comply to the standard TB regimen (2RHZE/4RH).

Patient was admitted for severe malnutrition programme. The total calories prescribed was 1700 kcal with 70 g protein. He planned for a high energy and high protein diet with ONS F75 2X200 cc. Parenteral nutrition in a composition of lipid emulsion, amino acids, electrolytes, and glucose were programmed for 1000 mL/24h.

DISCUSSION

Despite the advances in tuberculosis diagnosis and treatment, around 450.000 children died because M. tuberculosis infection. The prevalence of TB cases among children aged 0-15 reached 1.3 million in 2021.[8] Low and middle-income countries are being burdened by these issues due to poor environmental status, lack of nutrition for children, inadequate immunization, and HIV infections.[5]

Tuberculosis management in children poses a unique challenge compared to adults. 65% of pediatric patients initially didn't develop tuberculosis's symptoms and only able to be validated with radiology.[9,10] Children with positive radiological findings are prone to recurrent infection during their adulthood.[11]

Chest X-Ray features of active primary pulmonary TB are primary (Ghon) focus which can be seen as calcified nodule with or without mediastinal lymph node enlargement, perihilar lymph nodes enlargement, pneumonic consolidation, cavitation, miliary opacities, pleural effusion, or pulmonary edema.[12] Meanwhile the CXR finding of inactive TB are fibrosis, persistent calcification (Ghon's focus), and/or tuberculoma. CXR findings of secondary TB in adults are patchy consolidation with cavitary lesion or coarse reticulonodular densities which usually involve the upper lobe.[13] Proportion of the affected area of the pulmonary lobes determine the case mortality.

In this case report, we presented a patient with clinically confirmed tuberculosis infection with tetralogy of Fallot and malnutrition. Malnutrition is common in patient with CHD, especially in developing country like Indonesia. Based on some research malnutrition happens in more than half of patients with CHD. Malnutrition happens in CHD because of decreased intake, increased demands, or both. Underweight is the combination of acute and chronic malnutrition. Underweight can lead to secondary immunodeficiency which increases the

susceptibility to infection, including tuberculosis. Either protein-energy or micronutrients deficiencies can increase the risk of tuberculosis infection.[14,15]

Prevalence of tuberculosis is higher in CHD patients than normal population. A retrospective study indicated CHD patients, especially cyanotic-CHD, are at 2.5x higher risk of TB. Higher incidence of TB also found in patient with increased pulmonary circulation i.e., transposition of great arteries and acyanotic-CHD, like ASD and VSD.[3,16]

Previous cases of CHD and pulmonary tuberculosis was also reported in Sonipat, India. A 21-year-old male suffered from CHD reported complaints bloody cough, dyspnea, and other symptoms such as fever, loss of appetite, weight-loss, abdominal pain, and icterus. He was diagnosed with pulmonary tuberculosis after sputum examination with cartridge based nucleic acid amplification test. He was put on alternate tubercular regimen, as his liver function worsened. Even though the regimen was consumed regularly, he still reported persistent dyspnoea and suspicion of pulmonary embolism. CT pulmonary angiography was done, and there is no evidence of arterial thrombosis. From the CT scan found complex cardiac congenital anomaly.[3]

Recent development in testing kit and widely distributed capable healthcare centers allow enhanced diagnosis process of pulmonary tuberculosis in patient with CHD[14]. A study reported that among pediatric patients with normal immune system, 10% of them diagnosed with TB-positive culture. Tuberculin Purified Protein Derivative (TU PPD) test generated variance in the test results. Multiple factors associated with TU PPD validity to diagnose TB, such as age, nutritional status, bacterial load, and MTB count. Patients with low albumin level tend to show negative results.[10]

The sensitivity of PPD/TST/Mantoux test among pediatric patients was around 63% based on a report.[17] In Indonesia, screening for tuberculosis utilitizing PPD in primary care remains limited. It leads to delayed treatment administration and causes poor clinical outcome.

Considering its low sensitivity, PPD doesn't serve reliable diagnostic tool to diagnose tuberculosis.[17] In children ≥5 years old, IGRA has greater sensitivity than PPD and should be considered the preferred immunodiagnostic test.[18] The gold standard to diagnose tuberculosis is culture examination, followed by species identification and drug sensitivity testing.[19] WHO recommends bacteriologic diagnostic for adult's patient despite it taking 2-8 weeks to complete. Nevertheless, for pediatric population bacteriological confirmation is achievable in <50%; in such cases pulmonary TB is diagnosed by other clinical criteria or other examination modality.[20,21]

Either IGRA or PPD can be used to diagnose LTBI. PPD is one of the components in pediatric tuberculosis scoring system. Based on WHO guidelines, PPD still can be used to diagnose pediatric tuberculosis. PPD is considered safe and preferred over TB blood tests for children

less than 5 years old.[22] IGRA are more specific than PPD, but it hasn't been found to perform better than PPD. Although bacteriological confirmation of TB in children isn't always feasible, it should be sought whenever possible by microscopy, culture or TCM.[20,22]

Culture examination isn't the only one modality to diagnose TB. The other current modalities including BACTEC, ELISA, PCR, and Real Time-PCR (RT-PCR) are shown to be valid and reliable too. RT-PCR provides the fastest test result. However, it has low sensitivity (56%) and high specificity (97%) in pediatric tuberculosis.[2,23] Despite laboratory tests demonstrating effectiveness for diagnosis, it remains important to establish clinical case definitions based on physical examinations.

In 2019, WHO reported that 12% of all TB cases globally represented by children, 32% by adult women, and 56% by adult men.[24] According to the systematic review and meta-analysis performed by Charan et al in 2019, that prevalence of MDR-TB in newly confirmed cases was 3% and in the previously treated cases were 35%. The pooled proportion of MDR-TB confirmed in new cases group using BACTEC method was 21%; while with Alamar blue dye reduction assay was 5%; and MIC method was 1%.[25]

The study also indicated pooled proportion of confirmed MDR-TB among previously treated cases group using BACTEC method was 58%; the genotype MTB DR plus assay method 19%; RNTCP guideline 28%; the absolute concentration method 53%; the resistance ratio method was 8%; Alamar blue dye reduction assay 16%; MIC method 26%; and using Lowenstein Jensen method was 72%. In the other hand, according to the WHO Global TB Report of 2020, about 3.4% (95% CI, 2.5–4.4%) of new cases and 18% (95% CI, 7.6–31%) of previously treated cases had MDR/RR-TB from all age groups.[25]

Drug-resistant TB (DR-TB), especially MDR-TB, remains a threat for both children and adults. More than 30,000 children diagnosed with MDR-TB, globally. According to the systematic review and meta-analysis by Song et al. in 2021, from the 23,652 children with TB, there are 13.59% with DR-TB; 3.72% with MDR-TB; 6.07% with mono-resistant TB; 1.61% polydrug resistant TB, and 0.44% with extensively drug-resistant TB. DR-TB diagnosis in children remains challenging because bacteriological confirmation of pulmonary TB yield in no more than 40% of children and even less frequently for extrapulmonary TB.[26]

CONCLUSION

Patients with acyanotic-CHD have a higher risk of TB infection due to higher blood circulation in the pulmonary tissue and malnutrition condition. Appropriate management of cases improve patient outcomes and quality of life. Suspicion of pulmonary TB is supposed to be maintained among patients with CHD. Early screening, diagnosis and treatment should be introduced regardless of the patient's status. Family members and significant

others requested to limit the exposure to TB infection by implementing appropriate preventive measures.

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Case Report

Vancomycin-Allergy and Linezolid-Resistance in Patient with Methicillin-Resistance *Staphylococcus aureus* and Multi-Drug Resistance *Acinetobacter baumannii* Infection

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Abstract

Background: Hospital Acquired Pneumonia (HAP) has been burdening the healthcare system, especially when bacteria such as *Acinetobacter baumannii* and methicillin-resistance *Staphylococcus aureus* (MRSA) are involved. They created a dilemma regarding the appropriate antibiotic therapy utilized against them, especially when the patient is allergic/intolerant to their drug of choice.

Case: A 71-year-old man developed HAP while he was admitted for an ischaemic stroke. His bronchoalveolar lavage (BAL) culture showed MRSA and *Acinetobacter baumannii* infection with multiple drug resistance including one of the drugs for MRSA infection, linezolid. Amikacin and vancomycin were given, but he developed an allergy to vancomycin. Due to the difficulty in treating him, we opted to administer only amikacin. His clinical condition showed daily improvement. During the last day of hospitalization, his sputum culture showed only normal flora. He no longer needed oxygen therapy and there was no longer any indication for him to be hospitalized.

Conclusion: Individuals with multiple comorbidities, recent antibiotic use within the past 90 days, and immune-deficient conditions are at a higher risk of developing infections, including the possibility of dual infections. In this case, we found that the patient was unable to tolerate first-line drugs for MRSA like linezolid and vancomycin, which makes it difficult to decide upon effective treatments.

Keywords: *Acinetobacter baumannii*, MDR, MRSA, pneumonia, vancomycin allergic

INTRODUCTION

The emergence of multidrug resistance among gram-negative and gram-positive bacteria has caused difficulties in treatment. Bacteria such as *Acinetobacter baumannii* and methicillin-resistance *Staphylococcus aureus* (MRSA) are difficult to treat and can survive for a long time in hospital environments, increasing the risk of transmission between patients.[1]

Acinetobacter spp. is a significant cause of hospital-associated infections and

can persist on inanimate surfaces.[2] A study in a division of infectious disease and department of infection control in St. John's Mercy Medical Center, St. Louis, Missouri showed *A. baumannii* was isolated from environmental surfaces of hospital rooms that had been thoroughly cleaned and disinfected after being occupied by patients with multidrug-resistance *Acinetobacter baumannii complex* (MDRABC).[3] MRSA can also persist in the hospital environment[4] and its risk factors for infection or colonization often overlap those of MDRABC,[5] so its isolation from room surfaces was also studied.

MRSA and *A. baumannii* are serious nosocomial pathogens because of their environmental resilience, antimicrobial resistance, and potential to cause outbreaks.[3,6] Surface contamination has been linked to the transmission of these organisms,[7] and previous room occupancy by patients with MRSA or *A. baumannii* infection or colonization is an independent risk factor for the acquisition of these pathogens by subsequently admitted patients.[8]

According to a descriptive study by Dent et al, it was found that MDR *A. baumannii* infection was significantly associated with a higher mortality rate. A different case-control study indicates that the crude mortality rate linked to pan-drug resistance *A. baumannii* could be much higher compared to infection with a more antibiotic-sensitive strain of *A. baumannii*. In this study, it was found that 80% of patients with extremely drug-resistance *A. baumannii* died, in contrast to 14% of those infected with a sensitive strain of *A. baumannii*.[2]

Studies of multidrug-resistance (MDR) bacterial isolates like *A. baumannii* and MRSA are crucial not only for the proper management of infections caused by them, but also for the prevention of dissemination of such strains in the community and in hospitals.

In this paper, we review a case about vancomycin allergy and linezolid resistance of MRSA and MDR *Acinetobacter baumannii* isolates in clinical samples from patients of lower respiratory tract infections (LRTIs).

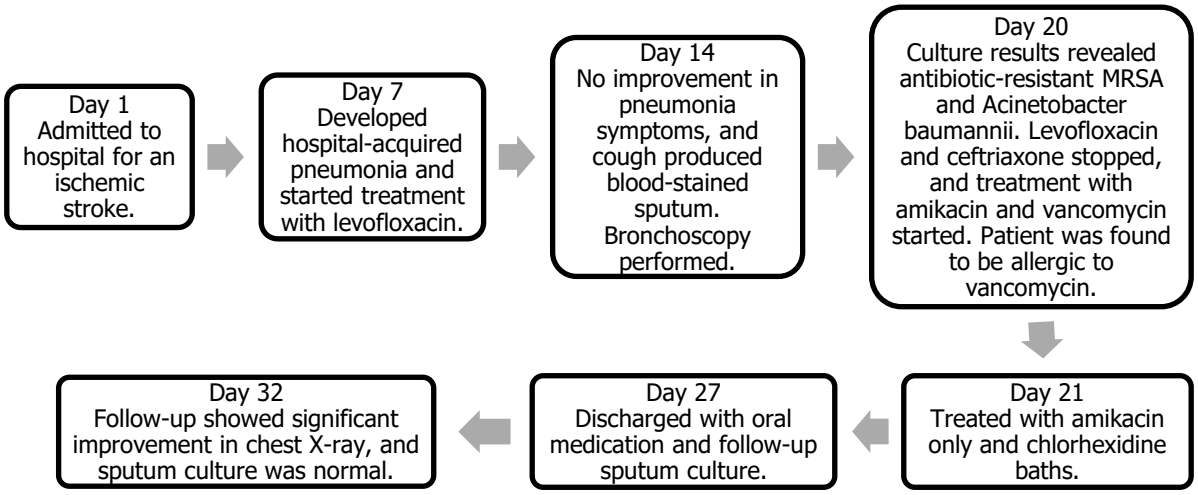

Figure 1. Patient's course of the disease from day one he was hospitalized with an ischemic stroke, on day 7 Hospital Acquired Pneumonia developed and discharged on day 27

CASE

A 71-year-old man, complained of dyspnea when he was on the 7th day of hospital stay for an ischemic stroke. Furthermore, he presented with a fever and a cough that was at times accompanied by bloody sputum.

He showed no sign of infection before coming to the hospital. On examination, the patient was febrile (38ºC) with decreased oxygen saturation from 95% to 90% measured by pulse oximetry. The patient had rhonchi on the left side of the lung and the chest X-ray showed more infiltration than before (Figure 2).

Laboratory findings also showed leucocytosis and neutrophilia (Table 1). He was diagnosed with Hospital Acquired Pneumonia and given levofloxacin as the drug of choice.

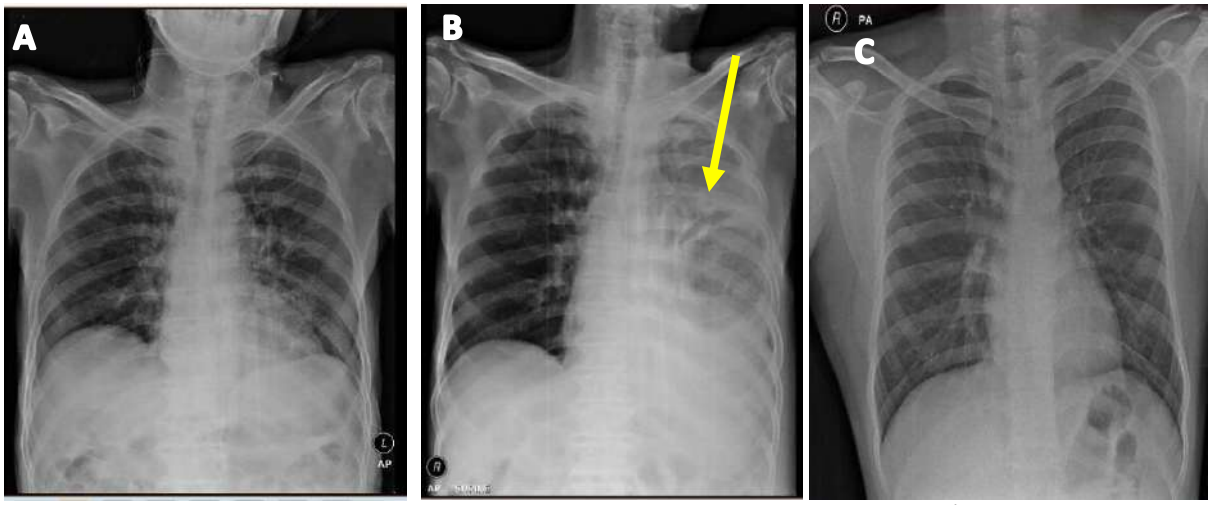

Figure 2. Chest X-ray comparison: (a) Chest X-ray on admission (b) Chest X-Ray on 7th day of hospital stay showing more infiltrate than chest X-ray on admission (yellow arrow) (c) A week after being discharged

Table 1. Laboratory Result: showing leucocytosis on 7th day of hospitalization

Indicators	On admission	On 7th day of hospitalization (when the patient complained of dyspnea)	Last day of admission
Leucocyte (10^3/µL)	11.25	16.60	11.61
Erythrocyte (10^6/µL)	5.7	3.74	3.9
Hemoglobin (g/dL)	17.9	11.5	12
Hematocrit (%)	53.6	34.2	35.7
Thrombocytes (10^3/µL)	212	353	384
Neutrophils (%)	90	84.6	79.9
Lymphocytes (%)	4.8	5.2	8.5
Neutrophils/Lymphocytes Ratio	18.92	16.12	9.37
SGPT (U/L)	41	---	---
Blood Gas Analysis	---	pH=7.47 PCO_2=34 PO_2=52 HCO_3=25 ABE=1 SBC=26 SO_2=90	---

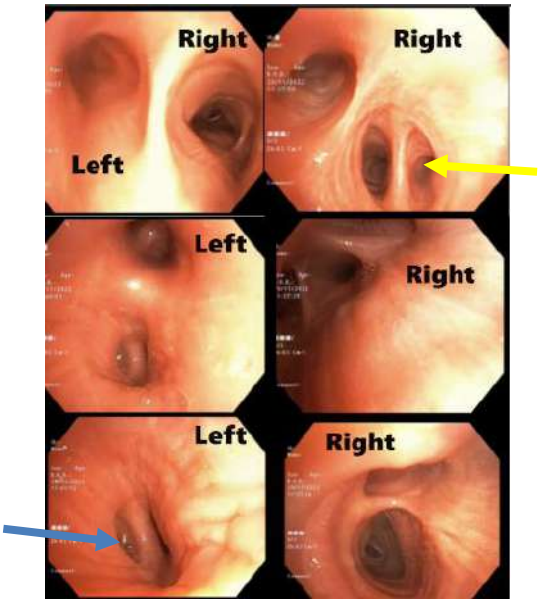

Figure 3. Bronchoscopy imaging. It showed edema and erythema upper and lower left bronchi (blue arrow). There is much sputum with a blood streak on his left bronchi. Right bronchi showed normal on bronchoscopy (yellow arrow)

A bronchoscopy was performed with xylocaine spray and atropine sulfate as premedication. Bronchial washing was performed and a sample of bronchoalveolar lavage (BAL) culture was taken. The bronchoscopy imaging revealed purulent bronchial secretions mixed with phlegm, as well as mucosal swelling and diffuse erythema in the upper lobe of the left main bronchus. Also, there were red purulent bronchial secretions covering the lower lobe lumen of the left main bronchus. The lumen appeared slightly narrowed, the mucosa was swollen, the surface was uneven, and the hyperemic mucosa easily bleeds (Figure 3).

The patient showed no sign of improvement with levofloxacin after being given for a week, while waiting for the BAL culture's result, ceftriaxone was given. The culture showed MRSA and *Acinetobacter baumannii* infection with multiple drug resistance including levofloxacin, meropenem, tetracycline, and one of the MRSA infection drug therapy, linezolid. His BAL culture results also showed that he was sensitive to amikacin and vancomycin (Table 2), so levofloxacin and ceftriaxone were stopped, and amikacin and vancomycin were given.

Table 2. Table of antibiotic list from the patient. The patient was resistant to linezolid and sensitive to Amikacin and Vancomycin.

Antibiotics Resistance	Antibiotics Sensitive
Ciprofloxacin	Gentamycin
Levofloxacin	Trimethoprim/ Sulfamethoxazole
Cefepime	Colistin
Meropenem	Gentamicin
Linezolid	Vancomycin
Tetracycline	Rifampicin
----	Amikacin

On the first day of therapy with vancomycin, the patient was getting harder to breathe and developed wheezing in both lungs and swelling on both palpebrae. He desaturated and vancomycin was quickly stopped. Steroid inhalations, steroid injections, and anti-histamine injections were given to settle his allergic reaction. Besides drugs, the patient was given chlorhexidine 2-4%. He received amikacin as his main treatment and his clinical condition showed better day by day. On the last day of admission, his sputum culture showed only normal flora. He no longer needed oxygen therapy and there was no longer any indication for him to be hospitalized.

DISCUSSION

Lower respiratory tract infections acquired in a healthcare setting, such as

hospital-acquired pneumonia (HAP), are highly common and place a significant burden on healthcare resources. HAP specifically is defined as pneumonia that occurs after a patient has been hospitalized for at least 48 hours and any infections incubating before admission to the hospital have been ruled out.[9]

To improve the accuracy and objectivity of early recognition of pneumonia, various scoring systems have been developed and new surveillance guidelines have been implemented. According to European guidelines, the term 'low probability of HAP' refers to patients with low Clinical Pulmonary Infection Score (CPIS) scores or a clinical presentation that is not highly suggestive of pneumonia at symptom onset and continuing up to 72 hours. In contrast, American guidelines rely on clinical criteria alone, rather than using the CPIS in conjunction with clinical criteria, to decide whether or not to initiate antibiotic therapy and do not use the CPIS to guide the discontinuation of antibiotic therapy.[9]

One key difference between the American and European guidelines for the treatment of pneumonia is their recommendations for the use of single versus combination therapies. While the American guidelines recommend combination therapy mainly for targeted therapy and de-escalation, the European guidelines recommend empirical combination therapy for patients with septic shock. It is worth noting that for patients with a low risk of mortality (defined as a 15% or less chance of dying), both guidelines agree that a 7-day course of antimicrobial therapy is preferred over a longer duration. However, European guidelines suggest that monotherapy may be more effective in these patients with serious infections compared to combination therapy.[9]

Pneumonia is typically characterized by the sudden onset of lower respiratory tract infection symptoms, including fever, cough, pleurisy, shortness of breath, and increased production of sputum with consistent radiographic findings. However, in some patients, the presentation of pneumonia may be atypical and primarily consist of non-respiratory symptoms like malaise, muscle pain, confusion, and diarrhea. Elderly individuals may be more likely to experience this type of atypical presentation, which can lead to delays in treatment and increased mortality.[10]

Pneumonia that occurs in a hospital setting (hospital-acquired pneumonia or HAP) that develops more than 5 days after hospitalization (late-onset) is often caused by certain types of bacteria, such as aerobic gram-negative bacilli (e.g., *Acinetobacter species*) or MRSA.[11] Pneumonia usually gets into lung parenchyma, but when the inflammation gets into the bronchi, the infections are highly contagious like in this patient.

MRSA is a type of bacteria that can cause infections. It is commonly found in hospitals (HA-MRSA) and can also be found in the community (CA-MRSA). Compared to HA-MRSA, CA-MRSA typically has smaller SCCmec cassettes and is less resistant to

antibiotics other than the β-lactams antibiotic group.[12]

Research on MDR bacterial strains, including the *A. baumannii complex* and MRSA, is important for understanding and managing infections caused by these bacteria, as well as for preventing the spread of these strains in hospitals and the community.[1] This patient developed MRSA based on his BAL culture and was allergic to its main treatment, vancomycin, while resistant to another treatment, linezolid. Those were the reasons that he had high mortality and morbidity.

Multidrug-resistance *Acinetobacter baumannii* (MDRAB) is a type of bacteria that is resistant to more than three types of antibiotics. A study looked at a database of *A. baumannii* isolates from patients in a city hospital. The study found that 72% (177 out of 247) of the A*. baumannii* isolates were MDR. Fifty-eight percent of the isolates (143 out of 247) were resistant to imipenem, amikacin, and ampicillin-sulbactam, which is considered to be a high level of resistance. Forty-six percent (113 out of 247) of the isolates were resistant to all commonly used antibiotics, including aminoglycosides, cephalosporins, carbapenems, extended-spectrum penicillins, and quinolones, and were therefore classified as pan-drug-resistance.[13]

Carbapenem resistance is a serious problem because it indicates the emergence of antimicrobial resistance and can make it difficult to treat infections. It is especially challenging to manage because it confers high resistance to many drugs. The major site of *A. baumannii* isolation in this study was the respiratory tract, and 86% of patients who died had a positive *A. baumanni* isolate recovered from the respiratory tract.[13]

Factors associated with MDR included the recovery of *Acinetobacter* from multiple sites, mechanical ventilation, previous antibiotic use, and the presence of co-morbidities, particularly neurologic impairment. MDRAB was also significantly associated with an increased mortality rate.[13] Patients with co-morbidities like this patient who had a stroke increased the chance of developing multiple-drug resistance.

Multidrug-resistance *A. baumannii* is resistance to at least two of the following classes of drugs, which are typically effective against these pathogens: antipseudomonal cephalosporins (e.g., ceftazidime or cefepime), antipseudomonal carbapenems (e.g., imipenem or meropenem), ampicillin/sulbactam, fluoroquinolones (e.g., ciprofloxacin or levofloxacin), and aminoglycosides (e.g., gentamicin, tobramycin, or amikacin).[14]

Acinetobacter spp. are a common cause of hospital-associated infections, and they can survive on inanimate surfaces for long periods. In a study, *A. baumannii* was found on the surfaces of hospital rooms that had been cleaned and disinfected after being occupied by patients with MDRAB infections or colonization. At the same time, the presence of MRSA on these surfaces was also investigated, as MRSA can also survive in the hospital

environment and has similar risk factors for infection or colonization as MDRAB.[3]

A study in Hong Kong reported that there has been an increase in the prevalence of multidrug-resistance organisms (MDROs) among 28 nursing homes in the Hong Kong West District. The study analyzed the epidemiological risk factors for colonization with carbapenem-resistance *Acinetobacter baumannii* (CRAB) and MRSA among nursing home residents. The results of the multivariate analysis showed that being bed-bound, using adult diapers due to incontinence, and having a nasogastric tube were common risk factors for both CRAB and MRSA colonization.[15]

Common criteria for diagnosis of HAP/VAP are based on a combination of new and/or progressive lung infiltrates on chest radiograph plus two or more additional criteria that include fever (>38.5°C) or hypothermia; leucocytosis, purulent tracheobronchial secretions, and reduction of partial pressure of oxygen (PaO_2)/FiO_2 ratio of at least 15% in the last 48 hours.[16] This patient was diagnosed with a clinical condition like fever, progressive lung infiltrates on chest radiograph and leucocytosis in laboratory findings. BAL also showed purulent tracheobronchial secretions.

In contrast to community-acquired pneumonia (CAP) in which the dominant typical pathogens are *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Haemophilus influenzae*, the etiology of HAP/VAP is quite different and challenging. It is noteworthy that obtaining a microbiological culture from the lower respiratory tract in patients developing VAP is relatively easy through the endotracheal tube. This collection appears more difficult to obtain in patients developing HAP, so microbial aetiologies remain poorly documented. However, microbial aetiologies in HAP and VAP are mostly identical. More generally, gram-negative organisms represented a large part of VAP/HAP etiology, ranging from 61.5% and 76.1% of isolates in the US and Europe respectively.[17]

Bronchoscopy was performed on this patient to take BAL culture and bronchial washing. *Bronchoscopy with bronchoalveolar lavage (BAL)* allows the sampling of the lung segments which are suspected to be affected by pneumonia decreasing the false-negative rate. This patient showed edema and erythema left bronchi both on the upper and lower bronchi. Purulent tracheobronchial secret and secret with a blood streak also showed and bronchial washing was performed to minimize hypoxia in this patient. When the bronchi become edema and erythema, the pathogen of pneumonia infection is highly contagious. BAL culture is a gold standard to diagnose pneumonia and accurately can show an antibiotic list for the pathogens.[18]

Vancomycin and linezolid were recommended for HAP patients with MRSA infection, specifically those with prior intravenous antibiotic use within 90 days and in hospitalization units like ICU.[18] This patient developed allergies to vancomycin and was resistant to linezolid, so he was

evaluated based on clinical response and microbiologic results. Amikacin was given and clinical response was evaluated and it was improved. Duration of antibiotic therapy in most patients with HAP or VAP of 7 days appears to be as effective as longer durations and may limit the emergence of resistant organisms.[19]

However, for patients with a severe illness, bacteremia, slow response to therapy, immunocompromise, and complications such as empyema or lung abscess, a longer duration of therapy is indicated.[19] As microbiological results are available, empirical treatment should be revised and possibly narrowed. Rapid molecular diagnostics could have a key role in early de-escalation due to their ability to get rapid pathogen identification and antimicrobial resistance patterns.

American Thoracic Society recommends that all hospitals regularly generate and disseminate a local antibiogram, ideally one that is tailored to their HAP population, if possible, and also recommends that empiric antibiotic regimens be based upon the local distribution of pathogens associated with HAP and their antimicrobial susceptibilities.[19]

A local antibiogram and empiric antibiotic were given to this patient but showed no better condition. Considerations should include their rate of change, resources, and the amount of data available for analysis. An endorsed strategy for the duration of antibiotic treatment in pneumonia consists in giving the shortest course of therapy that is likely to be effective to reduce risks of antibiotic resistance and adverse events.[16] So we concluded and gave the patient based on his culture and evaluated his condition after giving the antibiotics.

Managing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) requires an interprofessional team of specialists in infectious diseases, pulmonary diseases, critical care, anesthesiologist, and any clinicians and healthcare providers including nurses and pharmacists caring for hospitalized patients with nosocomial pneumonia. Without proper management the morbidity and mortality from HAP and VAP are high.[18]

CONCLUSION

Contracting infections, including dual infections, which could lead to severe consequences are more likely in individuals with multiple comorbidities, including chronic ailments, recent antibiotic usage within 90 days, and immune-deficiency conditions. Prompt diagnosis and treatment of double infections are particularly crucial in patients with MRSA and MDRAB.

Based on the case, it has been observed that the patient was not responsive to the first-line drugs for MRSA, such as linezolid and vancomycin, which makes it challenging to determine an effective treatment plan. These findings also indicate the possibility of heightened morbidity and mortality, emphasizing the importance of timely and effective

treatment by practitioners. Proper follow-up care, including microbiological, clinical, and radiological monitoring, is crucial for the patient's recovery.

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Literature Review

Dust Exposure and Lung Function Disorders

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Abstract

Dust is a particle floating in the air produced due to mechanical processes such as splitting, grinding, grinding, punching or blasting, cutting and destroying material. Dust particles in the air for a relatively long time can enter the human body through breathing. Dust less than 5 µm entering the human respiratory system can reach the inside of the lungs or alveoli can cause lung function disorders. Impaired pulmonary function is the inability to develop (elasticity) of the lungs as well as disorders of the respiratory tract both structural (anatomical) and functional which causes slowing of respiratory airflow. The International Labor Organization (ILO) defines pulmonary dysfunction as the accumulation of dust in the lung tissue and lung tissue reaction to the dust accumulation. Dust entering the alveoli can cause hardening of the tissue (fibrosis) and if 10% of the alveoli is hardening, it will reduce its elasticity in accommodating the volume of air so that the ability to bind oxygen is decreased. This condition causes a reduction in the supply of oxygen absorbed by blood capillaries to the brain tissue, heart, and other body parts.

Keywords: aluminum dust, coal dust, rice dust, lung function disorders, wood dust

INTRODUCTION

Clean air, water, and food are human rights that are considered basic needs. However, air pollution is the focus of the world's attention, is considered the largest environmental risk that affects health, and was responsible for one of nine deaths in 2012.[1] According to WHO, air pollution can cause uncommunicable diseases. There are around 24% of deaths from heart disease, 25% from stroke, 29% from lung cancer, and 43% from chronic obstructive pulmonary disease (COPD). Out of all those deaths, 3 million are caused by ambient/outdoor air pollution.[1,2]

High air pollution is caused by increasing industrial sector growth. One of the effects of industrial activities is the production of air contaminants such as dust. According to International Standardization Organization (ISO 4225 – ISO, 1994), dust is a small solid particle with a size under 75 µm that floats in the air for a long period. Dust is an aerosol formed by the mechanical subdivision of bulk material into airborne fines that have

the same chemical composition. Dust particles are generally solid and irregular in shape and have diameters greater than 1 µm.[3]

Dust is categorized into several types, such as silica dust, wood dust, mineral dust (SiO_2, SiO_3, coal), organic dust (cotton dust, leaf dust, tobacco, paddy, etc.), and metal dust (Pb, Hg, Cd, Ar).[4] Air containing dust can enter the respiratory system, especially the lung. Dust with a size of 5–10 microns will be stopped in the upper respiratory tract; 3–5 microns of dust will be stopped in the middle respiratory tract; and 1–3 microns of dust will be suspended directly on the surface of the alveoli.[2]

In the workplace, these types of dust can be found in farming activities, ceramic production, limestone, brick production, mining activities, bed production, traditional markets, street vendors, home industries, paddy grinding, etc. Data from International Labour Organization (ILO) shows that 2 million out of 2.5 billion workers in the world die every year from accidents or work-related diseases, and one-third, or 21%, of these diseases, are respiratory or lung diseases.[5,6] WHO also reported that 600 million people suffer from COPD. In 2012, around 3.1 million people died from lung problems, and it is predicted to be the third main cause of death around the world in the year 2030.[7]

The quality of air in the workplace also plays a role in occupational health, where there is a risk of respiratory issues. If the respiratory issues accumulate over a long period, lung fibrosis may form, which will cause hardened alveoli. Lung problems are commonly categorized as obstructive and restrictive respiratory disorders. Obstructive disorders are due to obstruction, narrowing, or resistance in the airways, while restrictive disorders are due to disturbances in the lung parenchyma.[8]

The risk faced by workers includes not only occupational accidents but also occupational diseases. Occupational diseases, found in various industries, are diseases that arise due to work and an unfavorable environment. One of the causes of pulmonary function disorders is exposure to dust such as wood dust, coal dust, rice dust, aluminum dust, and so on. Therefore, it is necessary to do proper handling so that there is no respiratory disease among workers.

RESPIRATORY SYSTEM DISORDERS DUE TO DUST

Work-related diseases experienced by workers can arise from the work environment that is exposed to dust, both industrial dust and dust from agricultural processing processes, and so on. Respiratory system disorders that can cause lung disease are divided into three types, namely:[9]

a. Diseases caused by organic dust, such as cotton dust (byssinosis), rice dust (grain worker's disease), and wood dust.
b. Disease caused by inorganic dust (pneumoconiosis), such as silica dust (silicosis), coal dust (coal worker's

pneumoconiosis), tin dust (stannosis), and asbestos dust (asbestosis).

c. Disease is caused by irritant gases, such as sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3).

THE EFFECT OF DUST SIZE ON RESPIRATORY DISORDERS

The effect of dust on respiratory disorders is distinguished by the size of the dust particles that settle in the respiratory tract. The various sizes of dust particles are as follows:[2,9]

a. Dust measuring 5-10 microns settles in the upper respiratory tract, which can cause an irritating effect characterized by symptoms of pharyngitis.
b. Dust measuring 3-5 microns settles in the middle respiratory tract, which can cause effects in the form of bronchitis, allergies, and asthma.
c. Dust measuring 1-3 microns settles and accumulates in the alveoli.
d. Dust measuring 0.1–1 micron will float on the surface of the alveoli because of its small size and weight. This dust does not stick to the alveoli but follows Brown's motion, which will hit the surface of the alveoli and can accumulate in the alveoli.

MECHANISM OF DUST COLLECTION IN THE LUNGS

The amount of dust that enters the lungs depends on the size of the dust. The size of dust particles that are harmful to health generally ranges from 0.1 – 10 µm. There are three mechanisms for the accumulation of dust in the lungs, as follows:[9]

a. Inertia Effect

   The effect of inertia will create moisture from the dust, which will be further propelled by the airflow as it moves through the bend. However, when the airway is straight, it will immediately go with a straight flow inward, while large particles do not participate in the airflow but look for an ideal place to stick or settle, such as in the grooves of the mucous membrane in the airways.

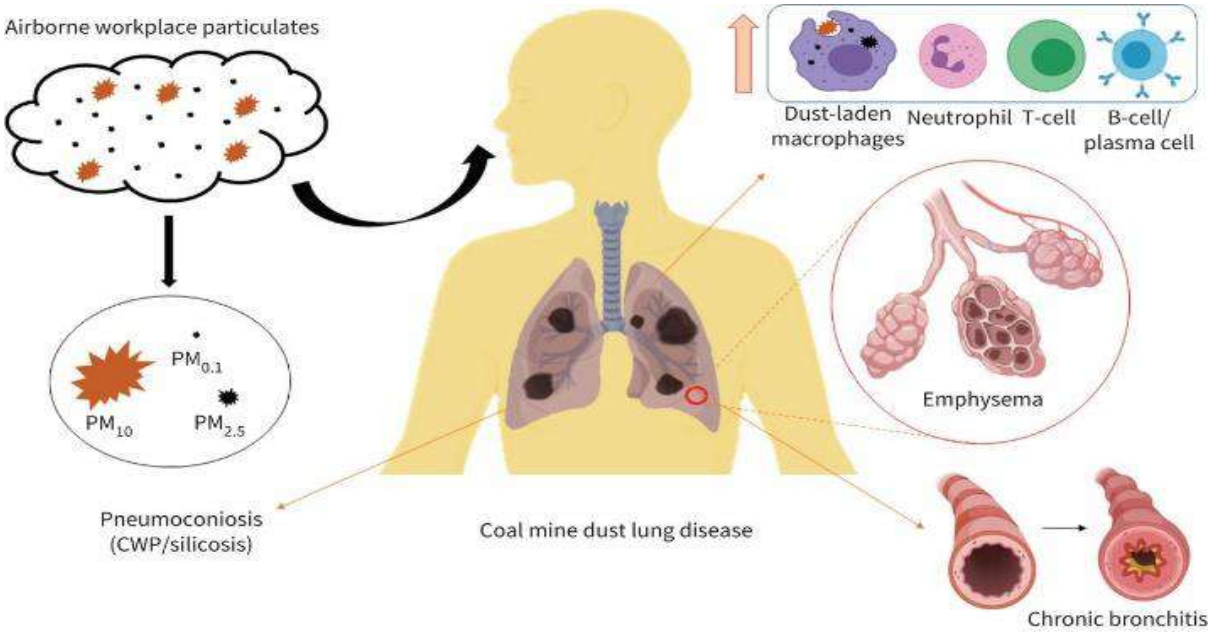
b. Effect of Sedimentation

   The effect of sedimentation occurs when the air current velocity is less than 1 cm/second so that the particles pass through gravity and settle.

c. Brown Movement

   Brownian motion applies to dust that is less than 0.1 microns in size through air movement, and dust particles that enter the body will disturb the alveoli and then settle.

Picture 1 shows an example of the dust collection mechanism in the lungs of coal miners. In the workplace, dust particles of various sizes enter the respiratory system of exposed workers through the nose. Larger dust particles will settle in the upper repiratory tract, and smaller ones will enter and settle in the alveoli. Each part of the respiratory system that is exposed to dust will react by showing symptoms of lung disorders.



Picture 1. Example of Dust Collection Mechanism in Lungs of Coal Miner[10]

In this case, the respiratory complications resulting from coal dust inhalation are the increase in cellular influx, destruction of alveolar parts (emphysema), and change in structure such as deposition of mucus and collagen, which leads to bronchitis.[11]

LUNG FUNCTION DISORDERS DUE TO DUST EXPOSURE

The cause of impaired lung function is dust exposure. Lung function disorders in the form of the inability to expand (elasticity) the lungs and respiratory tract disorders, both structural (anatomical) and functional, cause a slowdown in respiratory airflow caused by viruses, bacteria, dust, and other particles. Lung function disorders are divided into three types, namely:[10,12]

a. Obstructive Lung Disease

Obstructive lung disease is an airway disorder that is both structural (anatomical) and functional, causing a slowing of respiratory airflow. This abnormality can be detected by physical examination (auscultation found prolonged expiration), examination of FEV_1 <75% of the predicted value, and lung volume (Residual Volume (RV), Total Lung Capacity (TLC), and Functional Residual Capacity (FRC)). A study by Lange et al. stated that of 657 people who had an FEV_1 of less than 80%, 26% had COPD before they were 40 years old.[13]

b. Restrictive Lung Disease

Restrictive lung disease is a disorder of lung expansion due to any reason; it can be caused by allergens such as dust. The lungs become stiff, the inward traction is stronger so that the chest wall shrinks, the ribs narrow, and the lung volume decreases. Lung volumes decrease, namely Vital Capacity (VC), TLC, RV, FRC, and Expiratory Reserve Volume (ERV). As a parameter in spirometry, VC is measured with a value

<80% of the predicted value (normally 80-120%, whereas if the value is >120%, it is called over/hyperinflation). FEV_1 value is still above 75%.

Hutapea et al. studied the incidence of lung function disorders due to exposure to aluminum dust in CV X workers and found that 42.5% of workers had obstructive lung function disorders, 22.5% of workers had restriction disorders, and no workers had combined lung function disorders, so it could be concluded that there were 65% of workers experiencing impaired lung function (obstruction, restriction, and combination).[10] Rice mill workers in India exposed to husk dust showed significantly lower levels of FVC, FEV_1, and PEPR than controls.[14]

c. Combination of Lung Disease

Combination lung disease is a combination of obstructive and restrictive conditions that occur together due to the presence of particles that enter the lung through the top and stick together to cause pulmonary obstruction. As for the smaller size, it is not accommodated so that it can pass through and then enter the alveolus and cause lung restriction.

DISEASES DUE TO DUST EXPOSURE IN THE WORKPLACE

Various health problems can arise from the work environment. Chemical factors such as dust are very easy to find in the work environment and can expose workers. Dust is a chemical particle that can cause reduced work comfort, visual disturbances, lung health problems, and poisoning. Dust that is inhaled continuously and for a long time causes lung damage and fibrosis. The potential for impaired lung function depends on the size of the dust that can enter the alveoli or that only moves in and out of the alveoli but does not settle on the surface.[15]

Pneumoconiosis is a respiratory disease caused by dust particles that enter and settle in the lungs, causing a tissue reaction to the dust in the form of fibrosis.[16] Pneumoconiosis that is often reported in several countries includes silicosis, asbestosis, and coal pneumoconiosis. Several types of pneumoconiosis can be found in areas with industrial and technological activities caused by various types of dust and are very detrimental to the health of workers.

Diseases Due to Coal Dust and Silica

Coal is a dark organic rock with the main content of carbon, hydrogen, and oxygen atoms. It also consists of nitrogen, sulfur, and small amounts of mineral compounds.[17,18] Coal is used as a fuel to produce electrical energy. However, in its use, coal can cause air pollution by producing a mixture of earth crust dust and coal dust. Coal dust is a complex mixture of varying proportions of minerals, trace metals, and organic matter, with varying degrees of coal particulate.[19]

Coal dust can be generated from various work activities in an industry, such as mining and quarrying of coal and minerals, coal cracking, and activities at

coal stockpiles, as well as dust emissions from coal combustion.[20]

The threshold value for coal dust is seen from two angles based on the health effects caused by coal dust, namely as a cause of obstructive pulmonary function disorders and restrictive pulmonary function disorders. The threshold value based on the Regulation of the Minister of Manpower of the Republic of Indonesia Number 5 of 2018 concerning the Threshold Value of Physical and Chemical Factors in the Workplace for coal dust that causes obstructive pulmonary function disorders is 10 mg/m^3, while for coal dust that causes restriction lung function disorders, it is 0.023 mg/m^3 (silica, crystalline).[21]

One of the compositions in coal is silica.[22]Using the threshold value of silica (crystalline) with the assumption that, based on the literature, coal dust contains 10% free silica elements and is the most dangerous substance of all substances contained in coal.[23]

Free silica elements have the potential to cause pulmonary interstitial tissue fibrosis and can reduce the phagocytic capacity of phagocytosis so that silica inhaled into the worker's body cannot be excreted, causing restrictive lung function disorders and pulmonary fibrosis.[24] A study by Cohen et al. shows that contemporary miners experience an increasing number of severe dust-related diseases due to exposure to silica. They found a high proportion of progressive massive fibrosis (PMF) caused by silica (57%) in 85 coal miners in their samples.[25]

Meanwhile, coal dust in total dust concentration can cause obstructive pulmonary function disorders in exposed workers, so workers can suffer from COPD. Therefore, coal dust can also cause combined or mixed lung function disorders (obstruction and restriction).[22]

Diseases caused by coal dust can cause silicosis. Diseases caused by coal dust are related to the nature of the dust, which is flying and easily carried by the wind. The use of coal as fuel produces a lot of SiO_2-free silica dust. When burned, silica dust will come out and be dispersed into the air along with other particles such as alumina dust, iron oxide, and carbon in the form of ash.[9] Free silica is fibrogenic; if inhaled by workers, it will cause pulmonary interstitial tissue fibrosis and restrictive lung function disorders.[26]

In addition, free silica in the crystalline form has the potential to cause pneumoconiosis, or coal worker's pneumoconiosis (CWP). Silica has an incubation period of about 5 to 10 years. The incubation period will be shorter-only a few weeks or months-if the concentration of silica is very high.[26]

Symptoms of this disease are shortness of breath and coughing without phlegm. If the disease is at a moderate level, symptoms of shortness of breath will be seen, and there will be abnormalities in the lungs during the examination. However, if the disease is at a severe level, shortness of breath will get worse, followed by right heart hypertrophy, which can lead to heart failure. The diagnosis for this disease is made by performing a

physical examination, especially on the lungs, breathing tests, a high-resolution CT scan, bronchoscopy to evaluate the inside of the lungs and a lung biopsy.[27]

There is no specific cure for silicosis. Therefore, preventive measures are the most appropriate way to avoid this disease. This is because if the worker has previously suffered from pulmonary TB, bronchitis, asthma, and other respiratory diseases, silicosis will worsen the worker's health condition. Regular health inspections and inspections for workers will help prevent and control occupational diseases in the workplace. The use of PPE, such as masks, can also help prevent infection with this disease.[9,28]

Diseases Due to Aluminum Dust

Aluminum (Al) is the most abundant metal in the earth's crust and the third most abundant element after oxygen and silicon. Aluminum is a metal that can be molded and is widely used in everyday life, causing exposure to aluminum due to its presence and use in products such as canned food and beverages, cooking utensils, the aerospace industry, food additives, and so on.[29,30]

Aluminum dust is one of the contaminants resulting from industrial processes that have a toxicological impact on the human body. Aluminum (Al) in the form of dust will accumulate in the lungs. Aluminum dust has a highly toxic nature, so in the company's hygiene practice, it needs a separate reference (TLV) to prevent its impact on health. Based on the Regulation of the Minister of Manpower of the Republic of Indonesia Number 5 of 2018 concerning Occupational Safety and Health in the Work Environment, the threshold value of the physical and chemical factors of aluminum metal dust should not exceed 5 mg/m^3.[21]

Aluminum dust has a clinically irritating effect on respiration. The health effects of exposure to aluminum dust through inhalation can result in irritation of the upper respiratory system and interstitial lung disease, or pulmonary fibrosis.[11] Aluminum dust can form flammable or explosive mixtures with air, especially when wet, and react violently (explosively) with water, steam, and moisture to cause fire or explosion.[31]

Symptoms of pulmonary aluminosis are characterized by irritation of the respiratory tract, dyspnea, chronic cough, hemoptysis, and pleuritic pain. If exposure to aluminum dust is not addressed immediately, it will have a serious impact on the lungs and will eventually cause lung diseases in workers such as emphysema and pneumothorax. Some occupational diseases in the aluminum industry come from physical groups such as miliaria and chemical groups such as dust and steam.

In addition, exposure to aluminum dust can also cause obstructive pulmonary disorders. In addition to its effects on the lungs, aluminum exposure also has adverse effects on the skin, hematopoietic system, bones, central nervous system (Alzheimer’s Disease or dementia), and cancer. This disease is diagnosed by histological examination and chest

radiography to detect dust particles in the lungs.[32]

Aluminosis can be prevented by minimizing exposure to inhaled aluminum dust particles. This disease will cause complications if not immediately followed up, causing damage to the lungs. To overcome this problem, workers must have an awareness of the importance of health and safety at work, starting with using respiratory PPE, consuming nutritious food and drinking water, and conducting medical check-ups to determine their health condition.

Diseases Due to Wood Dust

Wood dust is a solid particle (wood) produced from several natural or mechanical forces such as processing, crushing, softening, fastpacking, blasting, and others and consists of organic and inorganic materials such as wood, seeds, metal, and charcoal. Wood dust is produced from wood processing or handling such as cutting, sanding, and shaving. Although not all wood species can be harmful to health (depending on the species), workers who are exposed to wood dust every day can pose a threat to health, especially wood dust that contains toxic materials.

The wood dust threshold value based on the Minister of Manpower Regulation Number 5 of 2018 is 5 mg/m^3.[21] Wood dust is included in the hardwood dust and softwood dust classification lists that have been determined by the TWA for hardwood dust of 0.5 mg/m^3 and softwood dust of 2 mg/m^3.[33] Dust levels that exceed the TLV can reduce the ability to see, cause deposits in the eyes, nose, and airways, and cause skin damage or irritation.[34]

Wood dust is divided into two types, namely softwood and hardwood. The size of the dust is very influential on the occurrence of diseases in the respiratory tract. The large size of dust particles will be captured by the upper respiratory tract. Dust that enters the respiratory tract will cause a respiratory reaction. Wood sawdust is one of the hazardous chemicals that has a negative impact if there is a buildup.[35]

The accumulation and movement of dust in the airways can cause inflammation of the airways. This inflammation can cause blockages in the airways. Dust that enters the respiratory tract will cause non-specific defense mechanisms such as sneezing, coughing, impaired mucociliary transport, and phagocytosis by macrophages.[35]

The smooth muscle around the airway can be stimulated to cause constriction of the passageway. This situation occurs when the dust content exceeds the threshold value. High exposure to wood dust can trigger dermatitis, lung cancer, and occupational asthma.

Symptoms of disease due to wood dust and dust are generally characterized by coughing, sore throat, wheezing, chest pain, shortness of breath, nasal congestion, eye irritation, and watering.[36] A study by Neghab et al. on wood dust-exposed workers obtained an association between wood dust exposure and the rise

in respiratory symptoms' prevalence among exposed workers, where restrictive lung disorder was the dominant pattern. Other respiratory symptoms experienced ranged from wheezing (37%), coughing (28%), and chronic phlegm (14%).[37]

Prevention of this disease can be performed by identifying the type of wood used in the workplace, using the LEV (Local Exhaust Ventilation) system to control exposure to wood dust, and using hand protection and masks or respiratory protective equipment (REP). In addition, it can also provide training on handling hazardous substances to workers so that they are always careful when working.

Diseases Due to Rice Dust

Rice is a type of grain crop that is harvested for its seeds. In the process, rice can produce dust. Rice dust is dust produced from the rice milling process. Rice dust exposure was found during the drying and milling processes. The rice dust threshold value based on the Minister of Manpower Regulation Number 5 of 2018 is 4 mg/m^3.[21]

Rice dust is produced from the process of rice milling activities whose disposal has not been properly regulated. The remnants of milling are called bran. Rice bran is often allowed to accumulate and fly when blown by the wind, causing air pollution. Dust is the second-most common hazard after noise in the workplace, but dust is the number one hazard that causes occupational diseases.[38] Dust produced by the process of rice milling business activities can cause respiratory organ disorders, including lung function disorders.[39]

Diseases Due to Asbestos

Asbestos is a generic name given to six fibrous minerals that have been used in commercial products. The six types of asbestos are chrysotile, crocidolite, amosite, anthophyllite asbestos, tremolite asbestos, and actinolite asbestos.[40] Chrysotile, also known as white asbestos, is a magnesium silicate belonging to the serpentine group and is the most widely used (about 95% of all asbestos use).[40–42]

The other asbestos types belong to the amphibole group and include crocidolite, known as blue asbestos, amosite, also called brown asbestos, and anthophyllite asbestos. All these types have stronger mechanical and chemical resistance than chrysotile. The most commonly used types of asbestos in the industry are chrysotile, crocidolite, amosite, and anthophyllite, which are available from mining activities, whilst actinolite and tremolite are only natural pollutants.[40–42]

All forms of asbestos have the potential to cause asbestos-related lung disease (ARD). All types of asbestos fibers are carcinogenic.[42] Liu et. al. concluded in their paper that epidemiological studies have established that exposure to asbestos fibers causes pulmonary fibrosis (asbestosis), pleural abnormalities (effusion and plaque), and asbestos-related cancer (malignant mesothelioma, cancers of the lung, larynx, and ovary).[42,43] Klebe et. al. have reviewed the scientific

literature on asbestos and lung cancer, concluding that all types of asbestos can cause lung cancer, such as amphibole, anthophyllite, and the noncommercial amphibole, tremolite.[44]

PREVENTION OF DISEASES DUE TO DUST EXPOSURE IN THE WORKPLACE

Prevention of diseases due to dust exposure in the workplace is the most important action that can be taken to prevent the onset of disease and prevent it from getting worse. Some preventive measures can be taken by controlling dust exposure in the workplace to below the threshold value using health promotion, engineering control, administrative control, and procedures related to occupational health, such as medical check-ups and audits.

a. Create procedures that can be used as company guidelines in carrying out programs related to worker health, such as hazard identification, risk assessment, and risk control.
b. Rotate work on workers who are exposed to dust.
c. Isolate the source of dust exposure with the "local exhauster".
d. Provide proper and adequate ventilation in a closed work area.
e. Provide good respiratory protective equipment for all workers.

CONCLUSION

There are three types of lung function disorders, obstructive, restrictive, and combination. Impaired lung function can occur due to various types of particulates or dust exposure. Fibrogenic or carcinogenic dust or particulates can cause pulmonary fibrosis or cancer. To prevent this, it is necessary to carry out various levels of control, from elimination to the use of PPE.

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Editor