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Pleural Fluid Leukocyte Level Test For Establishing Tuberculous Pleural Effusion in Patients with Exudative Pleural Effusion

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Abstract

Background: *Tuberculous pleural effusion is an accumulation of fluid in the pleural cavity produced by Mycobacterium tuberculosis (MTB). The gold standard of TB pleural effusion diagnosis is to obtain TB bacilli in pleural fluid or pleural tissue. However, this is often constrained due to the low identification level of these bacilli and the slow growth of MTB cultures. This study aimed to assess the pleural fluid leukocyte level in establishing a diagnosis of pleural effusion caused by TB.*

Methods: *This was a diagnostic study conducted on 111 patients with pleural effusion, caused by TB, malignancy or non-TB infections that were assigned by supporting examinations obtained from medical records, which then assessed for pleural fluid leukocytes. Statistical analysis was performed using Kruskal Wallis Test and Receiver Operating Characteristic (ROC) curve to attain the cut-off point of pleural fluid leukocyte level.*

Results: *Pleural fluid leukocyte levels in TB cases were significantly different when compared to pleural effusion caused by malignancy and non-TB infections (P<0.001). Pleural fluid leukocyte level ≥1100 cell/mm^3 was a cut-off diagnostic test for tuberculous pleural effusion with a sensitivity of 77% and specificity of 60.3%.*

Conclusion: *Pleural fluid leukocyte level ≥1100 cell/mm^3 could assist in diagnosing tuberculous pleural effusion.* ***(J Respirol Indones 2021; 41(3): 156–60)***

Keywords: *leukocyte level, pleural effusion, tuberculosis*

Uji Kadar Leukosit Cairan Pleura dalam Menegakkan Efusi Pleura Tuberkulosis Pada Pasien Efusi Pleura Eksudatif

Abstrak

Latar Belakang: *Efusi pleura tuberkulosis (TB) adalah akumulasi cairan dalam rongga pleura yang disebabkan oleh Mycobacterium tuberculosis (MTB). Baku emas diagnosis efusi pleura TB adalah ditemukannya basil MTB di cairan pleura atau jaringan pleura, namun hal ini sering terkendala karena rendahnya tingkat identifikasi basil tersebut serta pertumbuhan biakan MTB yang lambat. Penelitian ini bertujuan untuk menilai kadar leukosit cairan pleura dalam menegakkan diagnosis efusi pleura yang disebabkan oleh MTB.*

Metode: *Penelitian ini merupakan uji diagnostik yang dilakukan pada 111 orang pasien efusi pleura TB, keganasan atau infeksi non-TB yang ditegakkan berdasarkan pemeriksaan penunjang yang diperoleh dari rekam medis, lalu dilakukan penilaian leukosit cairan pleura dari masing-masing kasus. Analisis statistik dilakukan dengan uji Kruskal Wallis dan kurva ROC (Receiver Operating Characteristic) untuk mencari titik potong kadar leukoist cairan pleura.*

Hasil: *Kadar leukosit cairan pleura pada kasus TB berbeda bermakna jika dibandingkan dengan efusi pleura yang disebabkan oleh keganasan dan infeksi non-TB (P <0,001). Kadar leukosit cairan pleura ≥1100 sel/mm^3 merupakan titik potong uji diagnostik efusi pleura TB dengan nilai sensitivitas 77 % dan spesifisitas 60,3 %.*

Kesimpulan: *Kadar leukosit cairan pleura ≥1100 sel/mm^3 dapat membantu diagnosis efusi pleura TB.* ***(J Respirol Indones 2021; 41(3): 156–60)***

Kata kunci: *kadar leukosit, efusi pleura, tuberkulosis*

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INTRODUCTION

The high incidence of pleural effusion is led by the time delay of patients having an examination for their health complaint. Dirty environment brought in the risk factors for pleural effusion, namely the inadequate sanitation, dense population, low socio-economic conditions, as well as lack of health facilities and infrastructures and also the poor knowledge about health.[1]

Pleural effusions account for 2.7% of other respiratory tract infections.[2] Pleural effusions occur due to inflammatory or non-inflammatory processes. Non-inflammatory pleural effusions could develop due to decreased oncotic pressure or elevated hydrostatic pressure.[1] Diagnosis of pleural effusion must be confirmed through careful history taking and physical examinations, definite diagnosis through thoracocentesis/pleural puncture, pleural biopsy, and pleural fluid analysis.[3] Clinicians now spend a lot of effort looking for new parameters that could assist in diagnosing the etiology of pleural effusion.

One parameter that has been developed to determine the underlying cause of pleural effusion was pleural fluid leukocyte level. To date, pleural fluid leukocyte level has been widely used to diagnose empyema, which is generally induced by a spreading parapneumonic effusion. However, in recent years, various studies began to demonstrate the ability of this parameter to increase the probability of tuberculous pleural effusion. Therefore, this study aimed to determine the role of pleural fluid leukocyte level in diagnosing tuberculous pleural effusion.

METHOD

This was an analytical study with a diagnostic test design. The sampling was done using consecutive sampling. The results expected from this study were the level of sensitivity, specificity, positive predictive value, negative predictive value, and status of accuracy and cut-off value. This study was conducted for four months, starting from April to August 2019, at the Department of Pulmonology and Respiration Medicine, Faculty of Medicine Universitas Sumatera Utara/H. Adam Malik Hospital.

Study subjects were Tuberculosis (TB) patients who met the inclusion criteria, namely pleural effusion patients with known underlying etiology and were more than or equal to 18 years old. The exclusion criteria were pleural effusion patients who had coagulation disorders and pleural effusion patients with sepsis.

The expected sensitivity for protein content was 85%. If the deviation (d) was acceptable for a sensitivity of 15% and a confidence interval of 95% (α=0.05; z=1.96), then for the sensitivity test, a minimum sample was required. The minimum sample size needed in this study was 111 subjects with pleural effusions.

The data collected were processed using statistical software. To obtain the cut-off point of the pleural fluid protein content, ROC (Receiver Operating Characteristic) curve was used. This study was approved by the Health Research Ethics Commission of Faculty of Medicine Universitas Sumatera Utara, Medan.

RESULT

Table 1 showed that all study subjects were patients treated in the Pulmonary Ward of H. Adam Malik Hospital Medan.

Table 1. Characteristics of study subjects

Characteristics		n	%
Gender	Male	63	56.8
	Female	48	43.2
Age (years old)	<40	16	14.4
	40 - 49	28	25.2
	50 - 59	31	27.9
	60 - 69	26	23.4
	≥70	10	9.0
Level of Education	Elementary School	46	41.4
	Junior High School	37	33.3
	Senior High School	28	25.2
Occupation	Retired	4	3.6
	Farmer	28	25.2
	Government employees	12	10.8
	Driver	20	18.0
	Housewife	33	29.7
	Entrepreneur	8	7.2
	Unemployed	6	5.4
Diagnosis	Tuberculosis (TB)	48	43.2
	Pneumonia	35	31.5
	Malignancy	28	25.2
Total		111	100.0

A pleural fluid examination procedure was carried out to confirm exudative pleural effusion based on the results of the pleural fluid analysis. Of the 111 study subjects, 56.8% were male, and 43.2% were female. Most of the subjects were in the age range of 50–59 years (27.9%) and 40–49 years (25.2%).

The majority of the subjects had a primary education level of elementary school background (41.4%). Based on occupation mostly were, housewife (29.7%) and farmers (25.2%).

All the subjects underwent a series of examinations to determine the underlying etiology, including sputum cytology, sputum molecular rapid test (MRT), culture for aerobic and anaerobic bacteria of the sputum and pleural fluid, and pleural fluid analysis.

Patients who had bacterial growth in the sputum and pleural fluid with no signs of TB infection were declared to have pneumonia/pleuropneumonia as the etiology. Patients with malignant features from sputum cytology, pleural fluid cytology, or histopathology from bronchoscopy samples were stated to have malignancy as the etiology. Subjects with the presence of MTB detected either through direct smear or MRT of the sputum, or exhibiting a response from anti-TB drugs administration, were declared to have TB as the underlying etiology. Of the 111 study subjects, it was found that 43.2% had TB, 31.5% had pneumonia, and the remaining 25.2% had malignancy as their etiology of exudative pleural effusion.

Table 2 describes the results of pleural fluid analysis between patients diagnosed with TB and those with diseases other than TB. From table 2 it is shown that there was a significant difference in the number of WBC between TB and non-TB subjects (*P*=0.001), where the number of WBC on TB patients was higher (1546 cells/mm^3) than non-TB patients (635 cells/mm^3).

The ROC curve is a curve adequate to measure the capability of a diagnostic test in predicting disease. The basic concept of the ROC curve is that the wider the area under the curve (AUC), the better the diagnostic test is to diagnose.

Figure 1 describes the ROC curve where the pleural fluid WBC count is represented by a yellow line. The figure indicates that the line formed by the pleural fluid WBC does not intersect with the diagonal line, which means this parameter is suitable to be used as a diagnostic test.

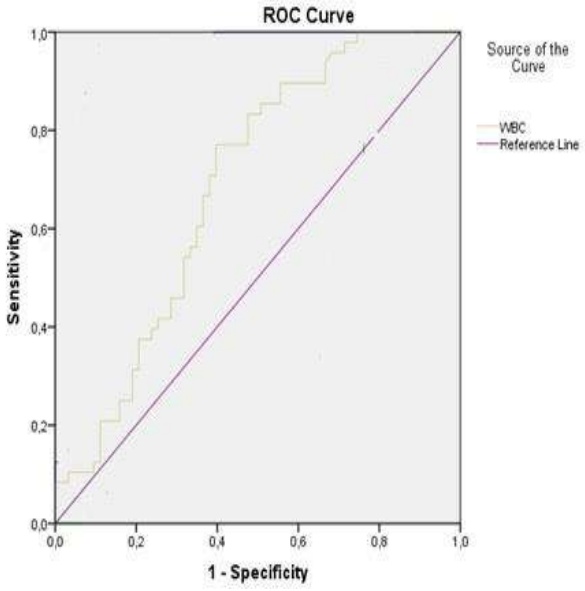

Figure 1. The ROC curve for pleural fluid protein, glucose and WBC levels

Since WBC level is intended as a screening tool to distinguish between TB pleural effusion and other cases, a ROC curve coordinate analysis was performed by looking for the value with the best sensitivity compared to the specificity. Hence, it was found that the best cut-off value for WBC was 1100 cells/mm^3 (number of pleural fluid leukocytes).

Table 2. Comparison of pleural fluid analysis results

		TB (n=48)		Non–TB (n=63)		*P* value
		median	min - max	median	min - max	
WBC	(cells/mm^3)	1546	172–33139	635	14–9474	0.001*
MN	(%)	84.3	50.8–97.7	84.3	0.3–99.5	0.34
PMN	(%)	17	2.3–55	15.7	0.0–112	0.97

Note: *) significant with *Mann-Whitney test*; WBC=white blood cells; MN=mononuclear cells; PMN=polymorphonuclear cells

Based on the previous explanation, there was one parameter that was good enough to be biomarkers of TB pleural effusion, namely the pleural fluid leukocyte level. Therefore, a diagnostic test was performed to see the sensitivity and specificity of pleural fluid WBC, as shown in Table 3 below.

Table 3. Diagnostic test of pleural fluid WBC count

WBC count	TB	Non-TB	Total
≥ 1100 mg/dl	37	25	62
< 1100 mg/dl	11	38	49
Total	48	63	111

Sensitivity	= (37/48) ×100% = 77%
Specificity	= (38/63) ×100% = 60.3%
Positive predictive value (PPV)	= (37/62) ×100% = 59.6%
Negative predictive value (NPV)	= (38/49) ×100% = 77.5%

DISCUSSION

Tuberculous pleural effusion is a manifestation of paucibacillary mycobacterial infection in the pleural space, which results from early parenchymal lesions and produces an immunologic response that increases the pleural fluid formation and reduces pleural discharge.

Initially, there is a rapid neutrophilic inflammatory response within the symptomatic pleura. This process is followed by a protracted lymphocyte-induced immune reaction accompanied by the formation of pleural granulomas and the release of adenosine deaminase (ADA). It is, therefore, plausible that the likelihood of positive pleural fluid culture decreases over time since the effusion becomes lymphocyte-dominated, while the number of TB germs that survive is minimal.[4]

Tuberculous pleural effusion is predominantly thought to develop as a result of a delayed hypersensitivity reaction. An experiment in which a substance containing tuberculin protein was injected into the pleural cavity of mice resulted in a pleural effusion that was very rich in protein within 24 hours of injection, which was completely suppressed by serum antilymphocytes. Based on this model and the fact that the investigators were unable to culture MTB from pleural fluid, the pathogenesis was thought to be due to delayed hypersensitivity. This is the most important pathogenesis, followed by the possibility of direct infection of the pleural space.[4]

The pathogenesis of tubular effusion due to TB is not much different from the pathogenesis of TB in the lung parenchyma. The pathogenetic hypothesis of pleural tuberculosis suggests that immunity such as strong type 1 T-helper cells (Th1-interferon dominant) is essential for the containment of MTB, while this protective effect is countered by the cytokines released by type 2 T-helper cells, particularly interleukins (IL-4). Activated CD3+ and CD4+ Th1 cells, through the release of interferon-gamma (IFN-γ) and other Th1 cytokines, activate macrophages to kill MTB, whereas Th2 cytokines can suppress this effect.[4]

Polymorphonuclear leukocytes are the first cells to respond, can persist predominantly for the first 24 hours, and are then followed by macrophages, peaking at 96 hours, and then by lymphocytes. It appears that the inclusion of polymorphonuclear leukocytes is a specific response to pleural injury either through itself or interactions with macrophages, playing a role in the host defense mechanism against tubercular bacilli.[4]

The predominance of Th1 immune reactions in TB pleural effusion is confirmed by high levels of IFN-γ, and other inflammatory cytokines (e.g., IL-12), while the proportion of T-helper cells in pleural fluid is also increased compared to serum, thus creating a localized pleural space. The frequency of T-cells producing IL-4, representing Th2 immunity, is significantly lower in pleural fluid compared to peripheral blood.[4]

The macroscopic appearance of pleural fluid is yellowish in more than 80% of cases. Microscopically, the identification of MTB in pleural fluid is found in less than 10% of cases. There is an exception in patients with empyema due to TB with HIV, where the result may be higher (>20%). Pleural fluid culture can be performed on both solid and liquid media as frequently used, the BACTEC MGIT semi-automatic system (Becton Dickinson-Franklin Lakes, NJ, USA), or by manual culture methods which allow for simultaneous drug resistance testing such as the

microscopic-observation drug susceptibility (MODS) assay.[4]

When using solid culture media, the sensitivity was reported to be low at about 12% to 30%. However, liquid culture media displayed better sensitivity, which was up to 70%. A further benefit of using liquid media was the significantly shorter culture time required to produce yields, being two weeks, whereas solid media was six weeks.[4]

A study from von Groote-Bidlingmaier et al compared positive culture results from large-volume (100 ml) pleural fluid with low-volume (5 ml) liquid culture media in patients with a high probability of TB. The results obtained were not significantly higher for larger volumes, namely 53.5% and 50%, respectively (P=0.75).[5]

In the same study, subjects with HIV positive had more frequent positive results of MTB pleural fluid cultures than those with HIV negative. The combination of pleural fluid culture and sputum culture in establishing TB pleural effusion was very reasonable for initial examination, with a combined diagnostic result of nearly 80%.[5]

In a recent study, the reported diagnostic results were 63% for pleural fluid culture, 48% for sputum culture and 79% for combined pleural fluid and sputum culture using liquid culture media.[4]

CONCLUSION

From our study, it can be concluded that there was a significant difference in pleural fluid leukocyte levels due to TB and non-TB (P <0.05). We could use pleural fluid leukocyte level ≥1100 as a cut-off diagnostic test for tuberculous pleural effusion with sensitivity and specificity of 77% and 60.3%, respectively, while the positive and negative predictive values were 59.6% and 77.5%.

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Pulmonary Health of Traffic Policemen in Low Air-Polluted Bogor Area

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Abstract

Background: *Traffic policemen are very susceptible to respiratory problems due to the potential for exposure to air pollution. Therefore, this study aimed to assess respiratory health aspects of traffic policemen in Bogor, West Java.*
Method: *Registered traffic policemen in Bogor were evaluated for respiratory symptoms, smoking habits, Fagerström Test for Nicotine Dependence (FTND) Questionnaire, chest x-ray, and spirometry. Air quality measurements were also carried out as a reference.*
Result: *During the study period, the air quality in Bogor was classified as "Good" and below the ambient air pollutant standard. A total of 95 traffic policemen participated with a mean age of 37.3±8.7 years (range 23–57 years), mean Body Mass Index (BMI) of 28.1±4.2 kg/m^2, and a length of service of 3-38 years (mean of 12.3 years). Mild pulmonary function impairment was found in 7.4% of subjects. About 61% of subjects had a smoking habit but with a low addiction index (FTND) and exCO. Decreased lung function was correlated to BMI and age (P<0.05).*
Conclusion: *Pulmonary function impairment in traffic policemen in Bogor City was correlated to age and BMI.* ***(J Respirol Indones 2021; 41(3): 161–9)***
Keywords: *lung function, traffic policemen, low air polluted area.*

Kesehatan Paru pada Polisi Lalu Lintas di Area Bogor yang Tercemar Udara Rendah

Abstrak

Latar Belakang: *Polisi lalu lintas merupakan profesi yang sangat rentan mengalami gangguan respirasi karena potensi pajanan polusi udara. Penelitian ini menilai aspek kesehatan respirasi polisi lalu lintas yang bertugas di Bogor.*
Metode*: Polisi lalu lintas yang terdaftar di Bogor dievaluasi terkait gejala respirasi, kebiasaan merokok, adiksi nikotin, foto toraks serta spirometri. Dilakukan juga pengukuran kualitas udara di daerah Gadog sebagai referensi.*
Hasil*: Kualitas udara di Bogor masih relatif baik saat penelitian dilakukan. Terdapat total 95 polisi lalu lintas berpartisipasi dengan rerata usia 37.3±8.7 tahun (rentang 23-57 tahun), rerata Indeks Masa Tubuh (IMT) 28.1±4.2 kg/m^2 dan lama bekerja sekitar 3-38 tahun (rerata 12.3 tahun). Gangguan fungsi paru ringan ditemukan pada 7.4% subjek. Sekitar 61% subjek memiliki kebiasaan merokok namun dengan indeks adiksi (FTND) dan ExCO rendah. Penurunan fungsi paru berhubungan dengan IMT dan usia (P<0.05).*
Kesimpulan: *Gangguan fungsi paru pada polisi lalu lintas di Kota bogor berkaitan dengan usia dan IMT.* ***(J Respirol Indones 2021; 41(3): 161–9)***
Kata kunci: *fungsi paru, polisi lalu lintas, area polusi udara rendah.*

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INTRODUCTION

Easy access to Jakarta Capital City had encouraged the development of nearby cities/satellite cities such as Depok, Bogor, Tangerang, and Bekasi. This development also brought an increase in transportation activities. Thus, the potential problem of air pollution shifted to satellite cities along with population growth and the rate of urbanization.[1] Bogor is one of the emerging satellite cities which is well-known for its greenery, comfort for living, location and easy access that is not far from Jakarta.[2] Data from Jasa Marga in 2011 showed that the number of motor vehicles entering Bogor through Jagorawi highway road and South Sentul until 2010 was around 772,529 vehicles per year. This high number of vehicles contributed to air pollutant emissions in Bogor.[1]

The Bogor Regional Police Station jurisdiction covers an area of 2,371.21 km^2 with a population of 3,268,671. This region consists of 40 districts with 461 villages/sub-districts. Bogor Regional Police Station is located at Tegar Beriman street. In performing the duty of protecting its jurisdiction from various security threats and maintain public order, the Bogor Police Station is divided into 26 sector police stations. The task forces that are often exposed to air pollution are the police who work on the roads every day, including the *Samapta Bhayangkara* (Sabhara) working unit and the traffic police.

The duties and authorities of Sabhara are to regulate traffic, organize and foster police security functions which include inter-regional patrols, public rally/demonstration control and community control, whereas the duties and authorities of the traffic policemen are to maintain traffic order, including guarding, regulating, escorting and patrolling, providing education to the public, conducting traffic control, performing registration and identification of motor vehicle drivers, investigating traffic accidents and enforcing laws in the field of traffics. The work system rotation of Sabhara and traffic police are divided into 2 shifts, each shift lasts about 12 hours a day on the road, with a break of 1 hour. The task rotation applied in these units is to use a rolling system tailored to the needs of personnel in each work unit, but usually they remain in the same unit for many years.

Traffic policemen is a profession with a very high risk of exposure to pollutants derived from motor vehicle emissions. Although personal protective equipment has been provided, not all police officers use them properly, such as masks, in carrying out their daily duties on the road. There were no studies on respiratory health and lung function of traffic policemen in Indonesia in low air pollution areas.

METHOD

The study was conducted at Bogor Regional Police Station and Gadog Regional Police Station from October to November 2014. Study subjects were all traffic policemen serving at Bogor Regional Police Station and met the inclusion criteria, including male aged 20–55 years, had been working as traffic policemen for more than 2 years, were able to perform lung function tests, were willing to participate in the study and signed the informed consent. The primary data such as lung function test using spirometry, exhaled carbon monoxide, chest x-ray (CXR), American Thoracic Society (ATS) respiratory questionnaire, and air quality data were used in this study. Secondary data namely Bogor Regional Police Station profile and data on the number of personnel on duty were obtained from the Bogor Regional Police Station.

The air pollution index (API) for Bogor region was obtained from the Regional Environmental Management Agency (Badan Pengelola Lingkungan Hidup Daerah/BPLHD) of Bogor City. Spirometry examination was performed following ATS standards using a calibrated MIR Spirobank® II S/N 004396 spirometer. Exhaled carbon monoxide (exCO) examination was carried out using piCO™ Smokerlyzer® according to the protocol from the manufacturer. The Fagerström Test for Nicotine Dependence (FTND) Questionnaire in Bahasa (Indonesian) was assessed to measure smoking

habits and nicotine addiction. The study has been approved by the Ethical Unit of the Faculty of Medicine Universitas Indonesia No.600/H2.F1/ETIK/2012.

RESULT

Geographically, the administrative area of Bogor District is located at coordinates 6º18' 6º47'10 South Latitude and 106º23'45-107º 13'30 East Longitude. The distance is about 60 km from the capital city of Jakarta. The regional topography is characterized by a cluster of lowlands in the north with an altitude of 50 to 70 meters, while the southern part is undulating and mountainous with an altitude of ±2,001 meters. Based on the classification of Schmidt and Ferguson, the rainfall climate in Bogor City is typed A (very wet) in the south and type B (wet) in the west. The temperature ranges from 20–30ºC while the average annual temperature is around 25ºC. Annual rainfall ranges from 2,500–5,000 mm/year, except for a small area in the north bordering Tangerang District and Jakarta City where rainfall is less than 2,500 mm.[3]

Air Pollution Index is a number that does not have a denomination unit that describes the condition of ambient air quality at a particular location and time, which is based on its impact on human health, aesthetic value and its effect on other living things. The API is determined by converting the measured air pollutants levels into a dimensionless number. Data of API were obtained from ambient air quality monitoring stations that measured pollutants including particulate matter $(PM)_{10}$, CO, nitrite dioxide (NO_2), sulfur dioxide (SO_2) and ozone (O_3). Converting air pollutants levels into API values can be done by calculations using formulas or graphs.

Standard equipment to measure levels of NO_2, SO_2, CO, O_3 and Total Suspended Particulate (TSP) was installed at the Gadog Traffic Police Station and collected 24 hours data during the study period. All equipment were provided by Regional Environmental Protection Agency (Badan Pengelola Lingkungan Hidup Daerah/BPLHD) of Bogor City. The description of API results for Bogor area is listed in Table 1. In this study, the air quality in Bogor area during the study was still quite good.

Table 1. The Air Pollution Index in Bogor during the study period

Parameter	Denomination	Test result	Quality standard
PM_{10}	µg/Nm^2	131,2	230
SO_2	µg/Nm^2	1,7	900
O_3	µg/Nm^2	133,3	200
NO_2	µg/Nm^2	15,6	400
CO	µg/Nm^2	3591	26000

About 88 subjects (92.6%) had normal results, 2 subjects (2.1%) had mild restriction, 4 subjects (4.2%) had mild obstruction whilst 1 subject (1.1%) had mixed mild obstruction and mild restriction. Chest X-ray examination pointed out that 87 subjects (91.6%) were normal and 8 subjects (8.4%) had abnormalities (Table 2).

Table 2. Clinical symptoms, CXR and lung function of traffic policemen in Bogor (n=95).

Examination	N	%
Clinical symptoms		
Cough	6	6.3
Sputum production	1	1.1
Productive cough	-	-
Dyspnea	-	-
Abnormal breathing sounds	-	-
Out of breath	-	-
Flu and chest pain	-	-
Chest X-ray		
Normal	87	91.6
Abnormal	8	8.4
Infiltrate	1	1.05
Calcification	1	1.05
Cardiomegaly	3	3.15
Left ventricle hypertrophy	1	1.05
Aorta elongation	1	1.05
Past clavicle fracture	1	1.05
Spirometry		
Normal	88	92.6
Abnormal	7	7.4
Mild restriction	2	2.1
Mild obstruction	4	4.2
Mild restriction and mild obstruction	1	1.1
Cigarette smoking		
Yes	58	61
No	37	39
Fagerström score (n=58)		
0-2 points (very low)	28	48.3
3-4 points (low)	21	36.2
5 points (moderate)	5	8.6
6-7 points (high)	4	6.9
8-10 points	-	-

Data were collected by conducting interviews, exCO levels measurement, spirometry examination, CXR examination and examination of air pollution levels in collaboration with the BPLHD of Bogor. About 180 traffic policemen on duty at the Bogor Regional Police Station were registered, however, only 98 traffic policemen fulfilled the inclusion criteria.

Most of the subjects were 41–50 years old (33.7%). The mean age was 37.3±8.7 years with a range of 23-57 years. Determination of nutritional status was based on Body Mass Index (BMI) and most subjects had overweight nutritional status (43.2%) with a mean BMI of 28.1±4.2 kg/m^2 and a range of 18.9–39.4 kg/m^2. A total of 61.1% of the subjects were active smokers, 3.2% were former smokers, and 35.8% were non-smokers (Table 2). The degree of smoking among smokers was based on the Brinkman Index (BI), which is the number of cigarettes smoked per day multiplied by the number of years of smoking. Based on the BI, in subjects who were smokers, 75.9% of them had mild BI, 22.4% had moderate BI, and 1.9% had heavy BI.

The analysis of PPE habits pointed out that 87.4% of subjects had poor habits, 9.5% had moderate habits, and only 3.2% had good habits in using face masks. The period of duty was calculated from the time the subject starts working as a traffic policeman. As many as 40 subjects (42.1%) had 6–10 years of service, 40 subjects (42.1%) had >10 years of service and 15 subjects (15.8%) had <6 years of service. The mean was 12.3 years of service (range of 3–38 years).

In this study, respiratory symptoms were obtained from questionnaires through interviews and lung function results were obtained using spirometry. The results of the lung function test are shown in Table 3.

Table 3. Mean and median of lung function test values

Lung function values	Mean±SD	Range		Median
		Min.	Max.	
FVC (liter)	3.7±0.5	2.0	4.8	3.7
FEV_1 (liter)	3.1±0.5	1.4	4.2	3.1
PEF (ml/s)	8.2±1.5	3.1	11.5	8.1
% FVC	97.7±14.8	9.0	129.0	98.0
% FEV_1/FVC	85.2±6.2	66.9	98.4	85.2

Note: FVC=forced vital capacity; FEV_1=forced expiratory volume in 1 second; PEF=peak expiratory flow

Table 4 describes the spirometry results and their factors. The subject's age and nutritional status had a significant correlation with impaired lung function.

Table 4. Correlation between demographics characteristics and impaired lung function

Characteristics	Spirometry disorders		*P*	OR	95% CI	
	Positive (+)	Negative (-)			Low	High
Age *)						
51–60 years	3	2	**0.024**	14.50	1.17	224.4
41–50 years	0	32	0.113	----	----	----
31–40 years	1	26	0.615	0.36	0.01	4.32
21–30 years	3	28				
BMI *)						
Obesity	1	29	0.078	0.13	0.01	1.33
Overweight	1	40	**0.023**	0.10	0.00	0.95
Normal/ Underweight	5	19				
Smoking habit *)						
Smokers	5	53	1.000	1.51	0.24	12.02
Former smokers	0	3	1.000	----	----	----
Non-smokers	2	32				
PPE usage *)						
Poor	6	77	1.000	----	----	----
Moderate	1	8	1.000	----	----	----
Good	0	3				
Period of duty *)						
>10 years of service	3	37	1.000	1.14	0.009	30.88
6–10 years of service	3	37	1.000	1.14	0.009	30.88
<6 years of service	1	14	----	----	----	----

Note: *) Fisher's exact test; BMI: body mass index; PPE: personal protective equipment usage

There were 58 subjects (61.1%) who had smoking habits. In this group, the level of nicotine dependence was evaluated using a Fagerström questionnaire that had been validated in Bahasa (Indonesian). One of the measurements to assess active smokers and air pollution is the assessment of exhaled CO. The exCO examination found that the mean exCO level of the subjects was 14.3 µg/Nm^2 with a standard deviation of 8.9 µg/Nm^2 and an interval of 3-43 µg/Nm^2. The correlations between smoking history (BI) and exCO levels can be seen in Table 5 and Table 6.

Table 5. Fagerström questionnaire nicotine dependence test (n=58) and exCO measurement.

Fagerström score	n	%	Addiction level
0-2 points	28	48.3	Very low
3-4 points	21	36.2	Low
5 points	5	8.6	Moderate
6-7 points	4	6.9	High
8-10 points	-	-	Very high

Table 6. exCO measurement.

Exhaled CO (µg/Nm^2)	n	Mean±SD
Non-smoker	34	7.9±3.5
Former smoker	3	7.0±3.2
Smokers		
Mild smoker	44	17.5±8.8
Moderate smoker	13	21.3±6.9
Heavy smoker	1	29.0

DISCUSSION

This study was conducted at Bogor Regional Police Traffic Unit using a cross-sectional study design. This design is widely used to examine occupational diseases as it can examine many variables at once, is relatively easy to implement and also feasible.[4] The results are still relevant today and can reflect lung function in conditions of minimal air pollution among traffic policemen. The mean age of the subjects was 40.9 years and mostly aged 41 to 50 years (33.7%). Most of the subjects were 40 years old or less (61%). Almost all subjects had good nutritional status with normal BMI or more. In general, the subjects in this study were considered to have good immunity. Nutritional levels play a very important role in health and working conditions.[5] Similar data were reported by Pravati et al, who conducted a study of the traffic police in New Delhi. On average, the traffic policemen had good nutritional status with BMI ranging from 24-25 kg/m^2 for both smokers and nonsmokers.[6]

Smoking habits were found in 61.1% of the subjects. This percentage was higher than the report from the Ministry of Health, Republic of Indonesia report in Basic Health Research (Riset Kesehatan Dasar/Riskesdas) in 2010 which was 22.8%.[7] The high smoking rate among traffic policemen requires serious attention since various studies stated that the impact of smoking on lung function was much greater than the effects caused by exposure to vehicle smoke experienced by traffic policemen daily when managing traffic. The prevalence of smoking in this study was consistent with the findings of the 2011 World Health Organization (WHO) Global Adult Tobacco Survey which found that 67% of Indonesian men smoked.[8] The reduction in lung function on smoker policemen was reported to be greater than the results of a cohort study of New York police who served during the explosion in the World Trade Center (WTC).[1]

The Fagerström questionnaire was used to measure nicotine dependence in /smokers,[9] and found that most subjects had low nicotine dependence (score <5). A score below 5 indicates that nicotine dependence is relatively low but efforts are needed to avoid progressing to higher levels. A score above 7 indicates that nicotine dependence is so high that a person cannot control him/herself to stop smoking. At this stage, a very strong effort is needed to quit smoking and medical assistance may also be needed to receive nicotine replacement therapy (NRT). The history of using PPE or masks during traffic control, or on duty, in this study was mostly poor (87.4%), while moderate and good use was only 9.5% and 3.2%, respectively. Several factors contributed to the poor use of masks. Subjects on duty felt uncomfortable when using both whistles and masks. Another reason was that the subjects felt hard to breathe and there were still lacks knowledge about the proper use of the mask.

The period of duty in this study was divided into three categories, namely 6 years of service, 6-10 years of service and ≥10 years of service. The

mean period of duty was 12.3±7.7 years with an interval of 3–38 years. Various problems such as the work environment, dust exposure and poor PPE use followed by smoking habits required special attention because they could have a cumulative impact on the emergence of occupational health problems. Zafar et al divided the study subjects into 2 groups namely a duty period of <10 years and ≥10 years. The study also compared groups based on pollution levels (mild, moderate, and severe).[10] Traffic policemen in Bangkok served in areas with high levels of air pollution showed a significant decline in FVC and FEV_1 and often complained of coughing and rhinitis compared to the control group.[11]

Spirometry is an important tool for detecting occupational lung disease. Lung function tests must be accurate, reproducible, sensitive, and can be performed at the workplace.[12] Lung function tests were performed using normal lung function values of Pneumobile Project Indonesia as a reference. These normal lung values were lower than the Caucasian or even Japanese values but were more appropriate in the Indonesian population. Most subjects had a normal lung function test with a mean FVC of 3700±500 ml. The mean %FVC was 97.7±14.8%. The mean FEV_1 was 3100±500 ml and the FEV_1/FVC ratio was 85.2% with the lowest being 66.9% and the highest 98.4%. The prevalence of lung function abnormalities was 7.4%, including 2.1% mild restriction, 4.2% mild obstruction, and 1.1% mixed mild obstruction and mild restriction. This finding was different from the Central Pollution Control Board 2008, Ministry of Environment and Forests of India which conducted an epidemiological study on the effects of air pollution on the health of adults in Delhi. The study found lung function abnormalities in 40.3% of respondents with 22.5% restriction, 10.7% obstruction, and 7.1% mixed obstruction and restriction.[13]

This dissimilarity was likely due to the great distinction of air pollution levels between Bogor and Delhi. The PM_{10} level of Delhi residential areas was 178 μg/m^3. The traffic-congested areas of Delhi even reached 250 μg/m^3, while the PM_{10} level in Bogor in this study was only 131.2 μg/m^3. Moreover, the mean SO_2 level at residential and traffic areas in Delhi was 9 μg/m^3 while in Bogor during this study was only 1.7 μg/m^3. The NO_2 level in residential areas of Delhi was 44 μg/m3 and at traffic-congested areas, it even reached 83 μg/m^3, while in Bogor during this study was only 15.6 μg/m^3. This study also assessed abnormalities of the chest cavity and lung parenchyma using CXR. There were 8.4% CXR abnormalities found (8 of the 95 people examined). Chest X-ray abnormalities found in this study included calcification, infiltrates, aortic elongation, cardiomegaly, and left ventricular hypertrophy.

Lung function is affected by several factors including age, gender, height, and race. In addition, it is also influenced by several diseases such as airway obstruction, emphysema, fibrosis, tuberculosis, atelectasis, chest wall deformities, neuromuscular disease, heart failure, and space-occupying lesions in the pleura or parenchyma.[14] Kohansal et al in 2009 pointed out that men who had never smoked would experience a decline in FEV_1 of 19.6 ml/year and that of smokers would decrease by 38.3 ml/year.[15] A classic study by Fletcher and Peto in 1977 indicated that subjects experienced a decrease in FEV_1 each year after the age of 25 but non-smoker subjects had never experienced obstruction (obstruction prevalence 0%). Subjects who were heavy smokers experienced obstruction as much as 46% while mild smokers were 24%.[16] In this study, the results of statistical analysis using Fisher's absolute test showed a significant correlation between the age of subjects and the spirometry results in the age group of 51-60 years (P=0.024), but not significant after multivariate analysis.

Based on the correlation between age and decreased lung function, 3 subjects were <30 years old, 1 subject was 40 years old and 3 subjects were >50 years old. From the Fisher's absolute test analysis, there was a significant correlation between the age of the subject and the spirometry results in the 51-60 years age group (P=0.024). Obesity is a complex problem that is often associated with

comorbidities and mortality. Data from New York Metropolitan Life Insurance showed that in the 48-69 years age group, the mortality rate of the obese male was 42% greater than the average and that of obese female was 36% greater than the average.[17] Study conducted on Norwegian subjects aged 25-34 years male and female with BMI >31 kg/m^2 discovered that those subjects had twice the mortality rate as subjects with normal body weight. One of the diseases associated with obesity is respiratory problems. Some literature stated that obese people tended to experience decrease respiratory function compared with those who were not obese.[14]

Obesity is determined by a simple indirect examination using BMI calculation that divides body weight (in kilograms) by height (in square meters/m^2). This method is frequently used by clinicians. Hakala et al in a study that used multiple regression analysis, showed that each kilogram of weight gain was associated with a 26 ml decrease in FVC and 23 ml decrease of FEV_1 in male subjects, whereas in female there were 14 ml and 9 ml decreases, respectively. Obesity affects respiratory mechanisms and lung volume through the increased amount of fat in the chest wall and abdomen which may have an impact on the mechanical properties of the chest and diaphragm and indicate changes in respiratory function. This mechanism decreases lung volume and changes ventilation with each respiration.[18]

Our study found out that there was no significant correlation between habitual use of masks and impaired lung function (*P*=1,000). This insignificant result was different from Wongsurakiat et al (19). who found that traffic policemen who did not wear masks had a significantly higher prevalence of abnormal FEV_1 and FVC compared to the control group, 35% vs 14%, respectively (*P*=0.046). The study by Wongsurakiat et al stated that traffic policemen who did not use protective masks had a relatively higher risk of experiencing abnormal FEV_1 and FVC compared to the control group who used protective masks.[20]

This difference was likely since API level in Bogor was still far below the national air quality standard. It was widely known that the inappropriate use of masks led to a higher risk of exposure to pollutant particles. Long-term exposure to pollutants and the inappropriate use of masks were associated with decreased lung function. Seven subjects with declined lung function had a history of inadequate use of PPE. Of the 3 subjects who never wore a mask, 1 subject experienced mild obstruction and 2 subjects had mild restriction. Four subjects wore masks but with poor use of masks. Of those 4 subjects, 3 subjects had a mild obstruction and 1 subject had mixed disorders (mild restriction and mild obstruction). There was no significant correlation between the period of duty with lung function (*P*=1,000).[10]

Although the correlation between the period of duty and lung function was not significant, it seemed that the period of duty tended to be associated with occupational lung disease and further study is needed to prove it. Zafar et al. categorized their study subjects into 2 groups: subjects who served less than 10 years and those who served ≥10 years. The study also compared the two groups based on the level of pollution (mild, moderate, and high).[10]

There was a significant decline in FVC and FEV_1 of the traffic policemen in Bangkok who worked in areas with high levels of air pollution. The traffic police also often complained of coughing and rhinitis compared to the control group.[19] There was no correlation between the period of duty and lung function abnormalities. Of the 7 subjects with lung function abnormalities, 3 subjects had a period of duty less than ten years (7 years), while the other 4 subjects had a period of duty more than ten years (23, 25, 26, and 38 years). In this study, the period of duty was categorized into 3 groups, namely 0 to 6 years, 6 to 10 years, and more than 10 years. In the group of subjects who worked between 0-6 years, none experienced lung function abnormalities. This may be due to the short period of duty and optimal lung function. Thanks to the Bogor Traffic Police Department for providing access to the study.

CONCLUSION

The Bogor area, as a satellite of the capital city of Jakarta, had a relatively good air quality during the study. The prevalence of lung function disorders based on spirometry results in Bogor traffic policemen during the study was 7.4%. The prevalence of smoking was still quite high and the proper use of PPE among traffic police officers was still low. There was no significant correlation between smoking habits, masks usage and period of duty with lung function but there was a significant correlation between age and BMI with lung function in this group.

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Correlation Between Type 2 Diabetes Mellitus and Pulmonary Tuberculosis at Atma Jaya Hospital

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Abstract

Background: *Diabetes Mellitus (DM) is considered one of the factors that increase the risk of pulmonary tuberculosis (TB). Tuberculosis in Indonesia is severe and ranked second in the world after India. Previous studies suggested that DM increased the risk of developing pulmonary TB by 2–5 times. This study was conducted to determine the effect of type 2 DM on the incidence of pulmonary TB at Atma Jaya Hospital.*
Methods: *This was a case-control study conducted at Atma Jaya Hospital from December 2016 to April 2017 using medical records. Data were further processed by pairing gender and age between case and control groups. A total of 121 samples were obtained and tested using McNemar paired correlation non-parametric analysis.*
Results: *The incidence of pulmonary TB was higher in men than women with a ratio of 2.1:1 and within the productive age range of 27–46 years. The percentage of type 2 DM in pulmonary TB cases was 70% (35 samples) compared to 30% (15 samples) without DM with a total of 50 samples in the case group. The percentage of type 2 DM in the control group without pulmonary TB was 46.5% (33 samples) compared to 53.5% (38 samples) without DM with a total of 71 samples in the control group. Based on the statistical analysis, the P=0.013 and the OR (odds ratio) was 2.20.*
Conclusion: *There was a significant correlation between type 2 DM and the incidence of pulmonary TB in Atma Jaya Hospital with the risk of pulmonary TB 2.20 times higher than those without type 2 DM.* ***(J Respirol Indones 2021; 41(3): 170–3)***
Keyword: *type 2 diabetes mellitus; pulmonary tuberculosis*

Pengaruh Diabetes Mellitus Tipe 2 terhadap Kejadian Tuberkulosis Paru di Rumah Sakit Atma Jaya

Abstrak

Latar Belakang: *Diabetes mellitus (DM) merupakan salah satu faktor risiko terjadinya tuberkulosis (TB) paru. Angka kejadian TB paru pada tahun 2019 di Indonesia berada di posisi kedua setelah India. Angka kejadian TB paru di Indonesia berada di posisi keempat setelah India, Cina dan Afrika Selatan. Berdasarkan penelitian yang ada, DM meningkatkan risiko terjadinya TB paru sebesar 2–5 kali. Kondisi DM memberikan dampak manifestasi TB yang lebih buruk. Penelitian ini dilaksanakan dilakukan untuk mengetahui pengaruh DM tipe 2 terhadap kejadian TB paru di RS Atma Jaya.*
Metode: *Penelitian ini menggunakan studi kasus kontrol yang dilakukan di Rumah Sakit Atma Jaya pada Desember 2016 sampai April 2017 menggunakan data rekam medik. Dilakukan* pairing *jenis kelamin dan usia antara kelompok kasus dengan kontrol. Jumlah sampel yang diperoleh121 pasien dan diuji menggunakan uji analisis non parametrik korelasi berpasangan McNemar.*
Hasil: *Tuberkulosis paru lebih sering terjadi pada laki-laki dengan perbandingan 2,1:1 dan pada rentang usia produktif, yaitu 27–46 tahun. Persentase DM tipe 2 pada kasus TB paru didapatkan sebesar 70% (35 sampel) dibandingkan 30% (15 sampel) yang tidak DM dengan total kasus sebanyak 50 sampel. Persentase DM tipe 2 pada kontrol yang tidak menderita TB paru sebesar 46,5% (33 sampel) dibandingkan 53,5% (38 sampel) yang tidak DM dengan total kontrol sebanyak 71. Berdasarkan hasil analisis statistik didapatkan nilai P=0,013 dan OR (*odds *ratio) sebesar 2,20.*
Kesimpulan: *Terdapat hubungan bermakna antara DM tipe 2 dan kejadian TB paru di RS Atma Jaya dengan risiko TB paru 2,20 kali lebih tinggi dibandingkan yang tidak menderita DM tipe 2.* ***(J Respirol Indones 2021; 41(3): 170–3)***
Kata kunci: *diabetes mellitus tipe 2; tuberkulosis paru*

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INTRODUCTION

Tuberculosis (TB) is an infectious disease that affects one-third of the population worldwide. Estimated every year, the death rate due to *Mycobacterium tuberculosis* (MTB) reaches two million people. In 2019, eight countries account for two-thirds of the total cases of TB, with India leading the count, followed by Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh and South Africa.[1]

Diabetes Mellitus (DM) is one of the risk factors for developing TB. Diabetes Mellitus is a group of metabolic diseases with a characteristic of hyperglycemia.[2] Patients of this chronic disease increased from 108 million people in 1980 to 422 million people in 2014.[3]

In Indonesia, based on Basic Health Research 2018 (Riskesdas 2018), the prevalence of Diabetes Mellitus (DM) among population ≥15-year-olds increased from 6.9% in 2013 to 10.9% in 2018.[4] Subjects with DM were more susceptible to infection than those without DM. This was due to a defect in immunity that resulted in susceptibility to infection.[5] Patients with DM have a higher risk of active TB than those without DM by 3.11 times.[6]

As DM interferes with the patient's immunity, it becomes a risk factor for infections such as TB.[5,7,8] In DM, there is an increase in blood glucose or hyperglycemia which causes the impaired function of neutrophils and monocyte so that chemotactic, phagocytosis and bacterial killing ability are attenuated. This reduced function of monocytes and chemotactic were not improved by insulin administration. Diabetes is associated with decreased cellular immunity, especially cytokine T-helper (Th1), which leads the subject to be more prone to developing TB.[6,8,9]

Several epidemiological studies had explained the correlation between DM and TB. Data from WHO showed that DM escalated the risk of TB infection three times greater than the normal population.[6,10] There is no precise data in Indonesia, therefore, this study aimed to determine the correlation of DM and pulmonary TB, mainly in Atma Jaya Hospital.

METHOD

This study was conducted from December 2016 to April 2017 at Atma Jaya Hospital Jakarta using an analytical design with a case-control approach, retrospectively. A total of 121 study samples were obtained using medical record data. The control group was paired to the case group on age and gender. The inclusion criteria were samples more than or equal to 17 years old with or without pulmonary TB. Exclusion criteria were subjects with malnutrition status, HIV, malignancy, chronic kidney disease, using immunosuppressant drugs, history of alcohol consumption or smoking habits.

Data analysis was carried out univariately looking at the distribution of the essential characteristics of the study and bivariate samples to obtain the importance and magnitude of the correlation between type 2 DM and the incidence of pulmonary TB. The analysis of the meaning and magnitude of the correlation between variables was performed using the McNemar test, while the relationship between risk factors and influence factors was observed through the value of odds ratio (OR). The *P*-value used in this study was 0.05 with a confidence interval (CI) of 95%.

RESULT

Our study obtained 121 medical record data consisting of 50 cases of pulmonary TB and 71 controls without pulmonary TB. Table 1 describes the characteristics of the subjects.

Table 1. Characteristics of the subjects

Characteristic		Pulmonary TB	
		Positive	Negative
Gender	Male	34	45
	Female	16	26
Age	17–26	8	12
	27–36	14	17
	37–46	14	24
	47–56	4	7
	57–66	7	7
	67–76	3	4

In table 2, the statistical analysis of the correlation between type 2 DM and pulmonary TB obtained *P*=0.013. These results showed a significant

correlation between type 2 DM and pulmonary TB among patients at Atma Jaya Hospital. The study results achieved OR of 2.20, which means patients with type 2 DM have 2.2 times higher risk of developing pulmonary TB.

Table 2 Correlation between type 2 DM and pulmonary TB

Characteristic		Pulmonary TB		Total	*P*	OR
		Yes	No			
Type 2 DM	Yes	35	33	68	0,013	2,20
	No	15	38	53		
Total		50	71	121		

DISCUSSION

Out of 50 cases of pulmonary TB, there were 35 people (70%) with a history of type 2 DM. This result was similar to a study from Balakrishnan in India which stated that among 552 pulmonary TB patients, type 2 DM was observed in 243 patients (44%).[11] In addition to the correlation of pulmonary TB incidence and history of type 2 DM, according to a meta-analysis conducted by Jeon and Murray, type 2 DM was at risk of pulmonary TB with OR=3.11.[6]

Our study stated comparison of pulmonary TB cases in male and female by a ratio of 2.1:1. This result was supported by a study from Harianto conducted at Atma Jaya Hospital, which also acquired that TB patients were more common in men.[12] A study from Alisjahbana et al. in Indonesia, pointed out that men were more easily infected with MTB than women.[13] In addition, TB notification data worldwide in 2012 determined the comparison of TB occurrences between men and women was 1.9:1.19. These were in line with WHO that showed more men than women in Asia were diagnosed with TB at a ratio of 3:1. The incidence among adult men is more prevalent which accounted 56% of all cases in 2019 compared with 32% of cases in adult women and 12% in children.[10]

Pulmonary TB in our study occurred at the age of 27–46 years as many as more than half the case group, (28 patients). This result corresponded with a study from Dotulong et al. in Sulawesi, where TB was found in the productive age group (25–54 years).[14] In addition, Dobler et al. stated that DM and TB correlation were more common in the population under 40 years than those above.[15] In the literature, it was mentioned that in industrialized or developed countries, 80% of TB was observed in the age group above 50 years, whilst in developing countries, 75% of TB was inspected in the age group below 50 years.[16] In accordance to Begum and Chan-Yeung, the productive age group was more at risk of infection due to the work environment, such as physical or mental stress factors due to workloads which could trigger a decrement of the immune system.[17,18]

The McNemar test showed a significant correlation between type 2 DM and pulmonary TB with *P*=0.013 and OR=2.20. This data was similar to a study conducted by Alisjahbana et al. in Indonesia.[13] Patients with pulmonary TB were more likely to have a history of type 2 DM than non-TB. The prevalence of such infectious diseases was 2–5 times higher in patients with DM than in non-DM controls. According to Cahyadi et al. DM was the most common risk factor in culture-confirmed TB patients.[19]

This study obtained OR 2.20, which means patients with type 2 DM were more susceptible to pulmonary TB as much as two times than those non-DM. This OR was slightly lower than in previous studies. A meta-analysis conducted by Jeon and Murray found that DM increased the risk of TB infection by 3.11 times compared to those without DM.[6] In a longitudinal study conducted by Dooley and Chaisson for 3 years in Korea, DM was 3 times more likely to develop pulmonary TB infection.[7]

CONCLUSION

Patients with type 2 DM had 2.2 times higher risk of developing pulmonary TB infection compared to those without DM.

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Covid-19 Patient Condition at Early Pandemic in Jakarta

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Abstract:
Background: *Covid-19 is a disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) that has become a pandemic. It became apparent that Covid-19 transmitting from person to person. The clinical manifestations and characteristics of Covid-19 encompassing from asymptomatic infection until severe pneumonia and death. This study aimed to describe and compare the characteristics between Covid-19 suspected patients and confirmed patients at an early pandemic in Jakarta, Indonesia.*
Methods: *A cross-sectional design was used in this study. Data were collected from March to April 2020 using the electronic health record reporting database, initial laboratory tests, and RT-PCR for SARS-CoV-2 results. There were 58 subjects: 43 Covid-19 confirmed patients and 15 Covid-19 suspected patients.*
Results: *Male was found predominantly in Covid-19 confirmed patients than female. The mean age of confirmed patients was 49,6 years old. Nearly half of the confirmed patients had comorbidities namely hypertension and diabetes mellitus. Fever and cough were the most common presenting symptoms, and they were also found in suspected patients. Confirmed patients tended to have lymphopenia and neutrophilia. Pulmonary infiltrate was the most common feature in both confirmed and suspected patients.*
Conclusion: *There were no significant differences found between Covid-19 confirmed and suspected cases regarding demographic characteristics, comorbidities, presenting symptoms, physical examination results, laboratory tests, and chest x-ray results. Covid-19 confirmed patients had a history of exposure to Covid-19 confirmed patients.* ***(J Respirol Indones 2021; 41(3): 174–9)***
Keywords: *coronavirus, Covid-19, Indonesia, Jakarta, SARS-CoV-2.*

Karakteristik Pasien Covid-19 pada Awal Pandemi di Jakarta, Indonesia

Abstrak:
Pendahuluan: *Covid-19 merupakan penyakit yang disebabkan oleh Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) yang saat ini telah menjadi pandemi. Covid-19 dapat menular dari orang ke orang. Manifestasi klinis dan karakteristik Covid-19 mencakup infeksi tanpa gejala hingga pneumonia berat dan kematian. Penelitian ini bertujuan untuk mendeskripsikan dan membandingkan karakteristik antara pasien terduga Covid-19 dengan pasien terkonfirmasi Covid-19 pada awal masa pandemi di Jakarta, Indonesia.*
Metode: *Penelitian ini menggunakan studi potong lintang. Pengumpulan data dilakukan dari Bulan Maret hingga April 2020 menggunakan basis data pelaporan rekam medis elektronik, uji laboratorium awal dan RT-PCR untuk hasil SARS-CoV-2. Subjek penelitian berjumlah 58 orang terdiri dari: 43 pasien terkonfirmasi Covid-19 dan 15 pasien terduga Covid-19.*
Hasil: *Pasien terkonfirmasi Covid-19 didominasi oleh laki-laki dengan rerata usia 49,6 tahun. Hampir setengah dari pasien yang terkonfirmasi memiliki penyakit penyerta di antaranya hipertensi dan diabetes mellitus. Demam dan batuk adalah gejala umum yang sering muncul, dan gejala tersebut ditemukan juga pada pasien terduga. Pasien yang terkonfirmasi cenderung memiliki limfositopenia dan neutrofilia. Infiltrat paru adalah gambaran yang paling umum pada pasien terkonfirmasi dan pasien terduga.*
Kesimpulan: *Tidak ditemukan perbedaan bermakna antara kasus Covid-19 terkonfirmasi dan terduga terkait karakteristik demografi, komorbiditas, gejala yang muncul, hasil pemeriksaan fisis, pemeriksaan laboratorium, dan foto toraks. Pasien terkonfirmasi Covid-19 memiliki riwayat kontak dengan pasien terkonfirmasi Covid-19 sebelumnya.* ***(J Respirol Indones 2021; 41(3): 174–9)***
Kata Kunci: *coronavirus, Covid-19, Indonesia, Jakarta, SARS-CoV-2.*

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INTRODUCTION

Coronavirus disease 2019 (Covid-19) is a disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has become a pandemic. Covid-19 was first reported in December 2019, on Wuhan city, the capital of Hubei province in China. Although SARS-CoV-2 did not have a mortality rate as high as the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) or Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), SARS-CoV-2 is much more infectious than MERS-CoV and SARS-CoV.[1,2] As of May 25th 2020, the total number of Covid-19 cases worldwide was 5.494.461, with total deaths of 346.434. In Indonesia, the total number of cases was 22.750 with total deaths of 1.391 as of May 25th 2020.[3]

This Covid-19 outbreak was likely started from a zoonotic transmission event associated with a large seafood market that also traded live wild animals in Wuhan, however, the highly infectious person-to-person transmission was also occurring and that was the reason for the outbreak.[4] The spectrum of clinical manifestations and characteristics of SARS-CoV-2 infection appears to be wide, encompassing from asymptomatic infection, mild upper respiratory tract illness, to severe pneumonia with acute respiratory failure and even could end up in death.[5–7]

Therefore, although most patients have mild symptoms and a good prognosis, some Covid-19 patients have developed severe pneumonia, pulmonary edema, multiple organ failure or ARDS that concluded in death.[7] The clinical manifestations and severity of Covid-19 could also be similar to other viral pneumonia or respiratory diseases.[1,2]

In this study, we aimed to describe and compare the characteristics between Covid-19 suspected patients and Covid-19 confirmed patients in St. Carolus Hospital as a private hospital located in Central Jakarta.

METHOD

This cross-sectional study was conducted in Carolus Hospital from March to April 2020. Data were collected from the electronic health record reporting database. Data collected included patient's demographic information, comorbidities, triage vital signs, presenting symptoms, history of contact with Covid-19 confirmed case, initial laboratory tests, diagnoses during the hospital course, chest x-ray (CXR) result, and real-time reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 result.

All consecutive patients who enrolled or were hospitalized in the Carolus hospital who were suspected as Covid-19 patients underwent RT-PCR testing, and had the available RT-PCR result data were included. A suspected case of Covid-19 was defined as someone who had a fever of >38^{o} C with respiratory symptoms such as cough, dyspnea, sore throat, or runny nose. The confirmed case of Covid-19 was defined as a suspected case that had a positive RT-PCR result. The suspected Covid-19 patients who had negative RT-PCR results were labeled as COVID-19 suspected patients in this study. There were a total of 58 patients included in this study.

Data were cleaned, entered, stored, and managed with an excel database and IBM SPSS Version 25. Categorical data were described as a count and percentage that were tested using Fisher's exact test. Scaled variables with normal and abnormal distribution were expressed as mean (±SD) and median (interquartile range [IQR]) values, respectively, then were tested using an unpaired t-test and the Mann-Whitney test, respectively.

RESULT

A total of 58 Covid-19 patients were included in this study, divided into 43 Covid-19 confirmed patients and 15 suspected patients. About 26.7% of Covid-19 suspected patients were males (n=4) and 11 females (77.3%). For COVID-19 confirmed patients, 55.8% were males (n=24) and were 19 females (44.2%). The age of suspected patients ranged between 32 to 55 years with a mean were 44.3±6.7 years. Confirmed cases ranged between 30 to 71 years with a mean were 52.4±6.6 years.

Table 1. Patients, clinical and laboratory characteristic of suspected and confirmed Covid-19 cases.

Characteristics	Total (n=58)	Covid-19 Confirmed Patients (n=43)	Covid-19 Suspected Patients (n=15)	*P*
Age (SD)	44.1 (2.8)	49.6 (17.9)	55.6 (18.0)	0.27
Sex				
Male	28 (48.3%)	24 (55.8%)	4 (26.7%)	0.05
Female	30 (51.7%)	19 (44.2%)	11 (73.3%)	
Comorbidities				
Hypertension	10/63 (15.9%)	6/46 (13.0%)	4/17 (23.5%)	--
Diabetes Mellitus	10/63 (15.9%)	7/46 (15.2%)	3/17(17.6%)	--
COPD	2/63 (3.2%)	2/46(4.3%)	0 (0.0%)	--
Tuberculosis	1/63 (1.6%)	1/46 (2.2%)	0 (0.0%)	--
Thrombocytopenia	2/63 (3.2%)	2/46 (4.3%)	0 (0.0%)	--
Chronic Heart Disease	2/63 (3.2%)	1/46 (2.2%)	1/17 (5.9%)	--
Others	1/63 (1.6%)	1/46 (2.2%)	0 (0.0%)	--
None	32/63 (50.8%)	25/46 (54.3%)	7/17 (41.2%)	--
Presenting Symptoms				
Fever	39/45 (86.7%)	31/35 (88.6%)	8/10 (80.0%)	0.61
Cough	34/44 (77.3%)	27/34 (79.4%)	7/10 (70.0%)	0.67
Runny nose	10/44 (22.7%)	9/34 (26.5%)	1/10 (10.0%)	0.41
Sore throat	14/41 (34.1%)	11/31 (35.5%)	3/10 (30.0%)	1.00
Dyspnea	23/45 (51.1%)	18.35 (51.4%)	5/10 (50.0%)	1.00
Headache	7/41 (17.1%)	5/31 (16.1%)	2/10 (20.0%)	1.00
Nausea	15/41 (36.6%)	9/31 (29.0%)	6/10 (60.0%)	0.13
Diarrhea	4/41 (9.8%)	3/31 (9.7%)	1/10 (10.0%)	1.00
Exposure history	13/43 (30.2%)	11/33 (33.3%)	2/10 (20.0%)	0.69
Physical Examination				
Respiratory rate >24 breaths per minute	4/33 (12.1%)	4/23 (17.4%)	0 (0.0%)	0.29
Bilateral/unilateral lung rhonchi	11/24 (45.8%)	9/19 (47.4%)	2/5 (40.0%)	1.00
Epigastric pain	3/24 (12.5%)	3/19 (15.8%)	0 (0.0%)	1.00
Laboratory Findings				
Hemoglobin, g/dL	14.1(8.6–1.07)	14.0 (11.9–18.1)	14.9 (14.2–14.9)	0.84
Hemoglobin <13,7 g/dL (male) or <11,9 g/dL (female)	8/31 (25.8%)	5/23 (21.7%)	3/8 (37.5%)	0.39
Hematocrit	40.3 (0.8) 95% CI: 38.64–41.94	40.9 (17.9) 95% CI: -2.1–5.28	39.3 (4.7) 95% CI: -2.1–5.28	0.38
Total white blood cell	6298.6 (448.2) 95% CI: 5393.3–7203.9	7641.8 (7096.8) 95% CI: -4668.9–5381.3	7285.6 (3548.8) 95% CI: -4668.9–5381.3	0.87
<4.000	5/37 (13.5%)	3/28 (10.7%)	2/9 (22.2%)	--
4.000 - 10.000	26/37 (70.3%)	21/28 (75%)	5/9 (55.6%)	--
>10.000	6/37 (16.2%)	4/28 (14.3%)	2/9 (22.2%)	--
Basophil	0.3 (0.027) 95% CI: 0.204-0.315	0.3 (0.16) 95% CI: -2.47–0.06	0.4 (0.23) 95% CI: -2.47–0.06	0.22
Eosinophil	0.4 (0–9.0)	1.5 (0–3)	0.0 (0.0–1.9)	0.64
Neutrophil	70.6 (1.8) 95% CI: 66.96-74.28	69.8 (11.1) 95% CI: -9.89–8.36	70.5 (10.1) 95% CI: -9.89–8.36	0.87
40-60%	8/31 (25.8%)	7/23 (30.4%)	1/8 (12.5%)	0,64
>60%	24/31 (74.2%)	16/23 (69.6%)	7/8 (87.5%)	
Lymphocyte	20.3 (1.5) 95% CI: 17.30–23.20	21.5 (8.6) 95% CI: -5.09–8.55	19.7 (9.2) 95% CI: -5.09–8.55	0.61
< 20%	17/36 (47.2%)	12/27 (44.4%)	5/9 (55.6%)	0.70
20-40%	19/36 (52.8%)	15/27 (55.6%)	4/9 (44.4%)	
Monocyte	7.6 (0.45) 95% CI: 6.73–8.54	6.5 (2.7) 95% CI: -4610–3832	8.16 (2.5) 95% CI: -4610–3832	0.12
ESR	42 (3–115)	68.5 (9–115)	31.0 (6–31)	0.52
CRP	59 (2–314)	59.0 (2–135)	11.0 (11–314)	0.91
AST	76.3 (18.4) 95% CI: 35.87–118.8	64.5 (21.1) 95% CI: 10.36–118.64	136.3 (50.6) 95% CI: -81.37–354.04	0.63
ALT	72.4 (1.2) 95% CI: 32.46-112.37	53.3 (14.3) 95% CI: 16.64-90.36	154.33 (39.2) 95% CI: -14.27-322.93	0.66
Ureum	18.5 (10–38)	23,5 (15–38)	10.0 (10–16)	0.01
Creatinine	0.8 (0.6–1.2)	1.05 (0.6–1.2)	0.60 (0.6–0.9)	0.07
Imaging features				
Pulmonary infiltration	29/44 (65.9%)	21/32 (65.6%)	8/12 (66.7%)	--
Pericardial infiltrate	1/44 (2.3%)	1/32 (3.1%)	0 (0.0%)	--
Pleural effusion	2/44 (4.5%)	1/32 (3.1%)	1/12 (8.3%)	--
Aorta elongation	2/44 (4.5%)	2/32 (6.3%)	0 (0.0%)	--
Cardiomegaly	3/44 (6.8%)	2/32 (6.3%)	1/12 (8.3%)	--
Normal	7/44 (15.9%)	5/32 (15.6%)	1/12 (8.3%)	--

Note: ALT=Alanin Transminase; AST=Aspartate Transminase; CRP=C-Reactive Protein; ESR=Erythrocyte Sedimentation Rate

No significant differences were found between confirmed and suspected cases regarding demographic characteristics.

Comorbidities were present in nearly half of the total patients, with hypertension and diabetes mellitus being the most common. In confirmed patients, more than half (54.3%) of the patients had comorbidities, with diabetes mellitus being the most common; this number was not distant from suspected patients with 41.2% of them having comorbidities and hypertension being the most common followed by diabetes mellitus. The most common presenting symptom was fever, both in confirmed and suspected patients, followed by cough and dyspnea. Amongst Covid-19 confirmed patients, only 33.3% had a history of exposure to Covid-19 confirmed patients.

From physical examination upon entering the hospital, 17.4% of confirmed patients had a respiratory rate (RR) of more than 24 breaths per minute, whereas none of the suspected patients had a respiratory rate of more than 24 breaths per minute. About 47.4% of confirmed patients and 40.0% of suspected patients had bilateral/unilateral lung rhonchi. The Covid-19 confirmed patients also have epigastric pain (15.8%). There were no significant statistical differences between confirmed and suspected cases in terms of physical examination results.

Laboratory findings show that lymphopenia occurred in 44.4% of confirmed patients. Around 10.7% of confirmed patients had white blood cell (WBC) count <4.000, while 22.2% of suspected patients had WBC count <4.000. Neutrophilia was found in 69.6% of confirmed patients and 87.5% of suspected patients. Anemia was observed in 21.7% of confirmed patients and 37.5% of suspected patients. There were no significant statistical differences between confirmed and suspected cases regarding laboratory findings.

Bilateral/unilateral pulmonary infiltrations were the most usual radiological feature in both confirmed patients (65.6%) and suspected patients (66.7%). Pleural effusion was only seen in 1 out of 32 confirmed patients (3.1%). Normal imaging result was observed in 15.6% of confirmed patients.

DISCUSSION

We analyzed demographical characteristics, comorbidities, presenting symptoms, laboratory findings, and imaging features of Covid-19 confirmed and suspected patients. The mean age of confirmed patients was 49.6 years. Male was more prevalent in confirmed patients, composing 55.8% of them. This finding was consistent with previous studies which showed that Covid-19 confirmed patients were more often male.[4–8] The cause of this phenomenon was still unknown, yet a possible explanation for this might have something to do with the protection provided by the X-chromosome and sex hormones, which play an important role in innate and adaptive immunity.[6] Within the confirmed patients, 45.7% had comorbidities with hypertension and diabetes mellitus being the most common. This was similar to the finding from previous studies that reported those with pre-existing hypertension and/or diabetes were highly prevalent in Covid-19 confirmed patients.[9]

At the beginning of the outbreak, the diagnosis of Covid-19 was challenging because of the very diverse symptoms and imaging findings and in the severity of the disease at the time of presentation. In this study, we pointed out that 88.6% of Covid-19 confirmed patients had a fever. Nevertheless, this number was similar to the 80.0% of the suspected patients who also had a fever. The second most usual symptom of confirmed patients was cough. Approximately 79.4% of confirmed patients had a cough, which was also found in 70.0% of suspected patients. This finding was in line with previous studies that discovered similar symptoms characteristics between Covid-19 and the other SARS-CoV.[4–7,10] Gastrointestinal symptom was not often found in Covid-19 confirmed patients.

The proportion of patients with lymphopenia was commonly observed in Covid-19 confirmed patients (44.4%). This result was similar to previous studies which reported lower total WBC in confirmed cases, even in patients with severe symptoms.[2] It was suggested that SARS-CoV 2 might mainly act

on lymphocytes, especially T lymphocytes, as does SARS-CoV. Particles of the virus would infect through the respiratory mucosa then could infect other cells, induce cytokine storm, generate a series of immune responses, and cause changes in peripheral WBC and immune cells. Some patients could rapidly progress into ARDS and septic shock, which eventually resulted in multiple organ failures. Damage to the T lymphocytes could be an important factor leading to exacerbations of patients. Neutrophilia that was found in this study was also consistent with results from previous studies.[7]

Pulmonary infiltrate was the most common imaging feature found in Covid-19 confirmed patients, even though it was not analyzed between unilateral and bilateral pulmonary infiltrates. In a study by Chen et al, it was reported that 74 patients (75.0%) had bilateral pneumonia, with just 25 (25.0%) having unilateral pneumonia.[2] Consolidation and ground-glass opacity appearance were not found in the confirmed patients in this study, unlike that reported by other studies.[2] Pleural effusion was not a major imaging feature in confirmed patients with only 1 of 32 patients having it, which was compatible with findings in previous studies that did not find pleural effusions in Covid-19 confirmed patients.[7]

This study had several limitations that should be mentioned. The number of subjects included in this study was relatively small, with a total of 58 subjects consisting of 43 were Covid-19 confirmed patients and 15 were Covid-19 suspected patients. Of all subjects, not all data were available in the medical records during the time of analysis. The cause of non Covid-19 pneumonia infection was still unclear because Covid-19 infection was ruled out by a negative RT-PCR result. However, the data in this study could allow an early assessment of the epidemiological and clinical characteristics of Covid-19 in Indonesia. Further studies with a larger number of subjects and more comprehensive data are needed to investigate more clinical characteristics of the disease.

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CONCLUSION

No significant differences were found between confirmed and suspected cases regarding demographic characteristics, comorbidities, presenting symptoms, physical examination results, laboratory tests, and CXR results. Covid-19 confirmed patients had a history of exposure to Covid-19 confirmed patient.

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Risk Factors Affecting Respiratory Symptoms and Impaired Lung Function of Palm Oil Mill Workers in the District of Kandis

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Abstract

Background: *Air pollution that exposed to human have been a problem all over the world and caused a variety of lung disease. Gases and particles emitted from industry including sulfur oxide, nitrogen oxide, and particulate matter may lead to decreasing lung function. Sulfur dioxide is one of the highest causes of air pollution at the highest level. Workers exposure to gases were vulnerable to respiratory function abnormality.*

Methods: *A study on the effect of risk factors and sulfur dioxide exposure on lung function of palm oil workers in the district of Kandis was carried out in December 2019–January 2020. The research aim at describing sulfur dioxide air ambient in palm oil mill as well as respiratory state of palm oil workers and analyzing sulfur dioxide exposure and lung function relationship.*

Result: *The result showed that sulfur dioxide concentration in outdoor 25.7 µg/Nm^3 and indoor 20.6 µg/Nm^3. The result of spirometry showed obstruction in 13% of the workers. Breathlessness and productive cough are the most common symptoms. Several factors correlated with lung function namely as personal protective equipment (P=0.001), length of working (P=0.003), and smoking habit (P=0.004). From multivariate analysis, personal protective equipment has a significant correlation with lung function (P=0.038).*

Conclusion: *Increasing the concentration of sulfur dioxide may cause the decrease of lung function but other factors like personal protective equipment showed correlation is directly proportional with lung function.* ***(J Respirol Indones 2021; 41(3): 180–6)***

Keywords: *lung function, pollution, sulfur dioxide*

Faktor Risiko yang Mempengaruhi Keluhan Respirasi dan Gangguan Fungsi Paru Pekerja Pabrik Kelapa Sawit PT. X di Kecamatan Kandis

Abstrak

Latar Belakang: *Polusi udara yang terpajan pada manusia merupakan masalah di seluruh dunia dan menyebabkan berbagai penyakit paru. Gas dan partikel yang dihasilkan industri seperti sulfur dioksida, nitrogen dioksida dan* particulate matter *dapat menyebabkan penurunan fungsi paru. Sulfur dioksida merupakan salah satu penyebab polusi udara tingkat tertinggi. Pajanan gas toksik pada pekerja rentan menimbulkan kelainan fungsi paru.*

Metode: *Studi tentang pengaruh faktor risiko dan pajanan sulfur dioksida terhadap fungsi paru pekerja pabrik kelapa sawit di kecamatan Kandis telah dilakukan pada bulan Desember 2019–Januari 2020. Studi ini bertujuan mengetahui gambaran udara ambien sulfur dioksida di pabrik kelapa sawit serta fungsi paru pekerja pabrik dan menganalisis pajanan sulfur dioksida terhadap fungsi paru.*

Hasil: *Hasil penelitian menunjukkan bahwa konsentrasi sulfur dioksida pada outdoor 25,7 µg/Nm^3 dan indoor 20,6 µg/Nm^3. Pekerja pabrik yang mengalami gangguan fungsi paru sebanyak 13% (obstruksi) dari hasil pemeriksaan spirometri. Keluhan pernapasan yang paling banyak adalah sesak napas dan batuk berdahak. Terdapat hubungan bermakna antara fungsi paru dengan penggunaan alat pelindung diri (APD) (P=0,001), lama kerja (P=0,003) dan kebiasaan merokok (P=0,004). Dari ketiga variabel tersebut dilakukan analisis multivariat dengan hasil penggunaan APD memiliki hubungan signifikan dengan fungsi paru (P=0,038).*

Kesimpulan: *Peningkatan konsentrasi sulfur dioksida dapat menyebabkan penurunan fungsi paru tetapi faktor lain seperti penggunaan APD menunjukkan korelasi berbanding lurus terhadap fungsi paru.* ***(J Respirol Indones 2021; 41(3): 180–6)***

Kata kunci: *fungsi paru, polusi, sulfur dioksida*

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INTRODUCTION

Sources of air pollution can be divided into indoor air pollution and outdoor pollution. Air pollution in urban areas is a serious problem. Increased use of motor vehicles and energy consumption, if not controlled, will exacerbate air pollution. Based on the World Health Organization (WHO) data, air pollution in Indonesia has experienced an alarming level compared to WHO standards. The cause of air pollution 80% comes from the transportation sector and 20% from industry and domestic waste. Increased air pollution in urban areas will increase the risk of lung cancer, respiratory system infections, chronic obstructive pulmonary disease (COPD), and trigger asthma attacks.[1,2]

Based on WHO data in 2018, the current high level of air pollution in the world is an environmental issue that is disturbing to the wider community, causing a high incidence of several diseases caused by air pollution, namely diseases related to the respiratory system. Various pollutants, especially from industrial fuels and motor vehicles, such as nitrogen oxides (NO), sulfur oxides (SO), ozone (O_3), and particulate matter (PM), are risk factors for acute respiratory infections (ARI), lung cancer, COPD and asthma triggers.[3] Sulfur dioxide (SO_2) is one of the causes of air pollution at the highest level. Sulfur dioxide causes respiratory problems, especially in children and the elderly, and triggers pre-existing heart and lung diseases. Injury to the larynx, trachea, bronchi, and alveoli occurs in significant exposures above 50 parts per million (ppm).[1]

The result of a survey by the Directorate General of Infectious Disease Eradication and Environmental Health, Ministry of Health Indonesia in 2015 showed ARI and lung infections, especially tuberculosis and pneumonia, are contribute to morbidity (35%).[4] In 2017, respiratory diseases such as tuberculosis, pneumonia, and ARI are 10 infectious diseases in Siak Regency. In addition, asthma and COPD rank second and fifth out of 10 non-communicable diseases in Siak Regency.[5] The purpose of this study was to obtain an overview of respiratory symptoms and lung function of palm oil mill workers and ambient SO_2 concentrations at PT. X Kandis district.

METHODS

This research is a descriptive-analytic study using a cross-sectional research design. The research has been conducted at the palm oil mill of PT. X Kandis sub-district, Siak district in December 2019–January 2020. The materials and tools in this study were the European Community Respiratory Health Survey (ECRHS) questionnaire, spirometer, spectrophotometer, disposable mouthpiece, weight scale, height meter, stationery, and digital camera.

The research inclusion criteria were the workers of the palm oil mill of PT. X in the Kandis sub-district with a minimum working period of 2 years. The exclusion criteria were the workers of the PT. X in the Kandis sub-district has Post Tuberculosis Obstruction Syndrome, which is concluded from data history and chest x-rays in the last 6 months.

The types of data used were quantitative and qualitative. The data used in this study came from primary data through filling out a modified ECRHS questionnaire and measuring the value of the VEP_1 and KVP ratio using a spirometer for factory workers at the specified location. Furthermore, measurements of SO_2 concentration were carried out using a spectrophotometer at the location of the factory workers doing activities (outdoor) and the palm oil mill office space (indoor). Determination of the location of the measurement of SO_2 concentration was carried out by purposive sampling, namely by considering the characteristics of the area's activities, namely in the palm oil mill area (outdoor) and the palm oil mill office space (indoor).

The population in this study were workers at the palm oil mill of PT. X Kandis sub-district in 2019 as many as 104 people. The sample in this study were factory workers who met the inclusion criteria and did not have the exclusion criteria from the

population. Based on the calculation of the Slovin formula, the minimum sample size to be studied is 48 people. A multivariate test will be carried out in this study, and there are 6 variables for which statistical analysis will be carried out. Each variable has a minimum of 10 samples so that the total sample in this study is at least 60 people. In this study, the sampling technique used a stratified random sampling technique. Sampling was divided into two groups according to the activities of the factory workers, namely, the factory area (outdoor) and the office space (indoor) of the PT. X Kandis sub-district using the proportional allocation formula.

RESULT

This research was conducted from December 2019–January 2020. The palm oil mill of PT. X was established in 2002 and is one of the largest factories in the Kandis sub-district, Siak district. There were 69 eligible subjects, 47 outdoor workers and 22 indoor workers. The dependent variable in this study was lung function. In contrast, the independent variables assessed in this study included SO_2 concentration, age, gender, length of work, smoking history, use of Personal Protective Equipment (PPE), respiratory symptoms, and history of respiratory disease. Subjects filled out the modified ECRHS questionnaire in a guided manner and a spirometry examination was performed. The measurement of SO_2 concentration using the spectrophotometer method was carried out in two places, namely the factory area (outdoor) and the office room (indoor).

The characteristics of subjects in this study are mostly under 40 years old (88.4%), male predominantly (97.1%). Most of the study subjects work less than 5 years (53.6%). Smoking history measured with Brinkman's Index (BI), most subjects are moderate-heavy smokers with BI more than 200 (31.9%). There are only a few subjects who did not wear PPE in this study (36.2%) and most of the subjects work in the outdoor area (68.1%). Based on the history of respiratory disease, 14 people (20.3%) had a history of respiratory illness. From the lung function test, it was found that 13% had an obstruction. The characteristics of research respondents are described in Table 1.

Table 1. Characteristics of Palm Oil Mill Workers PT. X

Variable	n	%
Age		
>40 years	8	11,6
<40 years	61	88,4
Gender		
Male	67	97,1
Female	2	2,9
Length of Working		
≥5 years	32	46,4
<5 years	37	53,6
Smoking History		
BI ≥200	22	31,9
BI <200	47	68,1
Use of PPE		
No	25	36,2
Yes	44	63,8
Job Location		
Factory area (outdoor)	47	68,1
Office space (indoor)	22	31,9
History of Respiratory Disease		
Exist	14	20,3
None	55	79,7
Lung Function		
Obstruction	9	13
No Obstruction	60	87

This study showed, 76.6% of outdoor subjects experienced respiratory symptoms. Most indoor subjects (54.6%) had no respiratory complaints. From the results of the lung function test using spirometry, it was found that 17% of outdoor workers and 4.5% of indoor workers had obstructive diseases ($FEV_1/FVC<75\%$). An overview of respiratory symptoms and lung function is presented in Table 2.

Table 2. Description of Respiratory Complaints and Lung Function of Factory Workers

Variable	Respondent *Outdoor* (n=47)	Respondent *Indoor* (n=22)
Respiratory		
Complaints	36 (76,6%)	10 (45,4%)
Exist	11 (23,4%)	12 (54,6%)
None		
Lung Function		
Obstruction	8 (17.0%)	1 (4,5%)
No Obstruction	39 (83.0%)	21 (95,5%)

Based on the results of research conducted by filling out guided questionnaires using modified ECRHS, it was found that the distribution of the characteristics of clinical respiratory complaints in both respondents. Shortness of breath complained most by outdoor respondents (70.2%). Some of the outdoor respondents experienced cough (17%) and productive cough (17%) but no wheezing symptoms found, while in indoor workers, as many as 2 people (9,1%).

Table 3. Factory Worker Respiration Complaint

Symptoms	*Outdoor* Respondent (n=47) (%)	*Indoor* Respondent (n=22) (%)
Cough	8 (17.0%)	2 (9.1%)
Phlegm Cough	8 (17.0%)	6 (27.3%)
Shortness of Breath	33 (70.2%)	6 (27.3%)
Wheezing	0 (0.0%)	2 (9.1%)

History of phlegm cough attacks experienced by as many as 8 people (17%) in outdoor workers and as many as 6 people (27.3%) in indoor workers. However, only a small proportion had wheezing (9.1%) in indoor workers. An overview of the characteristics of respiratory symptoms is presented in Table 3.

Measurements and observations were carried out at the palm oil mill of PT. X Kandis district. SO_2 concentration was carried out within 24 hours in the factory area (outdoor) and office space (indoor) using a spectrophotometer. Based on the Belfast Metropolitan Urban Area (BMUA) standard, SO_2 concentration in 24 hours should not exceed 365 µg/Nm^3. The SO_2 concentration in the outdoor of the factory area is 25.7 µg/Nm^3. Furthermore, in the indoor setting, the SO_2 concentration is 20.6 µg/Nm^3.

Furthermore, bivariate analysis was carried out using the chi-square statistical test. Bivariate analysis statistically gave a significant value. Based on the results of statistical analysis of respondents who experienced obstruction disorders, 17% were outdoor respondents, and 4.5% were indoor respondents. Statistical tests showed, that there was no significant relationship between SO_2 concentration and lung function (*P*=0.254). The relationship between SO_2 concentration and lung function is presented in Table 4.

Table 4. The Relationship between SO_2 Concentration and Lung Function

Variable	Lung Function			
	Obstruction	No obstruction	*P*	OR (95% CI)
SO_2 concentration in the factory area (outdoor) 25,7 µg/Nm^3	8 (17.0%)	39 (83.0%)	0.254	0.23 (0.03–1,98)
SO_2 concentration in the office (indoor) 20,6 µg/Nm^3	1 (4.5%)	21 (95.5%)		

Table 5. Relationship of Age, Length of Work, History of Smoking, Use of PPE and History of Respiratory Diseases with Lung Function of Factory Workers

Variable	Lung Function			
	Obstruction	No obstruction	*P*	OR (95% CI)
Age				
>40 years	2 (25)	6 (75)	0.278	2.6 (0.4–15,3)
<40 years	7 (11.5)	54 (88.5)		
Length of Work				
≥5 years	9 (24.3)	28 (75.7)	0.003	10.3 (0.26–0.46)
<5 years	0 (0)	32 (100)		
Smoking History				
IB Risk (≥200 cigarettes)	7 (31.8)	15 (68.2)	0.004	10.5 (1.9–56.2)
No IB Risk (<200 cigarettes)	2 (4.3)	45 (95.7)		
The Use of PPE				
No	8 (32)	17 (68)	0.001	20.2 (2.3–174.3)
Yes	1 (2.3)	43 (97.7)		
History of Respiratory Diseases				
There is	3 (21.4)	11 (78.6)	0.373	2.3 (0.3–10.3)
There is no	6 (10.9)	49 (89.1)		

In this study, bivariate analysis using chi-square was performed to found the association between age, length of work, smoking habits, PPE, and history of respiratory disease the lung function. There was a significant relationship between the use of PPE (*P*=0.001), length of work (*P*=0.003) and smoking history (*P*=0.004) on lung function, which is presented in Table 5.

DISCUSSION

Based on the study results, 76.6% of outdoor/indoor subjects and 11% of outdoor/indoor subjects and 23.4% had no respiratory symptoms. In indoor respondents, 54.6% had no respiratory symptoms. This research is in line with Takeshi et al in 2017, a study conducted on 168 subjects who had a history of living in a mountain area and were exposed to volcanic eruptions. The study showed increased respiratory symptoms caused by higher risk exposure to toxic gasses.[6]

This study showed outdoor respondents showed more symptoms compared to the indoor respondents such as shortness of breath complaints of shortness of breath (70,2%), the cough was found to be higher in outdoor workers. History of coughing up phlegm was experienced by as many as 8 people (17%) in outdoor workers and as many as 6 people (27.3%) in indoor workers. Only a small portion of indoor respondents experienced wheezing (9,1%). This is similar to Wu et al that shortness of breath and coughing up phlegm were the most common symptoms, and there was a significant relationship between shortness of breath and an increase in SO_2 concentration 45.7 g/Nm^3 with an odds ratio (OR) value are 4.1 (95% CI=1.2–19.9).[7] Murgia et al in 2011 showed that factory workers had a high risk of experiencing complaints and limitations in the respiratory system with a hazard ratio (HR) value (HR=5.3; 95% CI=2.7–10.5).[8]

In this study, lung function test shows that 17% of outdoor workers had obstructive disorders (FEV_1/FVC<75%) and 1 person (4.5%) indoor workers had obstructive disorders (FEV_1/FVC<75%). Similar to Rantetampang et al, the population of the Kurulu area is at risk of exposure to toxic gases that can cause a decrease in lung function. It was found that significantly 92.3% of subjects experienced a decrease of FVC.[9]

From this study, SO_2 measurements in the factory area (outdoor) is 25.7 µg/Nm^3 within 24 hours. Meanwhile, in the office room (indoor), the SO_2 concentration is 20.6 µg/Nm^3. That was below the BMUA standard value. Based on the regulation of the State Minister of the Environment in 2010, the threshold value of SO_2 concentration for 24 hours of observation should not be more than 365 µg/Nm^3.[10]

From this study, there is no significant correlation between SO_2 concentration and lung function impairment (*P*=0.254). It may be due to the SO_2 concentration value was below the standard BMUA value. The concentration should not exceed 365 µg/Nm^3 in 24-hour observation.[10]

Based on research by Wu et al in 2016, an increase in SO_2 concentration with a value of 45.7 µg/Nm^3 caused the effect of clinical respiratory symptoms for example shortness of breath (OR=4.1; 95% CI=1.2–19.9).[7] Rantetampang et al found a significant relationship with decreased lung function with SO_2 exposure above 25 µg/Nm^3; from the results of the study, it was found that 92.3% experienced a decrease in FVC (*P*=0.0001).[9] Study by Wijiarti et al from 60 subjects of street vendors at the Pulogadung bus terminal showed 31.67% had a risk of health problems, especially the respiratory system with SO_2 exposure of 133.78 µg/Nm^3 within Respiratory Quotient (RQ) = 1.0470.[11] Gao et al in 2018 found that acute SO_2 exposure can reduce vital lung capacity, especially in COPD patients.[12] Andersson found that exposure to toxic irritant gases increased the incidence of chronic bronchitis in factory workers (HR=32; 95% CI=2.0–5.2).[13] Until now, there has been no study that explains the exact value of SO_2 concentration that can reduce lung function.

From the statistical test results, it was found that there was a significant relationship between the use of PPE (*P*=0.001), length of work (*P*=0.003), and smoking history (*P*=0.004) on lung function and multivariate analysis was performed. It was found

that the use of PPE had a significant relationship with lung function (*P*=0.038). In line with Awang et al that wearing PPE masks can affect the incidence of pulmonary function disorders. All workers must use respiratory personal protective equipment in industries that produce dust in the production process (OR=12.15; 95% CI=1.14–102.62).[14] Sholikhah et al in 2015 found that the use of PPE affected lung function, and PPE must be used in all industrial workers.[15]

This research is cross-sectional, so it cannot clearly describe the causal relationship. Therefore, it is necessary to conduct a cohort study to obtain a more relevant analysis. In addition, this study used a questionnaire to ask several things such as respiratory symptoms and a history of respiratory disease, which was assessed only subjectively so that there were no clear parameters to measure prior lung function. The data obtained that SO_2 concentration does not have a significant relationship with lung function causes a bias in this study because the factors that affect lung function may be due to exposure to other toxic gases such as CO, NO, O_3 and PM. In this study, there are also limitations because a bronchodilator test was not performed to rule out COPD diagnosis. Nevertheless, this research can be used as primary data for further research in evaluating irritant toxic gas exposure.

CONCLUSION

This study concluded that the most respiratory symptoms were in the palm oil mill workers of PT. X Kandis sub-district, namely shortness of breath and productive cough in the factory area (outdoor) and office space (indoor). There were 13% with impaired lung function (obstruction). The SO_2 concentration in the factory area (outdoor) is 25.7 µg/Nm^3 and in the office room (indoor) is 20.6 µg/Nm^3.

The most influential risk factors on the lung function of workers at the palm oil mill PT. X Kandis sub-district, namely the use of PPE, length of work and smoking history. Multivariate analysis showed a significant relationship between lung function and PPE use.

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Correlation Between Leukocyte Differential Counts with The Severity and Outcome of Coronavirus Disease 2019 (Covid-19) Patients in Jember

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Abstract

Background: *Coronavirus Disease 2019 (Covid-19) is an acute respiratory disease caused by a new strain of RNA viruses named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Hematological changes, especially leukocyte differential counts, are presumed to be a predictor of the severity and outcome of Covid-19 patients. This study aimed to analyze the correlation between leukocyte differential counts with the severity and outcome of Covid-19 patients.*

Methods: *This study was conducted using a cross-sectional analytic observational method, through secondary data analysis of Covid-19 patients who were tested positive by Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and hospitalized between April–November 2020 at Citra Husada Jember, Kaliwates Jember, and Jember Klinik Hospital.*

Results: *From 267 patients, there were 139 female patients (52.1%) and 128 male patients (47.9%). There was a positive correlation on leukocytes, neutrophils, and neutrophil-lymphocyte ratio (NLR) with the severity and outcome of the patients and a negative correlation on eosinophils, lymphocytes, and monocytes (P<0.001). Basophil had a positive correlation with patient severity (P<0.05), but no significant correlation with patient outcome (P>0.05)*

Conclusion: *Leukocyte differential counts examination could be a predictor of the severity and outcome of Covid-19 patients, especially neutrophils, lymphocytes, and NLR.* ***(J Respirol Indones 2021; 41(3): 187–95)***

Keywords: *Covid-19, leukocyte differential counts, outcome, severity.*

Hubungan Gambaran Hitung Jenis Leukosit dengan Tingkat Keparahan dan Luaran Pasien *Coronavirus Disease 2019* (Covid-19) di Jember

Abstrak

Latar Belakang: *Coronavirus Disease 2019 (Covid-19) merupakan penyakit pernapasan akut akibat virus RNA* strain *baru yaitu* Severe *Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Perubahan hematologi, khususnya hitung jenis leukosit, diduga dapat menjadi prediktor tingkat keparahan serta luaran pasien Covid-19. Tujuan penelitian ini adalah untuk menganalisis hubungan gambaran hitung jenis leukosit dengan tingkat keparahan dan luaran pasien terkonfirmasi Covid-19.*

Metode: *Penelitian menggunakan metode observasional analitik potong lintang melalui analisis data sekunder pada pasien terkonfirmasi Covid-19 yang dibuktikan dengan pemeriksaan Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) dan dirawat inap antara bulan April–November 2020 di Rumah Sakit Citra Husada Jember, Kaliwates Jember, dan Jember Klinik.*

Hasil: *Dari 267 pasien, didapatkan 139 pasien perempuan (52.1%) dan 128 pasien laki-laki (47,9%). Terdapat korelasi positif pada jumlah leukosit, kadar neutrofil, dan rasio neutrofil-limfosit (NLR) dengan tingkat keparahan dan luaran pasien, serta korelasi negatif pada kadar eosinofil, limfosit, dan monosit (P<0,001). Kadar basofil memiliki korelasi positif dengan tingkat keparahan pasien (P<0,05), namun tidak memiliki korelasi yang bermakna terhadap luaran pasien (P>0,05)*

Kesimpulan: *Pemeriksaan hitung jenis leukosit dapat menjadi prediktor tingkat keparahan dan luaran pasien Covid-19, khususnya neutrofil, limfosit, dan NLR.* ***(J Respirol Indones 2021; 41(3): 187–95)***

Kata Kunci: *Covid-19, hitung jenis leukosit, luaran, tingkat keparahan.*

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INTRODUCTION

Coronavirus Disease 2019 (Covid-19) is an acute respiratory disease caused by a single-stranded RNA virus that has a sheath, namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to the genus *Betacoronavirus* and subgenus *Sarbecovirus,* which was first discovered in early January 2020 as the time when there was an outbreak of pneumonia in Wuhan, China, at the end of December 2019.[1]

The spread of SARS-CoV-2 is very massive compared to other coronaviruses, namely Middle-East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). SARS-CoV first appeared in 2002 in Guangdong, China, with more than 8,000 confirmed cases, while MERS-CoV first appeared in 2012 in Saudi Arabia with 2,494 positive cases.[2] Based on global data on June 23rd, 2020, the number of confirmed Covid-19 cases reached 8,974,795 patients.[3] Meanwhile, in Indonesia, cases of confirmed COVID-19 reached 47,896 patients,[4] including in Jember Regency of 104 patients.[5]

The 5th revision of Covid-19 Control and Prevention Guidelines from the Ministry of Health Republic of Indonesia divides the criteria for the severity of Covid-19 patients into five groups, namely asymptomatic, mild, moderate, severe, and critical. In the mild group, patients have general non-specific symptoms, such as cough, fever, sore throat. The moderate group have signs of mild pneumonia. The severe ones have RR >30x/minute and/or SpO_2<90% while the critical patients have symptoms that develop into Acute Respiratory Distress Syndrome (ARDS). On the final evaluation of the patient's clinical status, the patient is declared cured if once confirmed, have met the criteria for completion of isolation, added with a statement letter of monitoring completion based on an assessment by the doctor at the health service facility.[6]

Transmission of SARS-CoV-2 from human to human can be through direct or indirect contact in the form of droplets from an infected person which enters the respiratory tract.[7] SARS-CoV-2 will infect host cells through the spike protein binding with Angiotensin-Converting Enzyme receptors-*2* (ACE-2).[8]

The body will produce an immune response via proinflammatory cytokines and chemokines, namely IL-1β, IL-6, IL-8, IL-12, and TNF-α, as well as late production of IFN-1 through macrophages. Uncontrolled production of proinflammatory cytokines due to persistent and worsening infections will cause cytokine storm which leads to worsening of the severity and outcome of Covid-19 patients.[9]

The gold-standard examination for SARS-CoV-2 infection is the nucleic acid test through real-time reverse transcription-polymerase chain reaction (RT-PCR).[3] In addition to the RT-PCR examination, there are supporting tests that are useful to evaluate the characteristics of Covid-19 patients, one of which is the leukocyte count. Leukocytes are divided into two groups, namely granulocytes (neutrophils, basophils and eosinophils) and agranulocytes (monocytes and lymphocytes). Leukocytes are thought to have contributed to the cytokine storm in Covid-19 patients, which resulted in the worsening of the patient's condition in ARDS.[10]

A study of 99 patients with confirmed Covid-19 in Wuhan, China, 24 patients (24%) experienced an increment in the number of leukocytes, neutrophils increased in 38 patients (38%) and lymphocytes decreased in 35 patients (35%).[11] In Covid-19 patients who died, the number of neutrophils continued to escalate and the number of lymphocytes continued to decline until death.[12]

The purpose of this study was to analyze the correlation between the type of leukocyte count and the severity and outcome of Covid-19 confirmed patients. The results of this study were expected to be able to identify Covid-19 patients with a high risk of poor prognosis and death so that appropriate treatment could be carried out.

METHOD

This study used a cross-sectional analytic observational method through secondary data analysis from medical records. The study sample was taken using a total population sampling and acquired 492 patient data. About 267 data met the inclusion criteria, namely patients who were confirmed positive for Covid-19 by RT-PCR and hospitalized between April to November 2020 at Covid-19 referral hospital in Jember Regency (Citra Husada Jember Hospital, Kaliwates Jember Hospital and Jember Clinic Hospital). The study exclusion criteria were patients with unclear outcomes such as being referred to another hospital during hospitalization or discharge on patient's request and incomplete medical records.

Patient severity was classified into mild, moderate, severe, and critical. Patient outcomes were divided into recovered and died. Meanwhile, the leukocyte count were grouped into decreased, normal, and increased categories, adjusted to the normal values of the laboratory for each hospital. The correlation test of categorical data on each type of leukocyte count with the severity and outcome of patients with confirmed Covid-19 was performed using the Spearman test by SPSS version 23.

RESULT

In this study, of the 267 patients with confirmed Covid-19, about 47.9% were male and 52.1% were female. The mean age was 44.44±0.96 years (95% CI=42.6–46.45), with the largest age group being 41–60 years (44.6%), followed by 21–40 years (34.8%), >60 years (15%), and <21 years (5.6%). About 63.7% of patients did not have comorbidities, while the rest 36.3% had at least one comorbid disease. The level of education in most patients was D3/D4/S1/equivalent (43.1%) and high school graduates (37.5%). Most of the patients were office workers (50.2%), unemployed (16.9%), housewives (16.1%), and medical personnel (6.4%). The general characteristics of the study sample can be seen in Table 1.

The correlation between leukocyte count and the severity of Covid-19 patients can be seen in Table 2. There were positive correlation with weak correlation strength in leukocytes (r = 0.283; *P*<0.001), neutrophils (r = 0.360; *P*<0.001) and NLR. (r = 0.374; *P*<0.001), positive correlation with very weak correlation strength for basophils (r = 0.159; *P*<0.05), and negative correlation with weak correlation strength for eosinophils (r = -0.214; *P*<0.001), lymphocytes (r = -0.397; *P*<0.001) and monocytes (r = -0.290; *P*<0.001).

The leukocyte count tended to be normal in all groups of Covid-19 patients, but when compared with severe and critical groups, more patients experienced an increase in leukocytes compared to mild and moderate groups (52.4%; 36.4% vs 5.4%; 11.5%). Neutrophils and NLR in severe and critical groups were also found to have elevated more (81%; 90.9% and 71.4%; 81.8%) while lymphocytes in severe and critical patients were found to have declined more (66.7%; 72.7 %).

Table 1. The general characteristics of patients (n=267) with confirmed Covid-19

Variable	n (%)[a]
Gender	
Male	128 (47.9%)
Female	139 (52.1%)
Age, average (year)[2]	44.44±0.96 (95% CI 42.6-46.45)
Age' Classification	
<21 year	15 (5.6%)
21-40 year	93 (34.8%)
41-60 year	119 (44.6%)
> 60 years	40 (15.0%)
Comorbid classification	
Non-Comorbid	170 (63.7%)
Comorbid	97 (36.3%)
Level of education	
No School	12 (4.5%)
Elementary School	27 (10.1%)
Junior High School	13 (4.9%)
Senior High School	100 (37.5%)
D3/D4/S1/equivalent	115 (43.1%)
Profession	
Not Working	45 (16.9%)
Housewife	43 (16.1%)
Medical Personnel	17 (6.4%)
Military/police	6 (2.2%)
Office worker	134 (50.2%)
Farmer	7 (2.6%)
Etc	15 (5.6%)

Note: [a]n (%) = total and percentage of each characteristic;
[b]Age, average (year) = *mean ± standard error (95% CI)*

Table 2. Correlation of leukocytes count and the severity of patients with confirmed COVID-19

Variable		Severity				Score
		Mild (n=93)	Moderate (n=131)	Severe (n=21)	Critical (n=22)	
Leukocyte	Decreased	4 (4.3%)	2 (1.5%)	1 (4.8%)	1 (4.5%)	r = 0.283 *P*= 0.0001
	Normal	84 (90.3%)	114 (87.0%)	9 (42.9%)	13 (59.1%)	
	Increase	5 (5.4%)	15 (11.5%)	11 (52.4%)	8 (36.4%)	
Neutrophils	Decreased	6 (7.1%)	6 (4.7%)	0 (0.0%)	0 (0.0%)	r = 0.360 *P* = 0.0001
	Normal	55 (64.7%)	62 (48.1%)	4 (19.0%)	2 (9.1%)	
	Increase	24 (28.2%)	61 (47.3%)	17 (81.0%)	20 (90.9%)	
Eosinophils	Decreased	44 (47.3%)	89 (67.9%)	15 (71.4%)	15 (68.2%)	r = -0.214 *P* = 0.0001
	Normal	36 (38.7%)	36 (27.5%)	6 (28.6%)	7 (31.8%)	
	Increase	13 (14.0%)	6 (4.6%)	0 (0.0%)	0 (0.0%)	
Basophils	Decreased	62 (66.7%)	89 (67.9%)	11 (52.4%)	5 (22.7%)	r = 0.159 *P* = 0.009
	Normal	31 (33.3%)	41 (31.3%)	10 (47.6%)	17 (77.3%)	
	Increase	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	
Limfosit	Decreased	13 (14.0%)	37 (28.2%)	14 (66.7%)	16 (72.7%)	r = -0.397 *P* = 0.0001
	Normal	67 (72.0%)	89 (67.9%)	7 (33.3%)	6 (27.3%)	
	Increase	13 (14.0%)	5 (3.8%)	0 (0.0%)	0 (0.0%)	
Monosit	Decreased	11 (11.8%)	30 (22.9%)	6 (28.6%)	16 (72.7%)	r = -0.290 *P* = 0.0001
	Normal	67 (72.0%)	88 (67.2%)	15 (71.4%)	4 (18.2%)	
	Increase	15 (16.1%)	13 (9.9%)	0 (0.0%)	2 (9.1%)	
NLR	Decreased	9 (9.7%)	7 (5.3%)	0 (0.0%)	0 (0.0%)	r = 0.374 *P* = 0.0001
	Normal	67 (72.0%)	80 (61.1%)	6 (28.6%)	4 (18.2%)	
	Increase	17 (18.3%)	44 (33.6%)	15 (71.4%)	18 (81.8%)	

Table 3. Correlation between leukocytes count and the outcome of patients with confirmed COVID-19

Variable		Outcome		Score
		Recovered (n=239)	Died (n=28)	
Leukocyte	Decreased	7 (2.9%)	1 (3.6%)	r = 0.272 *P* = 0.0001
	Normal	206 (86.2%)	14 (50.0%)	
	Increase	26 (10.9%)	13 (46.4%)	
Neutrophils	Decreased	13 (5.4%)	0 (0.0%)	r = 0.237 *P* = 0.0001
	Normal	122 (51.0%)	5 (17.9%)	
	Increase	104 (43.5%)	23 (82.1%)	
Eosinophils	Decreased	141 (59.0%)	22 (78.6%)	r = -0.131 *P* = 0.032
	Normal	79 (33.1%)	6 (21.4%)	
	Increase	19 (7.9%)	0 (0.0%)	
Basophils	Decreased	152 (63.6%)	15 (53.6%)	r = 0.062 *P* = 0.311
	Normal	86 (36.0%)	13 (46.4%)	
	Increase	1 (0.4%)	0 (0.0%)	
Limfosit	Decreased	64 (26.8%)	16 (57.1%)	r = -0.210 *P* = 0.001
	Normal	157 (65.7%)	12 (42.9%)	
	Increase	18 (7.5%)	0 (0.0%)	
Monosit	Decreased	50 (20.9%)	13 (46.4%)	r = -0.146 *P* = 0.017
	Normal	162 (67.8%)	12 (42.9%)	
	Increase	27 (11.3%)	3 (10.7%)	
NLR	Decreased	16 (6.7%)	0 (0.0%)	r = 0.236 *P* = 0.0001
	Normal	148 (61.9%)	9 (32.1%)	
	Increase	75 (31.4%)	19 (67.9%)	

Eosinophils tended to be lower in patients with mild symptoms (47.3%), moderate (67.9%), severe (71.4%), and critical (68.2%). In basophil levels, mild, moderate, and severe patients experienced a reduction (66.7%; 67.9%; 52.4%). However, more critical patients had normal basophil levels (77.3%). Meanwhile, more acute patients experienced a decrease in monocytes levels (72.7%).

The correlation between leukocyte count and the outcome of COVID-19 patients can be seen in Table 3. There were positive correlation with weak correlation strength between leukocytes (r = 0.272; *P*<0.001), neutrophils (r = 0.237; *P*<0.001), and NLR (r = 0.236; *P*<0.001), negative correlation with weak correlation strength in lymphocytes (r = -0.210; *P*<0.05) and negative correlation with very weak correlation strength for eosinophils (r = -0.131; *P*<0.05) and monocytes (r = -0.146; *P*<0.05).

Meanwhile, basophil levels did not have a significant correlation with the outcome of Covid-19 patients (r=0.062; *P*>0.05). Patients who were declared cured and died tended to have normal leukocyte counts (86.2% and 50%). Patients with mortality outcomes were also found to have elevated levels of neutrophils and NLR (82.1%; 67.9%). This contrasted with eosinophils, lymphocytes and monocytes that were found to decline more (78.6%; 57.1%; 46.4%) in patients with mortality outcomes.

DISCUSSION

Among the sample of 267 confirmed patients, Covid-19 were found to be more common in women than men. Nonetheless, they did not differ significantly (52.1% vs 47.9%). The mean age of the patients was 44.44±0.96 years (95% CI=42.6–46.45) with the 41-60 years age group as the most prevalent (44.6%). Most of the patients had at least one comorbid disease, worked as office workers (50.2%) and medical personnel (6.4%).[13]

A similar study conducted by Guan in 2020 showed that the mean age of Covid-19 patients was 47 years (35–58 years), with 41.9% of the total patients being female, 27.3% of patients had comorbid diseases, and 3.5% of patients were medical personnel. Guan explained that patients in the severe group tended to be older with a mean age of 52 years (40–60 years) and had comorbid diseases (38.7% vs 21.0%).[13]

The results of secondary data analysis showed that patients in the severe group had an escalated number of leukocytes compared to the mild and moderate groups (52.4% vs. 5.4% and 11.5%; *P*<0.001). However, this increase was not in line with the critical group, which was only 36.4%. Leukocytes that were increased in severe patients would then decrease to normal in critical patients, presumably due to persistent hyperinflammatory response as a consequence of cytokine storms that triggered an immunoparalysis state which was predisposed to secondary infection and resulted in multiple organ failure. This was characterized by a decline in lymphocytes and the function of monocytes/macrophages so that they were unable to produce IFN-γ, which played a role in cleaning infected cells to prevent sepsis.[14]

The percentage of neutrophil levels in COVID-19 patients was significantly increased in patients in the critical group than in the mild group (28.2% vs 90.9%; *P*<0.001). As with neutrophils, the neutrophil-lymphocyte ratio (NLR) of Covid-19 patients was also significantly increased in critically ill patients (18.3% vs 81.8%; *P*<0.001). This increment occurred in contrast to the eosinophil and lymphocyte levels of COVID-19 patients. Our study found significantly more eosinopenia and lymphopenia in the critical group than in the mild group ([47.3% vs. 68.2%; *P*<0.001]; [14% vs. 72.7%; *P*<0.001]).

This study was identical to a study conducted by Wang in 2020, which stated that leukocytes, neutrophils, and NLR of Covid-19 patients were significantly elevated in the severe group than in the moderate group (*P*<0.05) while lymphocytes and eosinophils declined significantly in the severe group compared to the moderate group (*P*<0.05).[15] Study conducted by Magdalena in 2021 also revealed a similar description. Patients with severe symptoms tended to experience leukocytosis (*P*=0.002; OR=0.636), neutrophilia (*P*<0.001; OR: 17.43) and lymphopenia (*P*<0.001; OR=50.21).[16]

Increased leukocytes and neutrophils are thought to be associated with persistent and worsening infection resulting in bone marrow hyperplasia compensating for the production of more granulocytes.[15] Pro-inflammatory cytokines play a role in stimulating neutrophil activation. When

the body experiences a persistent infection, neutrophils are overproduced and result in a cytokine storm event. At the same time, the decrease in lymphocytes in severe and critical patients is thought to be due to cytokine storm that accounts for lymphocyte apoptosis and atrophy of lymphoid organs, thereby inhibiting lymphocyte cell regeneration.[17]

The neutrophil-lymphocyte ratio (NLR) of Covid-19 patients in a similar study also discovered that severe patients had a higher NLR than the mild group (95% CI=0.72–1.04). In infectious diseases, NLR acts as an indicator of systemic inflammation which helps determine a patient's prognosis and outcome.[18] The decrease in eosinophils in this study was not yet known for certain regarding the role of eosinophils in SARS-CoV-2 infection. In infectious diseases, granular proteins derived from eosinophils exhibit antiviral properties against single-stranded RNA viruses. Cryptogenic eosinophils that occur in Covid-19 patients are thought to be a consequence of eosinophil secretion by the inhibited bone marrow, blockade of eosinophils, and delayed IFN-1 response resulting in eosinophil apoptosis.[19] During a cytokine storm, increased neutrophil levels lead to increased infiltration of neutrophil cells into lung tissue. This is believed to accelerate the production of neutrophils in the bone marrow, thereby suppressing eosinophil production.[20]

The correlation between basophil levels and the severity experienced by Covid-19 patients in this study had a weak correlation strength (r = 0.159). Meanwhile, in a survey conducted by Anurag in 2020, it was explained that basophil levels were not significantly associated with the severity of Covid-19 patients (*P*=0.166).[21] Like eosinophils, the role of basophils in SARS-CoV-2 infection was also not known with certainty and allegedly multifactorial. Basophils are thought to play a role in binding antigens and strengthening the humoral immune response so that the decrease in basophils during the acute phase can affect the effectiveness of IgG response against SARS-CoV-2.[22]

Significant reductions in basophils and eosinophils occurred in the majority of Covid-19 patients in the early stage or acute onset, regardless of the severity.[20] However, the decline in eosinophil and basophil levels was more serious in severe patients. In this study, more severe patients experienced a decrease in eosinophils and basophils than critical patients (71.4% vs 68.2% and 52.4% vs 22.7%); this might be due to some essential patients of this study were already in poor condition by the time of initial hospital admission or had passed the acute onset.

The monocyte levels of Covid-19 patients in this study were significantly negatively correlated in patients from the critical group compared to the mild, moderate, and severe groups (72.7% vs 11.8%; 22.9%; 28.6%; *P*<0.05). However, this phenomenon was not similar to a study from Pence in 2020, which pointed out a significant increase in monocytes that play a role in producing IL-6 in mild patients and continued to increase in severe patients.[23] Study of 32 Covid-19 patients with various severity levels and 18 healthy people as controls showed that $CD16^-$ monocyte count reduced significantly in critical patients compared to mild and severe groups (*P*<0.01). In contrast, pro-inflammatory $CD16^+$ monocytes were elevated compared to healthy controls (*P*<0.05). The study also stated that IL-6 levels had a positive correlation with the $CD16^+$ monocyte count.[24]

Monocyte $CD16^-$/classic subset, which plays a role in phagocytosis, has been significantly declined in critically ill patients, presumably due to impaired phagocytosis function because of innate immune function suppression. The results of the analysis for monocyte levels in this study were not like those of the study from Pence because they had limitations only to examine monocyte levels as a whole so that they could not identify the subset of monocyte that had lowered.

In the outcome of Covid-19 patients, the percentage of increased leukocytes was higher in patients who died (10.9% vs 46.4%; *P*<0001). Neutrophil and NLR levels were also higher in patients who died (82.1% and 67.9%; *P*<0001). At the same time, the lymphocyte levels declined more in patients who died (26.8% vs 57.1%; *P*<0.05). This

was identical to a study conducted by Zhao in 2020 which stated that the leukocyte types examination results of Covid-19 patients who died had a higher number of leukocytes ($7.85x10^9$/L vs $5.07x10^9$/L), higher neutrophil levels ($6.41x10^9$/L vs $3.08x10^9$/L), and lower lymphocyte levels ($0.69x10^9$/L vs $1.20x10^9$/L).[10] The NLR increase was also same as a study from Mousavi in 2020, which indicated that the deceased patient has a higher NLR (*P*<0,001).[25]

In this study, eosinophil levels in Covid-19 patients had a very weak negative correlation (r = -0.131; *P*<0.05) as seen in patients who recovered or died experienced a decline in eosinophils (59% and 78.6%). However, normal eosinophil levels were more common in cured patients who recovered (33.1% vs 21.4%; *P*<0.05). A corresponding study from Nair in 2020 found that eosinophil levels were negatively correlated with ICU duration, mechanical ventilation requirements, and oxygen supplementation (r = -0.34, -0.614 and -0.39; respectively, *P*<0.01).[26] A similar study suggested that eosinopenia could be a poor prognosis of Covid-19 patients outcome. Eosinophil levels that returned to normal during treatment were also considered as an indicator of clinical improvement. Nevertheless, there were no analysis of the leukocyte counts development of Covid-19 patients in this study.

Basophil levels on the outcome of Covid-19 patients in this study did not have a significant correlation (*P*=0.311), Same result was also discovered by Asghar in 2020, showing that basophil levels did not have a significant association with the outcome of Covid-19 patients (*P*=0.101).[27] Basophils do not have a significant correlation with the outcome of Covid-19 patients because most likely basophils do not have a direct contribution to cytokine storm in Covid-19 patients but instead play a role in mediating plasma B cells in response to IgG against SARS-CoV-2 infections, thus being decreased in most Covid-19 patients at acute onset.[28]

Complications from SARS-CoV-2 infection, Acute Respiratory Distress Syndrome (ARDS) are the leading cause of death for Covid-19 patients. The study has shown that cytokine storm is a mechanism for ARDS to occur in Covid-19 patients due to tissue damage.[29]

Leukocytes are thought to contribute to cytokine storms in the pathophysiology of SARS-CoV-2 infection. Cytokine storm results in the activation and infiltration of neutrophils into the alveoli, which are released by macrophages/monocytes. Injury to the alveolar epithelial cells increases the permeability of the barrier between alveolar and vascular spaces. This could bring in vascular leakage resulting in edema containing a lot of neutrophil cells and triggering the occurrence of ARDS.[30]

Lymphocytes play an important role in regulating cellular and humoral immunity. Lymphocyte levels declined more in deceased Covid-19 patients who were thought to have decreased immune function during systemic inflammatory responses. In addition, it was suspected that lymphocytes in peripheral blood vessels migrate to lung tissue during infection to eliminate the virus. This was confirmed by autopsy reports which showed that the lungs of deceased Covid-19 patients had elevated levels of lymphocytic infiltration.[31] In this study, hematologic changes in leukocytosis, neutrophilia, eosinopenia, lymphopenia, monocytopenia, and NLR increase were relevant to mortality in Covid-19 patients.

CONCLUSION

There was a significant correlation between the leukocyte count with the severity and outcome of Covid-19 confirmed patients, namely leukocytes, neutrophils, eosinophils, monocytes, lymphocytes, and NLR. Basophils, however, have a significant correlation with severity but had no significant correlation with the outcome of Covid-19 confirmed patients. Hematological examination of leukocyte counts could be a predictor of severity and outcome of Covid-19 confirmed patients, particularly the presence of neutrophilia, lymphopenia, and increased NLR.

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Correlation of Ceramic Dust Content in Workplace with Lung Function in Ceramics Industry Workers of X Company, Mabar, Medan

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Abstract

***Background**: Workers in the ceramics industry are often exposed to silica content which is unwittingly inhaled and deposited in the lungs. Macrophages will release Interleukin 8 (IL-8), a chemoattractant that causes neutrophil recruitment to the alveoli and releases proteolytic enzymes that damage the lung parenchyma and cause a decrease in lung function. This study aimed to determine whether dust levels correlates with IL-8 serum in ceramic industry workers.*

***Method:** This research is an analytic study with a cross-sectional design conducted in March–June 2019 in the X Ceramic Industry in Mabar, Medan. Personal Dust Sampler was used to measure the dust level of the study subjects at work sites. Lung function was measured by spirometry. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software.*

***Results:** A total of 35 male workers were divided into 3 working sections, 11 workers (31.4%) in the pre-compression section, 13 workers (37.1%) in the compression section and 11 workers (31.4%) in the sintering section. Dust levels at each working section were 24.8, 29.2, and 6.11, respectively. The lung function examination showed restrictive impairment in 21 workers (60%). Statistical analysis showed that the higher the level of dust in the workplace, the lower the value of Forced Expiratory Volume 1 (FEV_1) and Forced Vital Capacity (FVC) values, although this correlation was not statistically significant (r = -0.03 and -0.22 respectively; P>0.05).*

Conclusion:** There was no significant relationship between workplace dust levels and lung function in ceramic workers. **(J Respirol Indones 2021; 41(3): 196–99)

***Keywords:** Ceramics, dust levels, lung function, cigarettes*

Hubungan Kadar Debu Keramik di Tempat Kerja Dengan Fungsi Paru Pada Pekerja Industri Keramik Perusahaan X, Mabar Medan

Abstrak

***Latar belakang:** Pekerja industri keramik sering terpajan dengan silika yang tanpa disadari akan terinhalasi dan terdeposit di dalam paru. Makrofag akan mengekspresikan Interleukin 8 (IL-8), suatu kemoatraktan yang menyebabkan rekrutmen neutrofil ke alveolus dan melepaskan enzim proteolitik yang merusak parenkim paru dan menyebabkan penurunan fungsi paru. Tujuan dari penelitian ini adalah untuk mengetahui hubungan kadar debu dengan fungsi paru pada pekerja industri keramik.*

***Metode:** Penelitian ini merupakan studi analitik dengan desain cross-sectional yang dilakukan pada bulan Maret–Juni 2019 di Industri Keramik X di Mabar, Medan. Pengukuran kadar debu pada subjek penelitian di lokasi kerja dilakukan dengan menggunakan Personal Dust Sampler. Pengukuran fungsi paru dilakukan dengan spirometri. Analisis statistik dilakukan dengan menggunakan perangkat lunak SPSS.*

***Hasil:** Sebanyak 35 pekerja laki-laki dilibatkan sebagai subjek penelitian yang terbagi ke dalam 3 lokasi kerja, yaitu 11 pekerja (31.4%) di bagian prakompresi, 13 pekerja (37.1%) di bagian kompresi dan 11 pekerja (31.4%) di bagian sintering. Kadar debu pada masing-masing lokasi kerja adalah 24.8, 29.2, dan 6.11 berturut-turut. Hasil pemeriksaan fungsi paru menunjukkan 21 pekerja (60%) mengalami kelainan restriksi. Analisis statitsik menunjukkan bahwa semakin tinggi kadar debu di tempat kerja, maka semakin rendah nilai Volume Ekspirasi Paksa detik pertama (VEP_1) dan Kapasitas Vital Paru (KVP), meskipun korelasi ini tidak bermakna secara statistik (r = -0.03 dan -0.22 berturut-turut; P>0.05).*

Kesimpulan:** Tidak terdapat hubungan yang bermakna antara kadar debu di tempat kerja dengan fungsi paru pekerja keramik. **(J Respirol Indones 2021; 41(3): 196–99)

***Kata kunci:** Keramik, kadar debu, fungsi paru, rokok*

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INTRODUCTION

Silica dust exposure is still a worldwide health problem today. Between 1990 and 1993, approximately 600,000 workers in the United Kingdom, more than three million workers in Europe, and more than one million people in the United States were exposed to silica dust.[1] In Asia, it is estimated that nearly 11.5 million people working in India and 23 million people in China are exposed to silica dust.[2] There are no national data on the prevalence of silicosis in Indonesia currently.

The ceramic industry is one of the fastest-growing industries. The physical process of processing raw materials into ceramics tends to produce pollution such as ceramic dust particles, which in the manufacturing process produce silica. Silica is a chemical compound of silicon dioxide (SiO_2), one of the most abundant minerals. Most of the silica is present in the crystalline form, and in the amorphous form in lesser amounts.[3] Silicosis is an occupational lung disease and is a lung parenchymal disease caused by the inhalation of silicon dioxide or silica. It should be borne in mind that in workplaces that are places for collecting, processing and using materials containing silica or sand, there is a risk of suffering from silicosis.[4]

Prolonged exposure to silica dust causes inflammatory cells to secrete mediators such as cytokines, chemokines and chemoattractants, which can cause inflammation leading to an inflammatory cascade. The release of chemoattractants, such as leukotriene-B4 (LTB4) attracts neutrophils to secrete proteolytic enzymes such as elastase, proteinase-3, cathepsin G, and matrix metalloproteinase (MMP), which causes damage to the elasticity of lung tissue, which results in decreased lung function, generally as a restriction disorder. Still, it can also be an obstruction disorder or a combination of both.[5] This study aimed to determine lung function in ceramic industry workers.

METHOD

This research is an analytical study with a cross-sectional design conducted in a ceramic processing industry in Mabar, North Sumatra. Study subjects are workers aged 17–50 years who have worked for at least one year. Subjects who had a history of tuberculosis, diabetes mellitus, and malignancies were excluded from the study.

Subjects were divided into three working sections, precompression, compression and sintering sections. Measurement of dust level in the workplace was carried out at each working section using a *low volume dust sampler* in collaboration with the North Sumatra Company Hygiene and Work Safety Center. Dust measurements were done during working hours (1 hour continuously) and were placed at the average noise level of the worker and the total dust level was measured gravimetrically. All subjects underwent a spirometry examination, in which FVC, FEV_1. FEV_1/FVC and FEF_{25-75} are measured and noted.

RESULT

A total of 35 ceramic industry workers were involved in this study. The characteristics of the subjects are shown in Table 1.

Table 1. Characteristics of study subjects

Characteristics	n	%
Gender		
Male	35	100.0
Female	0	0.0
Age		
20-29 year	10	28.6
30-39 year	17	48.6
≥40 year	8	22.9
BMI		
Normal	12	34.3
Less	3	8.6
More	20	57.1
Smoking		
Yes	28	80.0
No	7	20.0
Use of PPE		
Yes	15	42.9
No	20	57.1
Working section		
Precompression	11	31.4
Compression	13	37.1
Sintering	11	31.4
Length of working		
0-4 year	9	25.7
5-9 year	8	22.9
≥10 year	18	48.6

Note: BMI=Body Mass Index; PPE=Personal Protective Equipment

All research subjects underwent a spirometry examination, then were measured for dust level in the workplace. Table 2 shows that more than half of the workers who were the subjects of the study had restrictive lung impairment.

Table 2. Characteristics of the lung function of the study subjects in ceramics industry workers of X company, Mabar Medan

Characteristics	n	%
Dust Content		
Sintering 6.11 ng/m^3	11	31.4
Precompression 24.82 ng/m^3	11	31.4
Compression 29.28 ng/m^3	13	37.1
Lung Function Test		
Normal	13	37.1
Obstruction	1	2.9
Restriction	21	60.0
Mix	0	0.0
FEV_1 (% Prediction)		
>80	14	40.0
51-80	20	57.1
31-50	1	2.9
<30	0	0.0
FVC (% Prediction)		
>80	14	40.0
51-80	20	57.1
31-50	1	2.9
<30	0	0.0

Furthermore, a statistical analysis was carried out to determine the correlation between the level of dust in the workplace and the lung function of workers. Table 3 shows no significant correlation between dust levels in the workplace and lung function (*P*>0.05). However, because the correlation coefficient value for the three lung function parameters is negative, it can be concluded that the higher the dust level in the workplace, the lower the pulmonary function of the workers.

Table 3. Correlation of Dust with Lung Function of Study Subjects

	Dust level	
	P	**r**
FEV_1 (% prediction)	0.25	-0.22
FVC (% prediction)	0.36	-0.17
FEF_{25-75} (% prediction)	0.28	-0.20

Note: Spearman's Correlation Test

However, because the correlation coefficient value for the three lung function parameters is negative, it can be concluded that the higher the dust level in the workplace, the lower the pulmonary function of the workers.

DISCUSSION

The ceramic industry is one of the rapidly growing industries. The physical process of processing raw materials into ceramics tends to produce pollutions, such as ceramic dust particles. Ceramics have the main raw materials and additional raw materials, the basic ingredients of ceramic floors. The raw materials for ceramic floors are the clay, feldspar, fat removal, and heat resistant materials (Mg and aluminum silicates). Long-term exposure to silica increases the risk of silicosis in ceramic factory workers.[3]

Prolonged exposure to silica dust causes inflammatory cells to secrete mediators such as cytokines, chemokines and chemoattractants, which can cause inflammation, leading to an inflammatory cascade. The release of chemoattractants such as (IL-8) and leukotriene-B4 (LTB4) attracts neutrophils to release proteolytic enzymes such as elastase, proteinase-3, cathepsin G, cathepsin B and (MMP), which cause damage to the elasticity of lung tissue.[5] Increased level of IL-8 causes the number of neutrophil cells to increase. One study showed an increase in inflammatory markers in serum correlated with the severity of airway obstruction.[6]

Based on the Circular of the Minister of Manpower No. 01 of 1997 concerning the Threshold Value (TLV) of Chemical Factors in the Air of the Work Environment, the TLV of dust levels that interfere with work enjoyment is 10 mg/m^3 where the dust does not contain asbestos. The content of free silica is < 1%. The dust levels obtained from the results of this study were 6.11 mg/m^3 in the sintering section, 24.82 mg/m^3 in the pre-compressed section and 29.28 mg/m^3 in the compression section. This means that only workers who work in the sintering section were in a healthy working environment. In contrast, workers in the precompression and compression sections were exposed to dust in concentrations that exceeded normal values throughout the day.

Sintering is a method of compacting ceramic powder at high temperatures to obtain bulk material. During the sintering process, the particles pollinated

by the ceramic will diffuse into each other until they become solid material. If the process is not perfect, the final result of the ceramics will still have pores that can reduce the quality of the ceramic. Lesser ceramic dust are floating in the air during this process because the sintering process aims to compact the semi-finished ceramic products compared to the precompression and compression processes where ceramic dust is still flying freely in the workspace so that its levels exceed the threshold value.

Based on the spirometry examination, the pulmonary function test results showed that as many as 60% of workers experienced restriction pulmonary function disorders. This was similar to the research results obtained by Tsao et al in 2017, which carried out pulmonary function examinations on 221 ceramic workers in Taiwan, where 53% of workers experienced restrictive disorders. Fortunately, most workers (57%) who experienced restrictive lung disorders were still in a mild restrictive degree (FVC=51–80% predictive value).[7]

There are several mechanisms in which silica can damage the lungs. Cytotoxicity of silica particles can trigger reactive oxygen/nitrogen species, secretion of pro-inflammatory factors, cytokines, chemokines, elastase, and fibrogenic factors. This mechanism can initiate changes in lung tissue resulting in respiratory obstruction.[8,9]

Moreover, the silica particles can cause epithelial cell injury, which facilitates the penetration of the silica particles into the walls of the small airways, resulting in localized fibrosis. The restrictive lung impairment is associated with collagen production and fibroblast growth factor, resulting in fibrosis of the alveolar wall and formation of silicotic nodules, all of which will result in restriction of lung function.[8,9]

CONCLUSION

There was no statistically significant correlation between dust level in the workplace and the lung function of ceramic factory workers.

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Exhaled Carbon Monoxide (eCO) and Serum CC16 Levels in Active Smokers

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Abstract

Background: *Toxic particles within tobacco smoke are responsible for several respiratory system problems. Among these toxic particles is Carbon Monoxide (CO), produced from environment and Heme Oxygenase induction. Expiratory CO levels can be measured using CO analyzer. Club Cell Protein 16 (CC16) is a pneumoprotein produced by club cells in distal respiratory tract. In acute condition, CC16 level will increase to maintain homeostasis and anti-inflammation. In chronic condition, i.e.smokers, Club cell destruction would lead to decrease level of CC16. This study aims to determine exhaled CO (eCO) levels and serum CC16 levels in active smokers.*

Methods: *This is a cross-sectional study on 40 healthy active smokers from October 2019-June 2020. Subjects who met the criteria; men, age between 19 until 60 years old, smoked at least 1 year and 1 cigarette/day, smoked in the Universitas Brawijaya and signed the informed consent. Exhaled CO levels are measured using CO analyzer, while ELISA is used to measure serum CC16 evels.*

Results: *Among 40 subjects, mean eCO level is 10.18 ± 7.42 ppm. Mean serum CC16 level is 3.17 ± 1.78 ng/mL, lower than normal value of 6.4 ng/mL. The mean serum CC16 based on the Brinkman Index were heavy smokers 5.24±0.45 ng/mL, medium 3.32±1.87 ng/mL, and light smokers 2.49±1.42 ng/mL. The highest serum CC16 level is 5.56 ng/mL included in the category of CO Analyzer levels smoker-heavily addicted, i.e 28 ppm, a number of 1 subject.*

Conclusion: *eCO levels and serum CC16 decreases in active smokers. This indicates that CO from tobacco smoke could damage the Club cells in the respiratory system, so the resulting of serum CC16 will be reduced.* ***(J Respirol Indones 2021; 41(3): 200–6)***

Keywords: *Active Smokers, Exhaled Carbon Monoxide (eCO), Serum CC16*

Kadar Karbon Monoksida Ekshalasi (eCO) dan Kadar CC16 Serum pada Perokok Aktif

Abstrak

Latar belakang: *Zat toksik yang terkandung di dalam asap rokok dapat menyebabkan masalah pada sistem respirasi. Salah satunya adalah gas karbon monoksida (CO) yang dapat dihasilkan dari lingkungan maupun akibat induksi Heme Oxygenase. Gas CO dapat diukur melalui udara yang diekspirasi menggunakan CO Analyzer.* Club Cell Protein 16 (CC16) *adalah pneumoprotein yang dihasilkan oleh Club cells di saluran nafas bagian distal. Pada kondisi akut CC16 akan meningkat dan berfungsi mempertahankan homestasis dan aktivitas anti-inflammasi. Pada kondisi kronis, seperti pada perokok Kerusakan Club cell dapat menyebabkan penurunan kadar CC16. Tujuan studi ini adalah untuk mengetahui kadar CO ekshalasi (eCO) dan kadar serum CC16 pada perokok aktif.*

Metode: *Studi menggunakan desain penelitian uji potong lintang pada 40 subjek perokok aktif yang sehat pada Oktober 2019-Juni 2020. Subjek yang memenuhi kriteria; laki-laki, usia 19–60 tahun, aktif merokok minimal 1 tahun dan 1 batang/hari, merokok di lingkungan Universitas Brawijaya dan telah menandatangani persetujuan penelitian. Pengukuran kadar eCO menggunakan CO Analyzer dan kadar serum CC16 menggunakan metode ELISA.*

Hasil: *Rerata kadar eCO pada 40 subjek penelitian termasuk kategori smoker-low addicted (10,18 ± 7,42 ppm). Rerata kadar CC16 serum pada penelitian ini yaitu 3,17 ± 1,78 ng/mL. Rerata serum CC16 berdasarkan Indeks Brinkman yaitu pada kelompok berat 5,24 ± 0,45 ng/mL, sedang 3.32 ± 1.87 ng/mL, dan ringan 2.49 ± 1.42 ng/mL. Kadar serum CC16 tertinggi menurut kadar CO Analyzer adalah perokok berat, yaitu 28 ppm sebanyak 1 subjek.*

Kesimpulan: *Pada perokok aktif terjadi peningkatan rerata kadar eCO disertai dengan penurunan rerata kadar serum. Hal ini menunjukkan CO dari asap rokok dapat menyebabkan kerusakan pada Club cell di bronkiolus respiratorius, sehingga produksi serum CC16 akan berkurang.* ***(J Respirol Indones 2021; 41(3): 200–6)***

Kata kunci: *Karbon monoksida ekshalasi (eCO), Perokok aktif, Serum CC16*

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INTRODUCTION

Smoking is one of unhealthy habit that is difficult to eliminate.[1] According to WHO in 2015, the global number of active smokers exceeding 1.1 billion with male predominant.[2] Health issues and death related to smoking are still a burden for the economic losses. Annual data from WHO, there are 7 million people death and 1.4 trillion USD losses due to lessen productivity and health cost related to smoking.[3] In smoked cigarettes contained Carbon Monoxide (CO) gas, which is invisible, odorless but poisonous.[4] The benefit of CO gas analysis is to measure the levels of CO gas exhaled by active and passive smokers on a non-invasive basis and not influenced by the use of nicotine-containing products.[5]

Air pollution, including cigarette smoke, will stimulate the secretion of Club Cell Protein-16 (CC16). In acute conditions, there will be increased production of CC16 by maintaining homeostasis and anti-inflammation activity in the airways exposed to irritants, allergens, and viruses. While in chronic conditions, such as in smokers, CC16 can decrease. This is due to the club cell that produces CC16 is damaged. Decreased production of CC16 in smokers results in increased proinflammation that eventually causes some lung diseases, one of which is PPOK.[6]

Measurement of CO gas exhaled by active smokers is one of the stages of efforts to quit smoking by identifying exhalation CO levels or exhaled carbon monoxide (eCO) as tools for smoking cessation. Previous studies with descriptive statistical design, obtained increased CO levels and decreased serum CC16 levels in smokers, but the association between the two substances is not widely understand. Further study regarding this issue will be conducted in a cross-sectional design and the minimum length of smoking is 1 year.

METHOD

This cross-sectional study was conducted from October 2019–June 2020. Subjects eligible for this study are men, age 19–60 years, minimum smoking is 1 cigarette per day for at least 1 year, and signed the informed consent. Passive or former smokers, history or current treatment of any pulmonary disease, and any kidney or liver disease were not included in this study. There are 40 eligible subjects whom we measured the levels of CO exhalation with a CO Analyzer and the levels of CC16 in serum by ELISA method.

RESULT

In this study, 40 eligible subjects with characteristic male, mean age 34±9.0 years and mean Body Mass Index (BMI) of 22.1±4 kg/m². The mean or median of the smoking duration is 1 to 40 years. The type of cigarettes that are often used are filter 70.0%, then the clove 20%, and mixture 10%. According to Brinkman index degree, this study has a proportion of mild degrees 65.0%, moderate degrees 30%, and heavy degrees 5.0%.

Table 1. Demographics on Research Subjects

Characteristic	Mean±SD or Percentage
Age (years)	34±9
BMI (kg/m²)	22.1±4
Smoking Duration (years)	15.17±9.5
Type of work	
Administration Officer	62.5%
Non-administration	25.0%
College student	12.5%
Type of Cigarette	
Filtered	70.0%
Unfiltered	20.0%
Mix	10.0%
Brinkman Index	
Light	65.0%
Medium	30.0%
Heavy	5.0%
Haematological Parameters	
Haemoglobin (gr/dl)	15.1±1.4
Leukocytes (/µl)	7.132±1,273.9
Haematocrit (%)	44.02±3.25
Platelets (/µl)	297.875±68.33
Serum CC16 (ng/mL)	3.17±1.78
eCO (ppm)	10.18±7.42

The haematological parameters of the study subjects for the haemoglobin average were 15.1±1.4 gr/dl, leukocytes 7.132±1.273,9 /µl, haematocrit 44.02±3.25% and platelets are 297.875±68.33/µl.

Table 2. Distribution Number of Study Subjects Based on Degree of Brinkman Index by Category CO Analyzer Level of eCO

eCO Category (Smokerlyzer)	Brinkman Index (n)			
	Light	Medium	Heavy	Total
Non-smoker	14	2	-	16
Borderline	4	3	-	7
Smoker-low addicted	4	-	1	5
Smoker-moderately addicted	4	7	-	11
Smoker-heavily addicted	-	-	1	1
Total	26	12	2	40

Table 3. eCO Level (ppm) Based on CO Analyzer Category with Serum CC16 Level (ng/mL)

Characteristic	Amount (n)	eCO (ppm)	CC16 Serum (ng/mL)
Non-smoker	16	3.25±1.18	2.93±1.95
Borderline	7	8±1	2.18±0.81
Smoker-low addicted	5	11.6±1.34	4.00±1.62
Smoker-moderately addicted	11	19.36±2.37	3.54±1.84
Smoker-heavily addicted	1	28	5.56

In this study, the average level of serum CC16 in the study subjects was 3.17±1.78 ng/mL, which showed a lower value than the normal value in non-smokers of 6.4 ng/mL based on Prior study by Lomas et al.[7]

While the average carbon monoxide exhalation (eCO) is 10.18±7.42 ppm. This value is based on the CO Analyzer category of eCO levels belonging to the smoker-low addicted category. The number of eCO levels in the study subjects based on the Brinkman Index was the most in the CO Analyser eCO non-smoker category with a light Brinkman Index of 87.5% subjects. The distribution of the number of study subjects by Brinkman index degree by CO Analyzer category eCO levels is described in Table 2.

There is no significant difference between CC16 levels and Brinkman Index (*P*=0.09). There are tiny gap of CC16 levels between every degree of Brinkman Index.

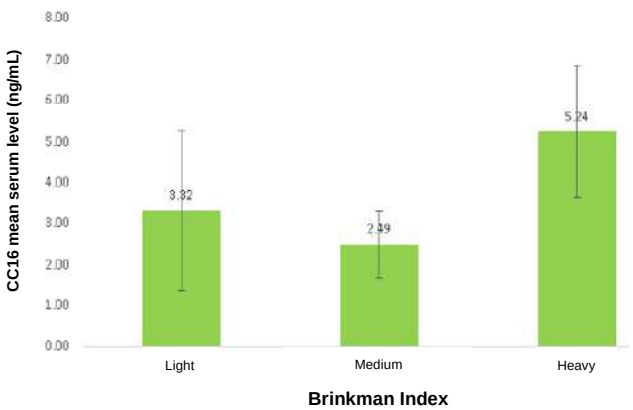

Figure 1. Mean CC16 serum levels based on Brinkman Index

Figure 2 explains the difference in serum CC16 levels to the CO Analyzer category of eCO levels. Heavily addicted smoker group had the highest serum CC16 levels, meanwhile the borderline group had the lowest level of CC16.

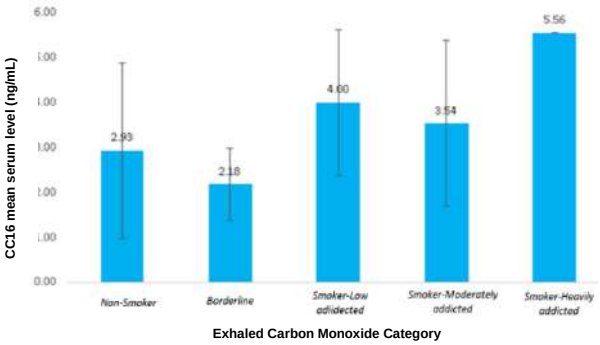

Figure 2. Mean of Serum CC16 Levels Based on Smokerlyzer Category Exhaled Carbon Monoxide (eCO) Levels

DISCUSSION

In this study, the average overall eCO level based on CO Analyzer was 10.18±7.42 ppm, including the smoker-low addicted category of 10-15 ppm.[8] The amount of carbon monoxide (CO) in cigarette smoke inhaled to the alveoli influenced by several factors, namely the type of cigarette, smoking pattern, and the depth of smoking. In addition, eCO can be affected by different environmental CO levels, especially for residents living in urban areas. The depth of smoking can affect carboxyhemoglobin (COHb) levels in a smoker and ultimately affect the expirated CO levels. This is due to tiny amount of CO diluted in

the mouth and larynx. Everytime the blood level COHb increase, the CO has reached the alveoli and diffused through the alveolar-capillary membrane to bind to haemoglobin, forming COHb. Carboxyhemoglobin values themselves have a strong correlation with eCO.[9,10] Physical activity, average ventilation, and respiration diseases such as infectious diseases can also affect eCO levels.[11]

Carbon monoxide is also produced endogenously due to the induction of Heme Oxygenase (HO), which accounts for about 85% of the body.[4] This induction is affected by stressful conditions, such as oxidative stress, hyperthermia, hypothermia, ischemia, hypoxia, inflammation, and ultraviolet (UV) light exposure.[12] Carbon monoxide produced from both endogenous and exogenous sources will go through several mechanisms: expiration, scavenging, and oxidation. These expirated air CO levels can be measured using a CO meter and applied for various clinical purposes.[8]

Based on this study, the average value of eCO levels (10–15 ppm) can be produced from exogenous and endogenous CO. Exogenous CO in the study subjects was influenced by the type of cigarette which were mostly filtered cigarette (70%) and number of cigarettes consumed measured by the Brinkman Index.

Filtered cigarettes provide filters to reduce co-production so that the level of CO that enters the respiratory tract will also be reduced. Smoking patterns and CO gases derived from the environment itself can affect the value of eCO levels in the study subjects. Endogenous CO in this study can certainly influence the value of eCO levels, namely by looking at the value of COHb (%), which correlates with eCO (ppm) values that can be measured using CO Analyzer.

The previous study also showed that the exhaled CO level in the smoker's group was higher 22 (4;48) ppm than the non-smoker gorup 5.83+1.82 ppm. Based on previous study, the results of the current research are not much different. Smoker-heavily addicted has the highest value of eCO, which is 28 ppm, smoker-moderately addicted 19.36±2.37 ppm, smoker-low addicted 11.6±1.34 ppm compared to non-smokers 3.25±1.18 ppm. The most correlated factor to CO levels in exhaled air in smokers is gender, men tend to have higher CO levels than women. The cut-off point for CO levels to determine smoking status in a person is 8 ppm with a sensitivity of 91% and a specificity of 90%.[9] From the previous, it can be concluded that exhaled carbon monoxide level was higher in smoker.

The average value of serum CC16 levels in this study was 3.17±1.78 ng/mL, indicating a lower value than the normal value in non-smokers of 6.4 ng/mL.[7] Other study by Rong et al (2020), the serum CC16 levels in COPD patients with smoking risk factors 3.10±2.23 ng/mL compared to those who had quit smoking 4.35±2.72 ng/mL. Meanwhile the serum CC16 levels in non-smokers could reach 102.5±20.3 ng/mL.[13] Research conducted by Naha et al. 2020 on ceramic workers in India, smokers with early detection of the onset of silicosis, had lower serum CC16 levels (2.6±2.72 ng/mL) compared to those, non-smokers and not exposed to silica (10.2±2.72 ng/mL).[14]

The serum CC16 levels was not affected by the severity of the Brinkman Index. The mean CC16 level on the Brinkman Index is 5.24 ± 0.45 ng/mL. However, the serum CC16 levels from this study are still below the normal value of 6.4 ng/mL according to a study by Lomas et al.[7] According study in 2018 by Lam et al., decreasing in lung function in smokers showed an insignificant relationship between serum CC16 levels and the number of cigarettes consumed packs per year (P=0.126).[15]

CC16 metabolism consists of three mechanisms. First, the increase in the permeability of the epithelial barrier in the lungs, thus causing the diffusion of CC16 into the blood. This is due to the release of vasoactive neuropeptides (tachykinins) through sensory nerves present in the respiratory tract, but the mechanism is reversible. The second is caused by a decrease in CC16 production by club cells due to chronic exposure to toxic substances, which is cigarette smoke. Third is increased creatinine clearance in the kidneys. Serum CC16 half-life is 2 to 3 hours in the serum. The study, according to Park et al, 25% variations in serum

CC16 levels do not differ between healthy subjects and smokers. Variations in CC16 serum levels can be used as specific biomarkers to the integrity of the epithelium of the airways in individuals who did not have impaired renal function.[16]

The club cell will undergo several structural changes after an hour of exposure to toxic substances. Such changes are clumping and margination of nuclear chromatin, oedema of mitochondria, and dilation of the endoplasmic reticulum. After exposure for approximately 24 hours, the club cell will enlarge, and some vacuole will approach the cell membrane. The existence of this process, the Club cell, is believed to provide host defence against toxic substances outside the body. However, the number of Club cells will significantly decrease in smoker with minimum smoking 10 packs per year.[17,18]

Research by Lam et al stated that, the result of an endobronchial biopsy followed by immunohistochemical painting after exposure to cigarette smoke for 96 hours, showed a decrease in mRNA and CC16 expression. But it will increasedagain after the exposure of cigarette smoke is eliminated.[15] Recent study by Laucho-Contreraset al al with immunostain in human bronchi in COPD sufferers, healthy subjects showed a more striking colour in healthy subjects. Similiarly, studies by Laucho-Contreraset al al, mice that have been exposed to cigarette smoke showed immunostaining is more prone.[6]

Decreasing serum CC16 levels are associated with damage to the club cell, as non-ciliated non-mucous secretory cells located in the respiratory bronchioles due to exposure to cigarette smoke. In addition, there is also damage in tracheal cells and the integrity of the pulmonary vascular barrier, and the influence of kidney cleansing. Decreasing serum CC16 levels are associated with damage to the club cell, as non-ciliated non-mucous secretory cells located in the respiratory bronchioles due to exposure to cigarette smoke. In addition, there is also damage in tracheal cells and the integrity of the pulmonary vascular barrier, and the influence of kidney cleansing. The CC16 level of the serum has the same gradient as the one in Club Cell. Even the CC16 content in the serum is 20 times lower. This is due to the permeability of the epithelium and damage to the integrity of the pulmonary vascular barrier so that CC16 can diffuse passively. The increase of Serum Protein (SP)-B, another product of club cell, also affects the increase in epithelial permeability.[13,15,17]

Cigarette smoke can increase epithelial permeability leakage in acute conditions by releasing vasoactive neuropeptides (tachykinins) through sensory nerves present in the respiratory tract, but this is reversible. While chronic conditions increase the initial damage of connective tissue alveoli.[18] Blood sampling will result in a variation in serum CC16 serum by 20% to 25%. This is likely due to circadian rhythms that affect the change of cycles in epithelial bonds in the Club cell resulting in CC16 leakage into blood vessels at certain times.[16]

The average decrease in serum CC16 levels in the study subjects was due to damage from the club cell. Exposure to cigarette smoke with an average smoking length of 15.17±9.5 years is enough to cause progressive damage. The CC16 capability produced by club cells in protecting the epithelium of the distal airway is reduced which could reduce its effectiveness. Similarly, in research subjects with a heavy Brinkman Index, although it has a higher mean value. However, the rate is still below the normal level. This may be due to the presence of a number of club cells that produce CC16 in acute conditions without causing impaired pulmonary function. This is based on anamnesis, physical examination, and normal chest x-ray from the subjects with heavy Brinkman Index not obtained abnormalities.

In this study, the entire study subjects were active smokers with a minimum smoking duration of 1 year. Elevated eCO levels in subjects were affected by the last time smoking, cigarrette type, and smoking patterns. Smokers who last smoked 2 hours earlier had a higher value than the last one who smoked 72 hours earlier. From this study, no respiratory disease could affect the value of eCO. The cause of the decrease in serum CC16 levels

caused by several factors, including exposure to cigarette smoke that cause damage in club cells, kidney cleansing in healthy subjects. The value of serum CC16 levels will also decrease rapidly due to the short half-life of serum CC16, which is 2 to 3 hours. Serum CC16 could influenced the circadian rhythms. In this study, the timing of samples obtained from each subject are different due to the availability of the subjects.

The results of this study showed that increased eCO levels would lower serum CC16 levels. Exhaled carbon monoxide and serum CC16 levels have different effects, especially the half-life. The increasing level of eCO is temporary and will decreased even the subjects has stopped smoking. While the level of serum CC16, if in active smoker is still actively smoking for a long time, will cause permanent damage to the club cell as a result, the production of CC16 will decrease even the subject has stopped smoking. However, club cells in active smokers in acute conditions can still produce CC16, but not exceed the levels in non-smokers. Based on the results of this study, the levels of eCO and serum CC16 are expected to be indicators and specific biomarkers in efforts to stop smoking.

CONCLUSION

The mean eCO levels in active smokers was 10.18±7.42 ppm (CO Analyzer smoker-low addicted category) following with low level of serum CC16 (3.17±1.78 ng/mL). This study showed the CO resulting from continuous exposure to cigarette smoke could cause damage to the club cells that produce CC16, thus resulting reduced CC16 levels.

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Case Report Tuberculosis of The Prostate: Findings of Post Transurethral Resection of Prostate (TURP) Procedure

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Abstract

Background: *Prostate tuberculosis (PTB) is one of extrapulmonary tuberculosis which potentially has more frequent fatal complications and more severe quality of life deterioration. It is a very rare disease, with a prevalence of 2.6% of all urogenital tuberculosis (UGTB). Prostate tuberculosis may be a sexually transmitted disease and leads to sexual dysfunction.*
Case: *Male, 54 years old, with urinary retention, dysuria, flank pain in the last 1-month, recurrent urinary tract infection in the past 1 year and decrease body weight of 8 kg in 1 month. Physical examination demonstrates enlarged prostate. The patient was referred to Wangaya Hospital with benign prostate hyperplasia (BPH) and suspect malignancy. After underwent clinical and supporting examination, the patient underwent a TURP procedure. Histopathology examination revealed PTB. The patient was then treated with a first-line anti-tuberculosis drug (ATD).*
Discussion: *Multiple risk factors are involved in TB disease. PTB spread occurs through hematogenous, lymphatic, or direct routes. Clinical features and supporting examinations of PTB are non-specific. Diagnosis is often made through incidental histology finding post-TURP. Standard ATD regiment administered based on World Health Organization (WHO) guidelines. Duration can be prolonged due to the suboptimal concentration of prostate tissue.*
Conclusion: *Multidisciplinary approach for extrapulmonary TB is needed. Thorough history taking and a high index of suspicion are important aspects. PTB diagnosis should be considered in patients with recurrent lower urinary tract symptoms refractory to standard therapy in TB endemic areas.* ***(J Respirol Indones 2021; 41(3): 207–13)***
Keywords: *tuberculosis (TB), prostate, anti-tuberculosis drug (ATD).*

Laporan Kasus Tuberkulosis Prostat: Temuan Pasca Prosedur Reseksi Prostat Transuretral (*Transurethral Resection of Prostate*/TURP)

Abstrak

Latar Belakang: Prostate tuberculosis (PTB) *termasuk salah satu tuberkulosis ekstra paru yang berpotensi memiliki frekuensi komplikasi fatal lebih banyak serta penurunan kualitas hidup yang lebih parah. PTB merupakan entitas penyakit yang sangat jarang dengan prevalensi 2.6% dari seluruh tuberkulosis urogenital (UGTB). Tuberkulosis prostat mungkin merupakan penyakit menular seksual dan dapat mengakibatkan disfungsi seksual.*
Kasus: *Laki-laki, 54 tahun, dengan keluhan retensi urin, disuria, nyeri panggul sejak 1 bulan yang lalu, infeksi saluran kemih berulang sejak 1 tahun yang lalu, dan penurunan berat badan 8 kg dalam 1 bulan. Pemeriksaan fisik menunjukkan pembesaran prostat. Pasien dirujuk ke RSUD Wangaya dengan* Benign Prostate Hyperplasia (BPH) *suspek malignansi. Setelah menjalani pemeriksaan klinis dan penunjang, pasien menjalani prosedur TURP. Pemeriksaan histopatologi menunjukkan PTB. Pasien kemudian mendapat obat anti tuberkulosis (OAT) kategori I.*
Diskusi: *Berbagai faktor risiko terlibat dalam penyakit TB. Penyebaran PTB terjadi melalui rute hematogen, limfatik, atau langsung. Gambaran klinis dan pemeriksaan penunjang PTB tidak spesifik. Diagnosis seringkali ditegakkan melalui temuan insidental pasca TURP. Rejimen OAT standard diadministrasikan berdasarkan pedoman Organisasi Kesehatan Dunia. Durasi pengobatan dapat diperpanjang karena konsentrasi suboptimal ke jaringan prostat.*
Kesimpulan: *Diperlukan pendekatan multidisipliner untuk TB ekstra paru, Anamnesis menyeluruh serta indeks kecurigaan tinggi merupakan aspek yang penting. Diagnosis PTB sebaiknya dipertimbangkan pada pasien dengan gejala salurah kemih bawah berulang yang refrakter terhadap terapi standard pada area endemis TB.* ***(J Respirol Indones 2021; 41(3): 207–13)***
Kata kunci: *tuberkulosis (TB), prostat, obat anti tuberkulosis (OAT).*

Note: This article was presented and won the first award in the Case Report Poster Presentation Scientific Meeting of Pulmonology and Respiratory Medicine (PIPKRA) 2020, 21-22 February 2020 at Hotel Borobodur, Jakarta

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INTRODUCTION

Tuberculosis (TB) is a significant health problem contributing to the leading cause of death worldwide. The bacterial infection that causes TB has a wide morbidity spectrum because it can infect multiple organs both in the lung and extra-pulmonary. Extra-pulmonary TB plays an essential role because of the greater frequency of fatal complications and a more severe deterioration in the quality of life.

Globally, TB is in the top rank of the cause of death due to a single infectious agent, namely *Mycobacterium tuberculosis (M.tb*). Nearly 90% of cases are found in countries with a high burden of TB, including Indonesia.[1] The most frequent location of TB disease is in the lung parenchyma. Extrapulmonary TB, especially urogenital TB (UGTB), is rarely reported.[1,2] One of the UGTB subtypes, prostate tuberculosis (PTB), is a rare disease. The PTB epidemiology data is still very limited. Mumu et al, reported that PTB was found in only 2.6% of all UGTB. The age range of PTB patients based on the literature is between 35–90 years, with a mean of 65.82 years.[2]

In Indonesia, there is no specific report on the prevalence of PTB. PTB has a significant clinical impact because of several factors, such as PTB may be sexually transmitted diseases; M.tb in the ejaculate is found in up to 50% of patients; it can cause infertility, chronic pelvic pain, and reduce sexual function. These various factors contribute to the decline in the quality of life.[3] In addition, PTB that is late diagnosed has the potential to have a distant spread. PTB causes significant morbidity.

The spread of PTB can occur hematogenous, lymphatic or direct route.[4] Several predisposing factors include previous TB infection, immunodeficiency conditions, low socioeconomic conditions, and a history of BCG vaccination.[5] However, PTB in the early stages is very complex due to a lack of pathognomonic symptoms and low excretion of bacteria. The majority of cases were not suspected at the beginning of the patient's visit to a health service center. Clinical manifestations can include the lower urinary tract, urinary incontinence, urinary tract infection; urinary retention; and low back pain.[2] However, these symptoms are usually refractory to standard treatment regimens, and PTB are easily underdiagnosed. Therefore, it is not surprising that patients are often treated as a common urinary tract infection.

Non-specific clinical features, low case finding frequency, and no specific guidelines globally make early detection difficult. Almost all cases of PTB are incidental findings or at autopsy. It is also known that the clinical presentation of PTB can mimic a malignant process.[6] The diagnosis of PTB is generally confirmed by histopathology. The authors report cases of prostate tuberculosis that were found after the Transurethral Resection of The Prostate (TURP) procedure.

CASE

Male, 54 years old, came to Wangaya Hospital and was referred from Siloam Hospital, Labuan Bajo. The patient presented with urinary retention, urinary incidence, dysuria, and back pain one month before admission. The patient also experiences a weight loss of 8 kg in the last 1 month. The patient often had similar symptoms and was treated as a urinary tract infection in the last 1 year ago. The patient denied prolonged cough, coughing up blood, cold sweat, shortness of breath, or chest pain.

Other symptoms including nausea, a history of unexplainable fever, malaise, and decreased appetite. Patients often experienced similar complaints and have been treated for urinary tract infections one year ago. The patient has never received immunizations and his occupation was a farmer. The patient's family member is an active smoker, smoking around one pack per day. Similar symptoms and family history of TB disease were denied.

From the physical examination, the patient was moderately ill, compos mentis, with vital signs as following blood pressure 120/80 mmHg, heart rate 97x/minute, respiratory rate 18x/minute, axillary temperature 36.7˚C, SpO_2=98% of room air, and pain scale 3. Physical examination of the lungs obtained

symmetrical inspection, normal palpation of vocal fremitus in both lung fields, percussion obtained resonance in both lung fields, and auscultation of bronchovesicular breath sounds at the apex of the right and left lungs, no rhonchi or wheezing were found. The digital rectal examination found a palpable prostate lump with solid rubbery consistency and the fingertips cannot touch the upper end of the prostate lump (enlarged size >4cm).

The patient had brought several results of the supporting examinations from the Siloam Hospital Labuan Bajo. The complete blood cells examination found an increase in white blood cells (12.04) The urinary sediment examination found high erythrocytes concentration, increased leucocytes (16–19) and squamous epithelial cells (8–12), and also positive for bacteria. The ultrasound examination found an enlarged prostate.

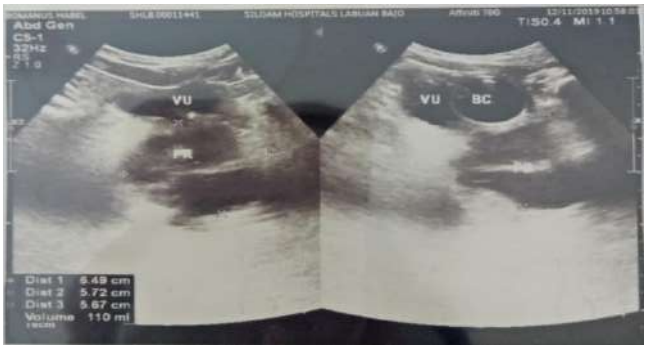

Figure 1. Prostate ultrasound showing an enlarged size with a volume of 110 ml, flat surface.

Based on clinical manifestations and investigations, the patient was diagnosed with BPH with a differential diagnosis of prostate malignancy. The patient was then further evaluated. The complete blood count found an increase in neutrophils (78.1%). The prostate-specific antigen (PSA) was normal (0.9 ng/mL). The PA chest X-ray (Figure 2) shows fibroinfiltrates in both lung fields and a minimal left pleural effusion. The patient then underwent TURP procedure. The prostate specimen was sent for histopathological examination.

The results of histopathological examination of prostate tissue showed granulomatous features with caseous necrosis and *multinucleated giant cells (Langhan's type)*, suggesting prostate tuberculosis.

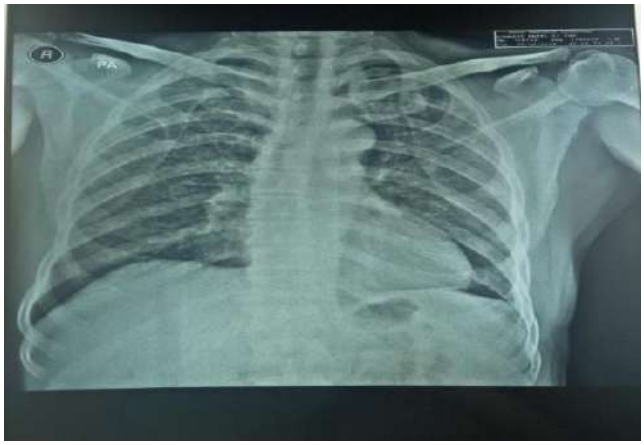

Figure 2. The PA chest X-ray at Wangaya Hospital. Fibroinfiltrates were seen in both lung fields and a minimal left pleural effusion also can be seen.

The patient was then consulted to the pulmonary clinic. Based on the history, a similar history with the first treatment was obtained. Physical examination found no significant abnormalities.

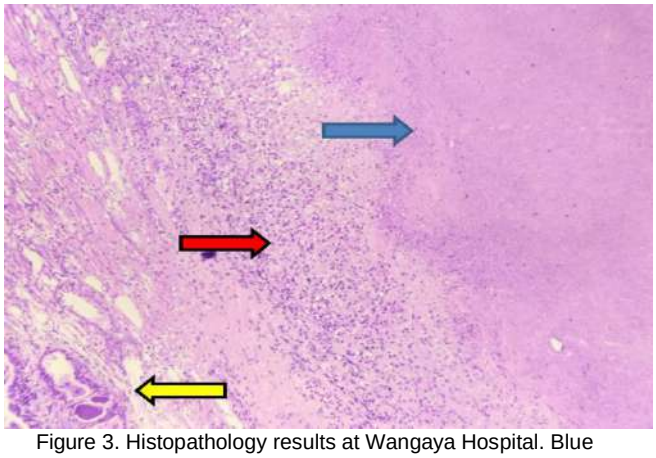

Figure 3. Histopathology results at Wangaya Hospital. Blue arrows show areas of caseous necrosis. Red arrows show granulomas with lymphocytes and plasma cells surrounding caseous necrosis. The yellow arrow indicates a normal prostate gland.

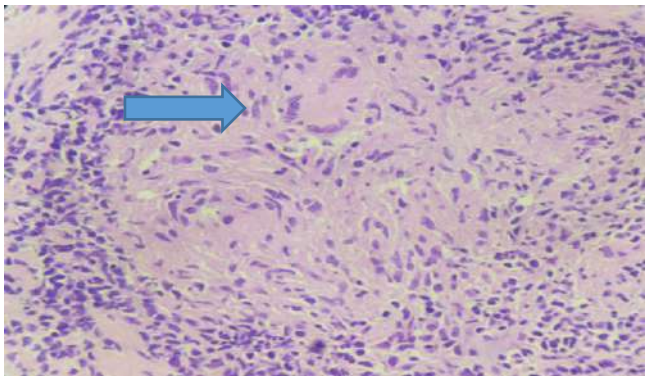

Figure 4. Patient histopathology. The blue arrow shows *Langhan's giant cell type.*

A rapid molecular test with Xpert MTB/RIF was carried out and the *M.tb* was not found. The HIV test result was non-reactive. The patient's diagnosis was

pulmonary tuberculosis (with prostate tuberculosis). The patient was then treated with category I ATD management for 6 months with 2 (HRZE)/ 4 $(HR)_3$.

DISCUSSION

The epidemiological data for tuberculosis in the prostate (PTB) is still very limited. This UGTB subtype is the rarest with primary PTB autopsy findings of only 1%.[7] Research by Kuchalvenya et al,[8] found that PTB contributed 32.7% of all male genital TB (epididymal TB, epididymal-orchitis, prostate, seminal vesicles, and penis). The demographic characteristics of age, socioeconomic, and localization of our TB patients are consistent with previous reports of increasing the risk of M.tb infection.

Based on the literature, the age of PTB patients varies from 26 to 90 years.[2] Yddoussalah et al reported that all PTB patients who had a low socio-economic level came from rural areas.[9] This condition is one of the risk factors for disease transmission. Several other determinants that increase the probability of TB disease include immunodeficiency conditions, alcohol and substance abuse, smoking, homelessness, poor housing, pneumoconiosis, genetics, and vitamin deficiency.[5]

In addition to socioeconomic status, patients have other risk factors that increase the risk of TB disease, which is a history of BCG vaccination. World Health Organization (WHO) guidelines stated that the BCG vaccine is the only vaccine for TB prevention. The protection obtained from the BCG vaccine varies from 44–99%. WHO recommends routine administration of the BCG vaccine in countries with high TB burden, including Indonesia.[10] However, the percentage of BCG coverage in Indonesia based on Riskesdas 2013 was only 87.6%.[11] Our patient is an example that illustrates that vaccine coverage is not yet optimal, causing TB disease.

The classification of TB is based on location, including pulmonary and extrapulmonary TB. If there is pulmonary and extrapulmonary TB together, it is classified as pulmonary TB. In this patient, lung involvement was found from the chest x-ray. Epidemiological data on pulmonary tuberculosis and PTB have been published. PTB patients reported having active TB from other locations as much as 33% (mostly lung) and a previous history of TB in 38.7%.[3] These data are supported by the theory that PTB is almost always secondary to *M.tb* infection in the lungs or kidneys. However, the primary focus may occur undetected in the majority of cases. Primary focus reactivation may also occur in individuals with a history of TB.[12]

The prostate can be infected with *M.tb* via the hematogenous, lymphatic, or direct route of transmission.[4] Sexual transmission of *M.tb* has been reported because the pathogen *M.tb* is found in semen, but it is rare. The pathogenesis of *M.tb* in humans has been extrapolated from animal models. However, the exact sequence of events following primary human infection by *M.tb* remains unclear. Certain individuals naturally have innate immunity to eradicate *M.tb* and are resistant to *M.tb* infection. Following primary infection acquired by inhalation or ingestion, *M.tb* bacilli replicate locally in the tissues and stimulate a complex immune response, resulting in the elimination or formation of primary granulomas (primary Ghon foci). Primary TB lesions can be found in various organ systems, most commonly in the lungs.[12,13]

Uncontrolled replication of M.tb increases the chance of active infection and distant spread. Clinical features take between 12 months–2 years post-primary infection to manifest because of the slow *M.tb* replication rate and intracellular location in macrophages. The latent period between the first pulmonary infection and presentation of the UGTB ranges from 1–50 years, 22 years.[6,14,15] Therefore, PTB patients are rarely seen at a young age.

Based on previous exposure, tubercular infection of the prostate causes chronic granulomatous inflammation with central caseous necrosis,[12] as seen in Figure 3. Furthermore, fibrosis or cavity formation occurs in extreme cases. The disease can spread rapidly and result in glandular destruction, reducing semen volume.[7] Advanced tubercular lesions show the perineal sinuses and are palpable on palpation of the prostate, i.e. fluctuating

bilateral enlargement and tender zones are found. In addition, dissemination of *M.tb* may perforate into the urethra, bladder, rectum, scrotum, perineum, and peritoneal cavity.[16] Patient complaints generally arise when prostate lesions reach an advanced stage.

The majority of patients present with signs of lower body obstruction, which is symptoms of an enlarged prostate. Common presentations are irritable urination, hemospermia, perineal pain, dysuria, and sterile pyuria. One case series noted that none of the patients presented with respiratory symptoms, and only one patient had a history of TB. Other characteristics that can be found include an increased frequency of urination, nocturia and hematuria. Physical examination focuses on finding abnormalities of the internal genital organs. Digital rectal examination may reveal an increase in prostate volume, elastic consistency, hardness, or nodularity.[15,17] It can be seen that the patient's clinical manifestations are not pathognomonic. Thus, diagnosis and management require a multidisciplinary team.

The patient, in this case, experienced a weight loss of 8 kg in the last one month, symptoms of prostate obstruction in the form of LUTS, and recurrent UTI for the last one year without clinical resolution. Non-specific constitutional symptoms of TB such as fever, weight loss, or night sweats are uncommon. If found, it indicates concomitant TB outside the urogenital tract, such as pulmonary TB. Kuchalvenya et al stated that the risk factors for UGTB include recurrent UTI that is resistant to standard therapy and UTI with persistent dysuria. Supporting statistics show the total prevalence of UGTB among UTI patients with poor antibacterial therapy results is 25.8%. Comorbid UTI was diagnosed in 65.1% of the UGTB.[3,6] The most common condition that masked the diagnosis of PTB was chronic prostatitis with recurrent UTI. Therefore, a thorough history and a high index of suspicion are important aspects of early detection. Chronic prostatitis with LUTS symptoms and recurrent UTIs refractory to standard antibiotics should raise suspicion of PTB, especially in TB endemic areas such as Indonesia.

On investigations, laboratory findings are less specific. Urinalysis and urine culture may show normal results due to the low excretion of *M.tb* in the urine. Examination of urine with *Ziehl Neelsen* (ZN) staining for acid-resistant bacteria has high specificity but low sensitivity of 50% for UGTB diagnosis. The culture of urine samples for detection of *M.tb* is positive in only 30–40% of cases. Thus, negative culture reports should be followed by *polymerase chain reaction* (PCR) studies. The advantages of PCR are that it can give faster results (within 24–48 hours) and only requires finding a few bacilli for detection. This examination has a sensitivity of 94.3% and a specificity of 85.7%.[15,18] However, the shortcomings of PCR are limited availability and high cost, thus it is not routinely used in health centers in Indonesia. Meanwhile, *prostate-specific antigen* (PSA) levels varied from normal (<4.0 ng/ml) to elevated. If the PSA level is elevated, the diagnosis of prostate cancer cannot be ruled out.[7,8,15,18]

Important imaging diagnostic modalities for PTB include X-rays, ultrasonography (USG), especially trans-urethral ultrasonography (TRUS), computed tomography scan (CT scan), and magnetic resonance imaging (MRI). The chest X-ray is one of the crucial initial investigations because a patient with PTB can also have active pulmonary TB simultaneously, as in this patient. Ultrasound images at early stage PTB may not show changes. Prostate TRUS examination can show the feature of an enlarged irregular glandular area with a solitary hypoechoic zone (rare) or multiple irregular zones of varying size.[15,18] TB lesions are typically located in the periphery and lateral lobes of the prostate.[3]

Imaging examination can aid the diagnostic, but there are still possibilities of overlapping with other pathological lesions of the prostate. The clinical and supporting data above remain devoid of pathognomonic characteristics and may even mimic prostate malignancy or chronic prostatitis due to other pathogens.[18] Due to the unusual presentation, almost all cases of PTB were found to be incidental in biopsy specimens from TURP procedure.[15,17] Histopathological examination of PTB shows a typical caseous granuloma consisting of a collection of

epithelioid cells, macrophages, lymphocytes, plasma cells, Langhans giant cells, fibroblasts with collagen, and characteristics of central caseous necrosis.[6,17,18]

The standard anti-tuberculosis drug (ATD) regimen based on WHO recommendations remain the treatment of choice. The patient in this case report is newly diagnosed with pulmonary TB and PTB. The standard types of ATD in pulmonary TB are isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) regimens. The duration of ATD is given for six months with a regimen of 2(HRZE)/4(HR)$_3$. The administration doses are listed in Table 1 in the form of a fixed-dose combination (FDC). In UGTB, the duration of ATD in several studies is 6–12 months. This duration may be extended depending on clinical response, disease severity and immunodeficiency conditions. Certain studies even suggest a longer duration of ATD, namely for two years.[15]

The challenge of prostatitis therapy from various etiologies is that only a few antibacterial agents are distributed to the prostate tissue and reach adequate concentrations at the site of infection. These agents include fluoroquinolones, macrolides, tetracyclines and trimethoprim. Standard ATD therapy, in addition to rifampicin, has suboptimal concentrations in prostate tissue. A study suggested using ofloxacin because it has a wide range of antibacterial activity, including a bactericidal effect against *M.tb*, making it the optimal drug for PTB. Other reports suggest streptomycin and kanamycin should not be used for TB. The same study also recommended ofloxacin and levofloxacin as fluoroquinolones suitable for UGTB. Amoxicillin/clavulanate should be prescribed together with meropenem or imipenem because it potentiates anti-TB effects. The administration of amikacin, streptomycin, and kanamycin is contraindicated because it induces the transformation from TB inflammation to fibrosis.[3] However, there are no other data to support this claim, so further research is needed.

Some complications that can occur in PTB that are not handled properly are strictures, fistulas, infertility, and sexual dysfunction.[15]

Table 1. Dosage of FDC ATD Category 1 (2 (HRZE)/ 4 (HR) 3)[19]

Weight	Daily intensive phase HRZE (150/75/400/275) for 56 days	Continuation phase 3 times a week RH (150/75) for 16 weeks
30–37 kg	2 tablet 4FDC	2 tablet 2FDC
38–54 kg	3 tablet 4FDC	3 tablet 2FDC
55–70 kg	4 tablet 4FDC	4 tablet 2FDC
≥71 kg	5 tablet 4FDC	5 tablet 2FDC

Note: FDC=fixed-dose combination

CONCLUSION

Tuberculosis contributes to the top ten causes of death worldwide. Prostate tuberculosis is very rare with limited epidemiological data. *Mycobacterium tuberculosis* infection of the prostate can occur in the hematogenous, lymphatic, or direct route. Non-specific clinical features and supporting modalities of PTB. A multidisciplinary approach is needed in the diagnosis and management of TB. A thorough history and a high index of suspicion are important aspects. The diagnosis of PTB should be considered in patients with both lower urinary tract symptoms and recurrent urinary tract infections (UTIs) refractory to standard therapy in TB endemic areas. The majority of PTB diagnoses were confirmed by histopathology incidentally after the TURP procedure. The standard anti-tuberculosis drug (ATD) regimen based on World Health Organization (WHO) recommendations remains the treatment of choice. The duration of ATD can be extended due to suboptimal concentrations of the prostate tissue. Complications that can occur include strictures, fistulas, infertility, and sexual dysfunction.

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Pediatric Hemoptysis

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Abstract
Hemoptysis or expectoration of blood is one of the respiratory symptoms in children, hemoptysis is hard to detect because it is often swallowed. The common causes of hemoptysis in adults include bronchiectasis, tuberculosis, pulmonary mycosis, and lung cancer. On the other hand, hemoptysis in children is often caused by tracheobronchitis, pneumonia, bronchiectasis in cystic fibrosis, and foreign body aspiration. Bleeding of the pulmonary artery or bronchial artery is the cause of hemoptysis. Upper airway examination is important to rule out epistaxis as the cause of hemoptysis. The primary objectives of hemoptysis management are asphyxia management, bleeding cessation, and treatment of the underlying disease. When all other treatments fail to stop the bleeding, surgery is recommended. ***(J Respirol Indones 2021; 41(3): 214–20)***
Keywords: *hemoptysis in children, pediatric hemoptysis*

Hemoptisis pada Anak

Abstrak
Batuk darah atau hemoptisis merupakan salah satu gejala penyakit paru. Pada anak, batuk darah sulit terdeteksi karena pada umumnya anak sering menelan dahak. Penyebab tersering batuk darah pada pasien dewasa adalah bronkiektasis, tuberkulosis, infeksi jamur di paru, dan kanker paru. Sedangkan pada anak, penyebab tersering batuk darah antara lain, trakeobronkitis, pneumonia, bronkiektasis pada fibrosis kistik dan aspirasi benda asing. Hemoptisis dapat terjadi akibat pecahnya arteri pulmoner atau arteri bronkial. Pemeriksaan saluran napas atas penting untuk menyingkirkan sumber perdarahan akibat epistaksis. Tujuan utama tatalaksana hemoptisis adalah memastikan jalan napas tetap terbuka untuk mencegah asfiksia, menghentikan perdarahan, dan menatalaksana penyakit dasarnya. Pembedahan merupakan pertimbangan terakhir jika tatalaksana lainnya tidak dapat menghentikan perdarahan. ***(J Respirol Indones 2021; 41(3): 214–20)***
Kata kunci: *batuk darah pada anak, hemoptisis pada anak*

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INTRODUCTION

Coughing up blood or hemoptysis is one of the symptoms of pulmonary disease. In children, the incidence of hemoptysis is difficult to estimate because, in general, children often swallow phlegm. Acute idiopathic pulmonary hemorrhage (AIPH) is the discovery of blood in the airway of a child aged ≤1 year without predisposition to other diseases and respiratory distress that can cause respiratory failure.[1] The etiology of hemoptysis in pediatric patients is different from that in adult patients. In adult patients, tuberculosis is one of the most common diseases, causing symptoms of coughing up blood. However, tuberculosis in pediatric patients is a systemic disease and rarely causes blood coughing. Therefore, information about coughing blood in pediatric patients is also important to be known by a pulmonary doctor. This library review covers the definition, etiology, pathophysiology, diagnosis, and management of hemoptysis in children.

DEFINITION

Hemoptysis or coughing blood is the expectoration of blood coming from the lower airway.[1] Another source specifically mentions that hemoptysis is the expectorant blood or bloody phlegm derived from the airways under the vocal cords.[2] Hemoptysis should be distinguished by hematemesis (vomiting blood) and epistaxis. Table 1 illustrates the differences between hemoptysis and hematemesis.[3] Department of Pulmonology and Respiratory Medicine Faculty of Medicine, Universitas Indonesia – Persahabatan Hospital using massive hemoptysis criteria as follows:[2]

a. Coughing up blood ≥600 ml/24 hours and does not stop during observation.
b. Coughing up blood ≥250 ml but <600 ml/24 hours and laboratory tests show hemoglobin <10 g% while coughing up blood continues.
c. Coughing up blood ≥250 ml but <600 ml/24 hours hemoglobin levels 10 gr%, and observation for 48 hours, with conservative treatment, this process has not stopped.

No consensus classifies the degree of hemoptysis in children. The American Thoracic Society distinguishes hemoptysis in patients with cystic fibrosis into scant (<5 ml), mild-to-moderate hemoptysis (5–240 ml and massive hemoptysis (>240 ml).[3] Department of pulmonology and respiratory medicine, Faculty of Medicine, Universitas Indonesia – Persahabatan Hospital applied the following criteria for massive hemoptysis in adults, which is the expectoration of blood: at least 600 mL in 24 hours, or 250–600 mL in 24 hours with hemoglobin (Hb) <10 gr/dL and still ongoing during observation, or 250–600 mL in 24 hours with Hb >10 gr/dL and still ongoing in 48 hours.[4]

Table 1. The Differences in Hemoptysis and Hematemesis

No	Hemoptysis	Hematemesis
Historical		
1	No complaints of nausea and vomiting	Nausea and vomiting
2	There is a history of pulmonary disease	There is a history of gastrointestinal disease
3	Asphyxia	Rarely asphyxia
Phlegm examination		
1	Foaming	Rarely foaming
2	Liquid or blood clot	Like coffee powder
3	Bright red or pink	Brownish to blackish
Laboratory		
1	Alkaline pH	Acidic pH
2	A mixture of macrophages and neutrophils	Mixed food

ETIOLOGY

The most common causes of hemoptysis in adult patients are bronchiectasis, tuberculosis, fungal infections in the lungs, and lung cancer.[5,6] Research at Persahabatan Hospital showed data from 323 hemoptysis patients admitted to the emergency room of Persahabatan Hospital caused by tuberculosis (64.4%), bronchiectasis (16.7%), and lung cancer (3.4%). Other research conducted at The Persahabatan Hospital also showed that tuberculosis (75.6%) is the main cause of inpatient hemoptysis and IGD, followed by the previous history of pulmonary tuberculosis (16.7%).[7] In children, hemoptysis can be caused by various diseases, such as the following.

a. Pulmonary Disease
   1. Tuberculosis
   2. Pneumonia

3. Aspergillosis
4. A parasitic infection (*P. Westermani*)
5. Bronchiectasis
6. Cystic fibrosis
7. Pulmonary abscess
8. Tumors (Adenoma, carcinoids, hemangiomas, metastases in the lungs, immunoblastic sarcoma, Kaposi sarcoma)
9. Aspirations of foreign bodies
10. Diffuse Alveolar Damage (DAD)
11. Acute Respiratory Distress Syndrome (ARDS)
12. Tracheobronchitis
13. Contusion or trauma
14. Bronchogenic cysts

b. Cardiovascular Disease
1. Heart failure
2. Eisenmenger syndrome
3. Mitral stenosis
4. Veno-occlusion disease
5. Venous artery malformations
6. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)
7. Pulmonary embolism
8. Pulmonary hypertension

c. Immune System Disorders
1. Purpura Henoch-Schonlen
2. Idiopathic Pulmonary Hemosiderosis
3. Goodpasture syndrome
4. Granulomatosis Wegener
5. Systemic Lupus Erythematosus
6. Polyarteritis nodosa
7. Heiner syndrome
8. Pulmonary alveolar proteinosis
9. Sclerosis tuberous
10. lymphangiomyomatosis or lymphangioleiomyomatosis

d. Other Conditions
1. Gastroesophageal reflux
2. Hyperammonemia
3. Kernicterus
4. Intracranial bleeding (in premature infants)
5. Poisoning
6. Diffuse alveolar injury (Smoke inhalation)
7. Post spinal cord transplant
8. Coagulation disorders

Among these diseases, the most common causes of hemoptysis in children are tracheobronchitis and pneumonia.[5] Foreign bodies are also one of the most common causes.[8] Aspiration of foreign bodies often occurs in children under 3 years of age. It is generally not immediately detected until symptoms such as chronic cough, pneumonia or hemoptysis occur.[10] In addition, tracheostomy-related bleeding is also a common cause.[9]

PATHOPHYSIOLOGY

The lungs are fertilized by two arteries, the pulmonary artery and the bronchial artery. Pulmonary arteries make up 99% of the lungs and play a role in gas exchange. The bronchial artery provides nutrients for the airways, mediastinum glands, nerves, visceral pleura, esophagus, vasa vasorum of the aorta, pulmonary arteries, and pulmonary veins.[6,7]

Hemoptysis can occur due to bleeding of the pulmonary artery or bronchial artery. Pulmonary arteries have a large volume with low pressure. The branched pulmonary artery follows the bronchi to the terminal bronchi. This branching of the pulmonary artery then branches out to form a capillary pad (anastomosis) that envelops the alveolus before returning to the left atrium through the pulmonary vein. The bronchial artery has a smaller volume but has high systemic pressure. This artery is an aortic branch or intercostal artery. Bleeding coming from the pulmonary artery is usually slow due to its lower pressure. Heavy bleeding usually originates from the bronchial arteries due to high hydrostatic pressure, increasing the rate of bleeding.[9]

The basic disease that causes hemoptysis can be estimated by knowing the source of the bleeding. Alveolar bleeding is usually caused by an autoimmune disease or post-spinal cord transplant. Bleeding in the airways can occur due to airway hemangioma, pulmonary artery-venous malformations (hereditary hemorrhagic telangiectasia), and collateral bronchial arteries that appear in patients with chronic infections, especially

cystic fibrosis. Pulmonary bleeding can occur locally as well as diffuse. Chronic infections or inflammation are common causes of hemorrhagic voices in isolated bronchial lesions.[1]

Massive hemoptysis usually occurs due to bleeding in the bronchial arteries.[7] Massive hemoptysis is also biased due to erosion caused by chronic inflammation of the airways located adjacent to the bronchial arteries. Blood derived from this erosion is generally bright red and spurts out. This is due to the dilation of the bronchial artery and systemic artery pressure. Within 48–72 hours of bleeding, alveolar macrophages convert iron inside erythrocytes into hemosiderin. Macrophages containing hemosiderin are in the alveolus for several weeks until finally eliminated from the alveolus.[1]

It can be used to distinguish between acute or chronic bleeding. Pulmonary bleeding is also often followed by an increase in neutrophils and other pro-inflammatory mediators. In cases of recurrent pulmonary bleeding or chronic bleeding, pulmonary fibrosis is one of the most commonly found abnormalities.[1]

Chronic infections and inflammation that occur in children with bronchiectasis or chronic fibrosis can cause airway damage, encourage the formation of new blood vessels (neovascularization), and cause dilation and fragility of the walls of the bronchial arteries. These fragile blood vessels form close to the mucosa where the inflammation occurs, making it easy to bleed from coughing or infections.[8]

When the child coughs strongly, coughing up blood can occur due to mechanical trauma of the airways. However, coughing up blood like this is generally mild and self-healing. Airway injury can also occur during the suction of tracheostomy pipes or endotracheal pipes.[8] In cystic fibrosis patients, endobronchial bleeding generally indicates the erosion of the secondary airway wall due to infection.[1] In children with pulmonary hypertension, hemoptysis occurs due to the rupture of pulmonary blood vessels. However, this is rare.[9]

DIAGNOSIS

Diagnosis of pulmonary bleeding is established if blood or hemosiderin is found in the lungs. Anamnesis and physical examinations are important for directing the causes of bleeding in the lungs, extra lungs (gastrointestinal tract and upper airway), or coagulation disorders. One of the most common complaints in children of greater age is a feeling of “bubbling” on the chest wall.[1]

Other symptoms that can be found in children who have experienced a lot of blood volume loss are cyanosis, respiratory failure, and shock. Laboratory examinations are conducted to evaluate whether or not coagulation disorders exist. In finding the source of bleeding, an upper airway examination is important to rule out the possibility of bleeding due to epistaxis.[5] Nasopharyngoscopy can help to perform such examinations. The examination modalities that can be used to evaluate the source of bleeding and basic diseases include thoracic photos, chest angiogram CT, bronchoscopy, and echocardiography. Biomarkers can be examined to rule out possible causes of autoimmune diseases.[5]

MANAGEMENT

The important thing to note in the treatment of hemoptysis is the amount of blood excreted and the primary disease that causes hemoptysis. The main purpose of hemoptysis management is to ensure that the airway remains open to prevent asphyxia, stop bleeding, and manage primary diseases.[10] Most cases do not require intervention because hemoptysis in children usually heals itself spontaneously. Calming children and families are one of the earliest things that can be done when hemoptysis occurs. Mild hemoptysis can be treated according to its symptoms, such as the administration of hemostatic agents, as well as overcoming its basic diseases and administration of antibiotics suitable for basic infectious diseases, antibiotics and corticosteroids in cystic fibrosis patients, anti-tuberculosis drugs (Anti-TB) for children with tuberculosis, and modifying suction

techniques in children with hemoptysis related to tracheostomy.[11]

Massive hemoptysis can progress to acute respiratory distress syndrome (ARDS) quickly. In children with massive hemoptysis can be carried out intubation and mechanical ventilation. Mechanical ventilation with PEEP (Positive End-Expiratory Pressure) also serves as a tamponade for active bleeding in addition to improving oxygenation. Other procedures for acute periods include oxygen administration, blood transfusions, and resuscitation fluid administration.[1,10]

Transfusions are administered in the case of hypotension or when the hematocrit decreases significantly. Antitussive drugs should not be administered. The child is laid on the side of the sick lung to prevent blood from filling the healthy side of the lung. In cystic fibrosis patients, vitamin K should be administered in patients with prothrombin disorders (PT).[12]

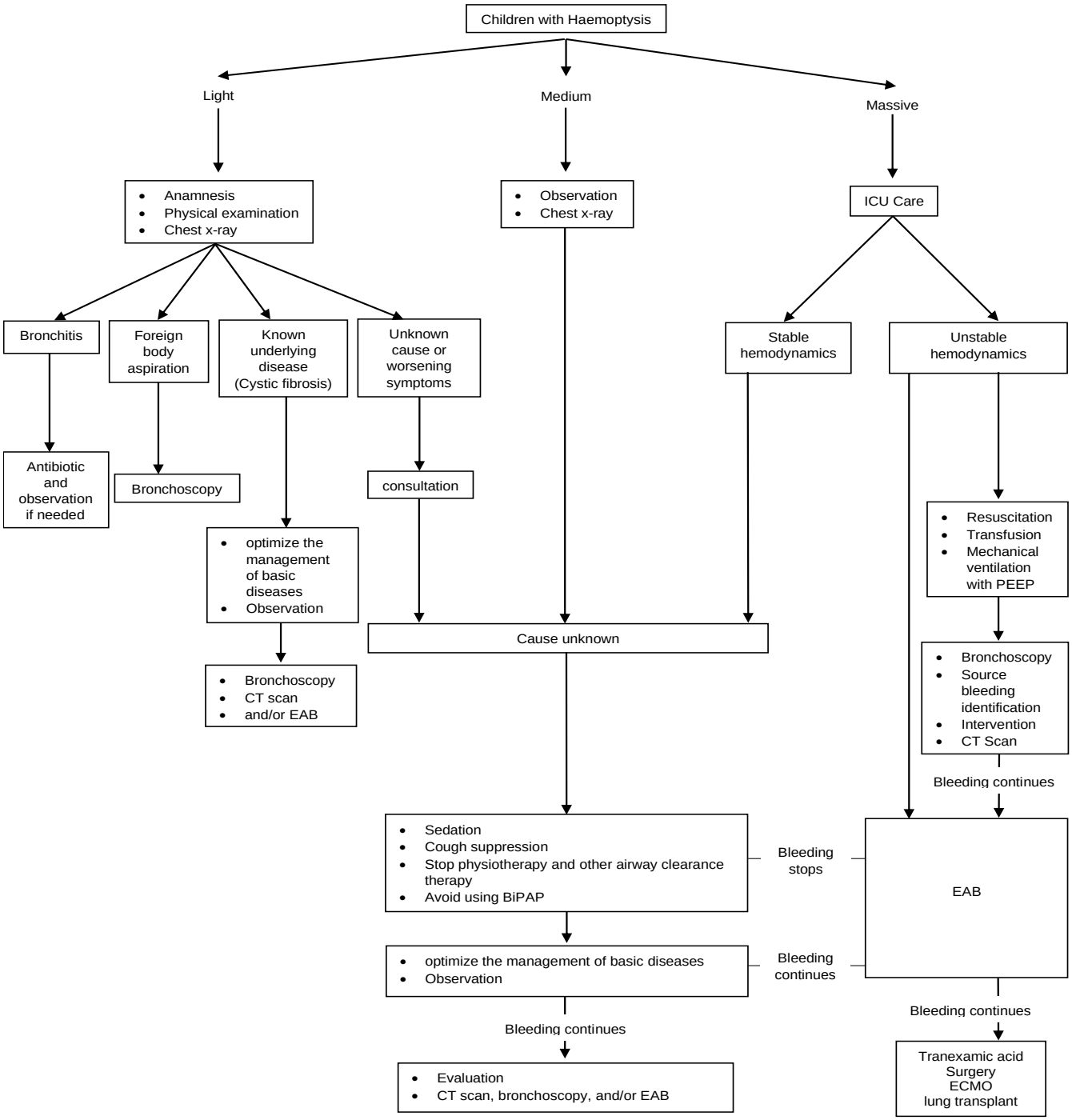

Figure 1. Hemoptysis Management Flow in Children.

Anti-coagulation drugs should be discontinued. Ticarcillin, salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs) can interfere with platelet function and aggravate hemoptysis.[12] The efficacy of anticoagulation agents such as tranexamic acid in treating hemoptysis is still unknown. However, the results of a new study found that the use of inhaled tranexamic acid may help stop non-massive hemoptysis.[14]

Bronchoscopy is a gold standard for seeing the location of the bleeding directly. However, in practice, bronchoscopy rarely shows the source of bleeding.[4] Other roles of bronchoscopy include removing foreign differences, taking biopsy specimens, and taking specimens for examination of microorganism cultures. Rigid bronchoscopy is better than flexible bronchoscopy because rigid bronchoscopy can be performed, such as administering vasoconstriction agents and endobronchial tamponades without interfering with ventilation.[10]

Meanwhile, the advantage of flexible bronchoscopy is that it can reach deeper branches of the bronchi compared to rigid bronchoscopy. Endobronchial tamponade techniques can be performed using Fogarty balloon catheters, double-lumen bronchus-blocking catheters, and modification of J angiography wire measuring 0.035 inches, or with pulmonary artery catheter balloons. Topical vasoconstrictors can be administered, such as oxymetazoline or epinephrine (1:20,000), saline 0.9% cold, or fibrinogen/thrombin (Botropase).[10]

Laser neodymium-yttrium-aluminum-garnet (Nd-YAG), laser CO2, and argon plasma coagulation (APC) can also be done to stop bleeding. However, the data on laser use in hemoptysis treatment in children is still limited. Angiography with or without embolization and surgery is performed in patients with vascular disorders if intervention with bronchoscopy is unsuccessful.[1]

Embolization of the bronchial artery is useful to control persistent hemoptysis in cystic fibrosis patients. The American Thoracic Society recommends that cystic fibrosis patients experiencing massive and clinically unstable hemoptysis should be Embolization Artery Bronchial (EAB).[12]

In cystic fibrosis patients, bronchoscopy should not be performed first in patients with massive hemoptysis if the EAB has not been performed. Bronchial arteriography helps determine the location of the bleeding and becomes a map of the direction leading to the location of bleeding. When performing angiography and embolization, the arteries that supply blood to the spinal cord need to be considered. The anterior spinal artery is the main artery that supplies the spinal cord. The arteries receive their blood supply from the same truncus that supplies the superior intercostal arterial branching and the right bronchial artery. The left bronchial artery rarely contributes to the anterior spinal artery. Therefore, when embolizing, especially the area of the right bronchial artery, it is necessary to pay attention not to disturb the anterior spinal artery.[15]

Embolization can be performed with a gelatin sponge that absorbs, rolled steel or platinum, or polyvinyl alcohol particles. The most effective treatment for overcoming massive hemoptysis, whether originating from the bronchial or non-bronchial circulation, is pulmonary artery embolization. The level of EAB in stopping bleeding is 73–99%, with a repeated incidence of hemoptysis 10–55% in monitoring for 46 months. Complications of EAB include neurological damage due to embolization of the spinal artery and recurrent hemoptysis.[6]

Lobectomy in children with hemoptysis is avoided to maintain the pulmonary functions of the child.[1] Surgery in patients with massive hemoptysis is performed as a last resort if other procedures do not manage to overcome the cough of blood.[12]

CONCLUSIONS

Hemoptysis is rare in children. However, massive hemoptysis can lead to death in children. Infections, particularly lower airway infections, aspiration of foreign bodies, and bronchiectasis,

particularly bronchiectasis in cystic fibrosis, are the most common causes of hemoptysis in children. Hemoptysis is usually mild and can heal itself, but in massive hemoptysis, the main principle is to prevent asphyxia and manage the primary disease. Bronchoscopy and EAB can be performed to stop bleeding. Surgery is performed if other procedures are unsuccessful.

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