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Winn WC, Allen SD, Janda WM, Koneman EW, Procop GW, Schreckenberger PC, et al. Koneman’s color atlas and textbook of diagnostic microbiology. 5th eds. Philadelphia: A Wolters Kluwer Company; 2006. p.1065-92.

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Tesis

Rassuna V. Pengamatan hasil akhir pengobatan tuberkulosis paru BTA negatif kasus baru di RS Persahabatan. Tesis Departemen Pulmonologi dan Ilmu Kedokteran Respirasi FKUI. Jakarta; 2008.

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TABLE OF CONTENT

Original Article

Lung Function Impairment Among Firefighter After Wildfire in Riau, Sumatra

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Abstract

Background: *The 2015 forest fire disaster affected almost 2.6 million hectares of land in Indonesia, and Riau was among the worst. Firefighters were the first responders to deal with the disaster, but a little was known about the influence of extinguishing forest fire activities with their health. This study aimed to evaluate respiratory symptoms and lung function among firefighters 6 months after forest fire exposure.*
Methods: *Interviews were conducted regarding sociodemographic factors, respiratory symptoms, and history of forest fire exposure during the disaster. Spirometry and chest X-ray were also carried out with standard techniques. Statistical analysis was performed based on the existing data. Ninety firefighters participated in this study, most were male with mean age of 33 years old. About 66% were smoker, had been working as firefighters for 2 to 10 years, and had been on extinguishing forest fire duty around 2–5 hours/day during the disaster.*
Results: *All firefighters reported respiratory symptoms after 3 months. Pulmonary function was abnormal in 50% of subjects with mild restrictive characteristic. The analysis showed that body mass index (BMI) and duration of exposure had a significant correlation with pulmonary function abnormality.*
Conclusion: *Pulmonary function was found abnormal in most subjects 6 months after forest fire exposure in Riau.* ***(J Respirol Indones 2021; 41(4): 221–7)***
Keywords: *Firefighter, forest fire, Indonesia, lung function.*

Gangguan Fungsi Paru Para Pemadam Kebakaran Setelah Bencana Kebakaran Hutan di Riau Sumatera

Abstrak

Latar Belakang: *Bencana kebakaran hutan tahun 2015 mencakup hampir 2.6 juta hektar lahan di Indonesia, dan Riau merupakan salah satu daerah terburuk. Pemadam kebakaran merupakan profesi utama yang menangani bencana tersebut, namun sedikit diketahui mengenai pengaruh kegiatan pemadaman kebakaran hutan dengan kesehatan mereka. Penelitian ini bertujuan menilai gejala respirasi dan fungsi paru 6 bulan pascakebakaran hutan.*
Metode: *Wawancara dilakukan untuk mengetahui faktor sosiodemografis, keluhan respirasi dan riwayat pajanan selama bencana kebakaran hutan. Spirometri dan foto toraks juga dilakukan dengan teknik standar. Analisis statistik dilakukan menggunakan data yang ada. Sembilan puluh petugas pemadam kebakaran turut serta dalam penelitian ini, sebagian besar laki-laki dengan rerata usia 33 tahun. Sekitar 66% subjek adalah perokok, telah bekerja sebagai pemadam kebakaran antara 2-10 tahun, dan bertugas memadamkan kebakaran hutan 2-5 jam/hari selama bencana.*
Hasil: *Semua pemadam kebakaran melaporkan keluhan respirasi setelah 3 bulan. Ditemukan penurunan fungsi paru pada 50% subjek penelitian dengan karakteristik restriksi ringan. Analisis statistik menunjukkan bahwa indeks massa tubuh (IMT) dan durasi pajanan kebakaran hutan memiliki hubungan bermakna dengan kelainan fungsi paru.*
Kesimpulan: *Ditemukan penuruan fungsi paru pada sebagian besar subjek 6 bulan setelah kebakaran hutan di Riau.* ***(J Respirol Indones 2021; 41(4): 221–7)***
Kata Kunci: *Pemadam kebakaran, kebakaran hutan, Indonesia, fungsi paru.*

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INTRODUCTION

Forest fires/wildfires in Indonesia have become a regional problem especially in Southeast Asia. Almost every year forests in Indonesia are affected by fire, particularly in the long dry season. In 1997, forest fires were very severe, estimated to hit an area of up to 300,000 hectares. In June to December 2015, forest fires in Indonesia were greater as it was estimated that 2.6 million hectares of land consisting of peatlands, palm oil plantation and tropical forests were burned. Riau, Sumatra was among the worst area affected by wildfires in 2015.[1] According to the Meteorological, Climatology and Geophysics Agency report, in September 2015, Tera and Aqua satellites monitored 390 hotspots on Sumatra Island and 14 of them were in Riau Province. During wildfires, one of the institutions authorized to extinguish the fire was the firefighter department.[2]

Firefighter is a very high-risk occupation with potential direct occupational hazard and accidents, also sometimes with fatal consequences such as permanent disability or death.[3] In addition, long term health effect of smoke exposure could directly increase the risk of respiratory diseases, cardiovascular diseases or cancer. During forest fires, firefighters have increased risks of noxious gas and haze exposure and have the potential to increase the health problems risks, including in short-term, medium-term and long-term period.[3]

This study aimed to assess mid-term effect of lung function among firefighters 6 months after the occurrence of wildfires on 2015 in Riau, Sumatra.

METHOD

Cross sectional study was conducted at Department of Firefighter in Pekanbaru, Riau on May 2016, six months after wildfires in Riau, Sumatra. Accessible population was all firefighters who were still active in Pekanbaru, had served actively in extinguishing fires and were exposed to forest fires smokes during June to December 2015 in Riau province. Sampling was carried out by consecutive sampling in which every affordable population that met the study criteria was included as a subject to meet the required sample size after signing the informed consent.

Indonesian version of American Thoracic Society (ATS) respiratory questionnaire was administered to measure pulmonary symptoms that consisted of cough, productive cough with sputum, difficulty in breathing or dyspnea, and wheezing.[4] We interviewed each subject over the last 3 months period. Smoking status was defined as “smoker “if subjects smoked 100 cigarettes during his or her lifetime; and ‘Non-smoker’ if never smoked or smoked less than 100 cigarettes during lifetime. Brinkman index (BI) was measured by the number of cigarettes smoked per day multiplied by the number of years of smoking and classified as mild if BI 1–200; moderate if 201–600, and severe if >600.

Duration of working as firefighter was defined as the duration of duty since registered as a firefighter and recorded in year. We measured duration of forest fire exposure based on the log book in Department of Firefighter Pekanbaru Riau during the disaster in June to December 2015 which recorded daily duty activities in forest fire. Exposure time was measured by total hours on duty divided by number of days on duty during the disaster period and categorized as follows: <2 hours/day; 2–5 hours/day; 5–8 hours/day and >8 hours/day.

Protective equipment used during wildfire smoke exposure were also obtained by asking the face mask usage during interview and classified as routine if subjects wear it more than 4 days in a week of working days, otherwise it was classified as rarely. Body Mass Index (BMI) was measured by dividing the weight (kg) per square meter of height and classify as obese if BMI >25; overweight if BMI 23–24.9; normoweight if BMI 18.5–22.9 and underweight if BMI <18.5.

Pulmonary function test of forced vital capacity (FVC) maneuvers was measured by spiroanalyzer ST 95, Fukuda Sangyo Japan in compliance with American Thoracic Society standard procedure recommendation.[5] The best of at least three technically appropriate measurements for forced expiratory volume in one second (FEV_1), FVC, and FEV_1/FVC were recorded. The results were classified

as restrictive type if FVC <80% of the predicted values; obstructive type if FEV_1 <80% of the predicted values; and combined type if both criteria were fulfilled. The severity of pulmonary function abnormalities was classified as mild (70–79%), moderate (60–69%), and severe (<60%).

Chest X-ray postero-anterior view (CXR-P/A) was performed to screen lung abnormality and examined by radiologist. The CXR was categorized as abnormal if there was an abnormal finding in lung and/or the thoracic cage structures.

Data were processed and analyzed using the Statistical Package for Social Sciences (SPSS) program 17. Descriptive analysis were shown using tables describing the frequency and percentage for categorical data as well as median and distribution values for numerical data. Statistical analysis was carried out appropriately based on the data characteristics with *P*<0.05 (two-tailed) considered as significant and a Power of 95%.

RESULTS

This study recruited 90 firefighters with the following distribution of subjects' characteristics: the majority of the subjects were male (96.7%), with median age of 33 years old, (ranged from 21 to 48 years old). About 66% of subjects were smoker and 51% used personal protective equipment (PPE) routinely but mostly only ordinary face masks, as seen in Table 1. We measured the duration of exposure based on the log book and most subjects worked for 2-5 hours a day in the frontline. In addition, there were less than 10 small forest fire spots and less than 10 household fires in Pekanbaru Riau between January and May 2016.

After 6 months off duty in wildfires in Riau, all firefighters reported respiratory symptoms during the last 3 months period. The most common respiratory symptoms reported were productive cough of 33.3% (30 subjects), followed by dyspnea 32.2% (29 subjects), wheezing 20% (18 subjects) and cough 14.4% (13 subjects). Almost all subjects had normal CXR images (89 subjects or 98.9%), as shown in Table 2.

Table 1. Characteristics of firefighters in Pekanbaru Riau (N=90)

Characteristics	N	%
Age		
<30 years old	32	35,4
30–39 years old	49	53,8
40–49 years old	9	10,8
Sex		
Male	87	96,6
Female	3	3,4
Education		
High school	66	73,3
College	24	26,7
Personal protective device usage		
Routine	46	51,1
Rarely	44	48,9
Body Mass Index		
Underweight	8	8,9
Normoweight	29	32,2
Overweight	14	15,6
Obesity	39	43,3
Duration of extinguishing forest fire during the disaster		
<2 hours/day	6	6,7
2–5 hours/day	53	58,9
5–8 hours/day	20	22.1
>8 hours/day	11	12,2
Duration of work as firefighter		
<5 years	18	20,0
5–10 years	61	67,7
10–15 years	5	5,5
>15 years	6	6,2
Smoking status		
Non smoker	31	34,4
Smoker	59	66,2
Brinkman index		
Mild	24	26,7
Moderate	30	33,8
Severe	5	5,4

Based on spirometry results, the pulmonary function of subjects 6 months after the wildfires in Riau were found abnormal in 50% (45 subjects) with mostly mild restrictive characteristic in 41.5% (37 subjects). Another spirometry parameters found were: vital capacity (VC) of 3922.36±622.30 ml (mean±SD), FVC of 3207.97±613.52 ml (mean±SD) and FEV_1 of 3163.21±3304.3 ml (mean±SD).

The correlation of sociodemographic characteristics with pulmonary function in firefighters in Pekanbaru can be observed in Table 3. The analysis pointed that statistically, sociodemographic factors of gender, age, education, PPE usage, smoking status did not have significant differences (*P* >0.05), while BMI and duration of exposure showed a significant correlation with pulmonary function abnormality, as seen in Table 3.

Table 2. The correlation of sociodemographic characteristics with pulmonary function test abnormality

Characteristics	Normal	Restrictive	Obstructive	Mixed pattern	*P*
Age					
<32 years old	15	18	2	2	0.523
≥32 years old	29	21	2	1	
Sex					
Male	43	37	4	3	0.853
Female	1	2	0	0	
Educational level					
High school	36	32	4	2	0.713
College	8	7	0	1	
PPE usage					
Routine	26	17	1	2	0.336
Rarely	18	22	3	1	
Smoking status					
Smoker	27	27	3	2	0.929
Non smoker	10	7	1	1	
Ex-smoker	7	5	0	0	
BMI					
Underweight	2	4	0	2	[a]0.035
Normoweight	17	9	2	1	
Overweight	8	6	0	0	
Obese	17	20	2	0	
forest fire exposure					
<2 hours/day	4	0	0	2	[a]0.006
2-5 hours/day	26	24	2	1	
5-8 hours/day	11	7	2	0	
>8 hours/day	7	4	0	0	

Note: [a]Kruskal Wallis test; BMI: body mass index; PPE: personal protective equipment

Table 3. Distribution of respiratory symptoms, CXR, and pulmonary function in firefighters in Riau (n=90)

Variables	N	%
Respiratory symptoms		
Cough	13	14.4
Productive cough	30	33.3
Dyspnea	29	32.2
Wheezing	18	20
No symptoms	0	0
Chest X-ray		
Normal	89	98.9
Abnormal	1	1.1
Spirometry		
Mild obstructive pattern	3	3.3
Restrictive	39	43.3
Mild restrictive pattern	37	94.9
Moderate restrictive pattern	2	5.1
Mixed	3	3.3
Normal	45	50

The analysis of the correlation between respiratory symptoms with pulmonary function in firefighters showed that subjects with cough (13 subjects) had restrictive pattern in 9 subjects (69.2%), subjects with productive cough (30 subjects) had obstructive pattern in 2 subjects, restrictive pattern in 12 subjects and mixed pattern in 1 subject. Subjects with symptoms of dyspnea (29 subjects) had spirometry result of obstructive pattern in 1 subject, restrictive pattern in 14 subjects and mixed pattern in 2 subjects. Meanwhile, subjects with wheezing (18 subjects) had obstructive type and mixed type result in 1 subject of each and restriction type in 6 subjects. In this study, there were no significant correlation between subjects' respiratory symptoms and pulmonary functions (*P*=0.582).

DISCUSSION

Firefighter is a job with very high occupational risk and the clinical outcomes could appear immediately/acute, mid-term or long term after the exposure. Firefighters in Riau Province were one of the very active units who contributed in extinguishing forest fires disaster in 2015. They also had the risk of being exposed to large amounts of forest fires haze compared to ordinary people. This study evaluated

mid-term respiratory effects of firefighters 6 months after wildfires.

All subjects recruited had reported respiratory symptoms during the past 3 months. The most common respiratory symptoms were productive cough (33.3%) followed by dyspnea (32.2%), wheezing (20%) and cough (14.4%). Our study was similar to Austin, et al. who discovered that both acute and chronic respiratory symptoms did occur after forest fires exposure in firefighters as stated that 76% of the subjects experienced respiratory symptoms i.e., cough, wheezing, and dyspnea; and 70% of them experienced at least one of the neurological symptoms such as vertigo, headaches, balance disorders, dizziness, and even loss of consciousness.[6] Gaughan, et al. in 2005 explained that acute respiratory symptoms often arose and experienced by firefighters due to exposure to smoke from forest fires. The symptoms could even be chronic in nature and lasted for years.[7]

Based on smoking habits, 66.2% of firefighters in Riau were smokers. A study conducted by Austin, et al. pointed out that firefighters who actively smoked or were exposed to cigarette smoke without proper protection would easily experience carbon monoxide (CO) intoxication and had more respiratory symptoms.[6] Adetona, et al. showed that more firefighters in their study were active smokers than non-smokers, but there were no significant differences in lung function impairment.[8] A possible explanation might be that cigarette smoking did induce lung function impairment after long period of time, but not in short term for exposure to less than 5 years. Smoking is still needed to be overcome since it causes the health risks not only for the respiratory system but also another system in the body as well.[8]

Of all the demographic characteristics in this study, it was found that BMI was significantly different ($P < 0.05$). The duration of being firefighters and age did not significantly correlate with lung function impairment in this study. This was likely due to 58.9% of the firefighters in our study were currently overweight or obese. This finding was in accordance with the pathophysiology that overweight subjects were more likely to have restrictive pattern[9] and in this study 43.3% of the subjects had restrictive pattern. Obesity problem should be the focus of these firefighters since it could induce other unhealthy morbidity, -such as diabetes and heart problem-, and reduce the working capacity in this highly, -fit and resilience-needed occupation.

In performing their duty to extinguish forest fires, firefighters in Riau had understood the importance of wearing PPE masks. This was proven by 95.6% of firefighters in Riau who had used masks, although they were still not in accordance with standard N95 mask. This was because the availability of the standard N95 masks was difficult, and some firefighters felt uncomfortable with the use of standard N95 masks on duty. Study by Austin, et al. stated that a better respiratory protection for firefighters was the N95 mask that was in accordance with the International Standards Organization (ISO) 2002 standard. Austin, et al. also explained that the improper use of respiratory protections which were not standard would not protect a person from the effects caused by fires, therefore, proper self-protections corresponding to the standards were needed for the firefighters.[6] More educations related to PPE usage were also needed in this study group.

The important finding of this study was a significant difference ($P <0.05$) between the duration of exposure during wildfires and lung function impairment in firefighters. Exposure duration was the length of time firefighters exposed to forest fires smoke or on duty extinguishing forest fire during June and December 2015. Based on the duration of exposure, on average the firefighters were exposed for more than 2 hours/day in 58.9% of subjects, more than 5 hours/day in 34.3% subjects and less than 2 hours/day in only 6.7 % of subjects. Austin, et al. found that the mean exposure time of firefighters in carrying out their duties in the event of a major catastrophic fire was around 8 hours.[6]

This occasion required proper self-protection to prevent any direct and indirect effects which could occur. Our study was similar to the explanation of the National De Santé Publique Du Quebec article which

stated that short-term exposure to several days of exposure could cause various respiratory symptoms from acute to chronic symptoms.[9] Ferguson, et al. described spirometry results in firefighters at three different times including before, during, and one day after the fires. The study found that FVC and FEV_1decreased.[10] Study in Korea also observed the similar result of which pulmonary function declined in firefighters compare with non-firefighters.[11] Lung function among firefighters also declined after prescribed burns in Australia. This study showed that the impairment of lung function could be detected even after 6 months post-exposure.[12]

Based on the CXR, only 1.1% have abnormalities with bronchovascular and infiltrates in the upper left lung field, while the other 98.9% were normal. Our study was dissimilar with studies in South Korea.[11] Almost all studies assessed radiological examinations after firefighters experienced chronic symptoms that required radiological examination, however, in our study almost all CXR results were normal since they were evaluated in all subjects including non-symptomatics subjects. Chest x-ray abnormalities could be found in acute diseases such as pneumonia, or in chronic diseases, so it takes a long time for firefighters to experience abnormalities in their CXR.

Based on the literature, increased levels of gas components and smoke particles from forest fires in the air were associated with increased respiratory symptoms, reduced lung function, increased acute exacerbation of bronchial asthma and chronic obstructive pulmonary disease (COPD), increased visits to emergency departments, increased hospitalization, and possibly even death.[13] The chemicals that have been observed in biomass smoke of forest fire include major inorganic gases, hydrocarbons, oxygenated hydrocarbons, trace metals and particulate matters. Wildland fire smoke could also contain persistent organic compounds such as dioxins and furans.[8] Based on analysis of $PM_{2.5}$ component in forest fires smoke in Borneo, the major components of $PM_{2.5}$ in peat smoke haze consisted of sulphur, biomass burning component (BC, K), and crustal components (Al, Fe, Si). Sulphur mainly comes from the peat as it is the earliest stage of transition from compressed plants to the coal formation. The characteristics of forest fires in Sumatra and Borneo were mostly from peat-land and different from forest fires outside Indonesia. Long term effects in humans related to the chemical composition of this type need to be evaluated in the future.[14]

Limitations of this study included the study design that was a cross-sectional study with consecutive sampling. This design was selected based on the consideration of funds, time and available facilities. Regarding the pulmonary function test, we did not have the baseline spirometry value of these firefighters since it was not a routine test during recruitment, so we did not understand the changes compared with the baseline. We recommend the screening of lung function impairment regulary in this highly susceptible group.

Pulmonary diseases due to inhalation of toxic substances usually begin as a disorder in the parenchyma related to the defects in oxygen diffusion capacity. This early abnormality can be detected using pulmonary diffusion capacity (DLCO) examination. Spirometry abnormalities could only be detected if the spectrum of the parenchymal or airway disorders is large enough. The assessment of lung function in this study was based on spirometry data only, nevertheless, the results were sufficient to reflect the pulmonary abnormalities which occurred in the firefighters even after 6 monthsdealing with 2015 wildfires. Further studies are urgently required to follow the long-term health effects after wildfires of this vulnerable firefighters to determine the nature of the pulmonary impairment and its effect on firefighters' wellbeing.

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CONCLUSION

Respiratory symptoms were commonly reported by firefighters in Riau 6 months after the 2015 wildfires (midterm effect) and this was in line with

lung function impairment obtained by spirometry in half of the subjects. Although most were mild impairments, it is important to follow up the respiratory function to better understand its nature and most importantly to support the firefighters' wellbeing in the future.

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The Differences in Urokinase Plasminogen Activator System in Lung Cancer Patients Before and After Chemotherapy

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Abstract

Background: *Lung cancer is still the leading cause of death for malignancies worldwide. Urokinase plasminogen activator (uPA), its soluble receptor (suPAR), and its inhibitor (PAI-1) play an important role in tumor invasion and metastasis. This study aimed to evaluate the differences in the urokinase plasminogen activator system (uPA, suPAR, and PAI-1) in lung cancer patients before and after chemotherapy.*

Methods: *This research was an observational analytical study with a cross-sectional design. The subjects were 30, consisting of 17 lung cancer patients before chemotherapy and 13 lung cancer patients after chemotherapy for 4 or 6 cycles. The levels of serum uPA, suPAR, and PAI-1 were measured by enzyme-linked immunosorbent assay (ELISA).*

Results: *In lung cancer patients before chemotherapy, there were no significant (P>0.05) differences in levels of serum uPA, suPAR, and PAI-1 between patients with stage III and IV. The highest serum uPA and suPAR levels were found in adenocarcinoma cell types and the highest serum PAI-1 level in adenoepidermoid cell types. After chemotherapy, serum suPAR and PAI-1 were significantly (P<0.05) decreased in lung cancer patients. However, there were no significant (P>0.05) differences in the levels of serum uPA, suPAR, and PAI-1 between patients with chemotherapy responses for stable and progressive diseases.*

Conclusion: *This study revealed that suPAR and PAI-1 levels were decreased in lung cancer patients who had received chemotherapy. This can occur due to decreased tumor cells activity.* ***(J Respirol Indones 2021; 41(4): 228–35)***

Keywords: *Lung cancer; Chemotherapy; uPA; suPAR; PAI-1*

Analisis Perbedaan Sistem Aktivator Plasminogen Urokinase pada Penderita Kanker Paru Sebelum dan Sesudah Kemoterapi

Abstrak

Latar Belakang: *Kanker paru masih menjadi penyebab utama kematian akibat keganasan di seluruh dunia. Aktivator plasminogen urokinase (uPA), reseptor terlarutnya (suPAR), dan inhibitornya (PAI-1) memainkan peran penting dalam invasi dan metastasis tumor. Penelitian ini bertujuan untuk mengevaluasi perbedaan sistem aktivator plasminogen urokinase (uPA, suPAR, dan PAI-1) pada pasien kanker paru sebelum dan sesudah menjalani kemoterapi.*

Metode: *Penelitian ini merupakan penelitian analitik observasional dengan rancangan cross-sectional. Subjek penelitian berjumlah 30 orang, terdiri dari 17 pasien kanker paru sebelum menjalani kemoterapi dan 13 pasien kanker paru setelah menjalani kemoterapi selama 4 atau 6 siklus. Kadar uPA serum, suPAR, dan PAI-1 diukur dengan enzyme-linked immunosorbent assay (ELISA).*

Hasil: *Pada pasien kanker paru sebelum menjalani kemoterapi, tidak terdapat perbedaan bermakna (P>0,05) kadar serum uPA, suPAR, dan PAI-1 antara pasien stadium III dan IV. Kadar uPA dan suPAR serum tertinggi ditemukan pada jenis sel adenokarsinoma dan kadar PAI-1 serum tertinggi pada jenis sel adenoepidermoid. Setelah mendapat kemoterapi, kadar suPAR dan PAI-1 serum menurun secara bermakna (P<0,05) pada pasien kanker paru. Namun, tidak ada perbedaan yang bermakna (P>0,05) pada tingkat serum uPA, suPAR, dan PAI-1 antara pasien dengan respons kemoterapi stabil dan progresif.*

Kesimpulan: *Hasil penelitian menunjukkan penurunan kadar suPAR dan PAI-1 pada pasien kanker paru yang menjalani kemoterapi. Hal ini dapat terjadi karena aktivitas sel tumor yang menurun.* ***(J Respirol Indones 2021; 41(4): 228–35)***

Kata kunci: *Kanker paru; Kemoterapi; uPA; suPAR; PAI-1*

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INTRODUCTION

According to the World Health Organization (WHO) data, lung cancer is the most frequent cancer worldwide. In 2020, there were an estimated 2.21 million new cases. The majority of cases occur in less developed countries. Lung cancer is also the leading cause of cancer mortality (1.8 million deaths).[1,2] Several biomarkers for lung cancer have been discovered in recent years, the most well-known of which are K-Ras, epithelial growth factor receptors, p53, p16, and Bcl-2. However, the outcomes are frequently contradictory.[3] In addition, there are no biomarkers that can evaluate the progress of lung cancer therapy so far. Therefore, further research is required to assess the progress of therapy and the prognosis of the disease.

The urokinase plasminogen activator (uPA) system consists of uPA serine protease, its receptors (uPAR or suPAR), and its inhibitor (PAI-1). These components have an important role in tumorigenesis, extracellular matrix degradation, angiogenesis, proliferation, migration, and adhesion of tumor cells. They are prognostic factors in various types of cancer. For example, high levels of uPA have a prognostic role in cancers of the breast, colon, esophagus, ovaries, and stomach. High levels of suPAR are associated with a poor prognosis in breast and colon cancers. In addition, PAI-1 levels correlate with survival in cancers of the kidneys, ovaries, and breast.[4–6]

The uPA and PAI-1 play an important role in tumor invasion and metastasis. They are new tumor biological factors validated based on a very high level of evidence (level I) related to their clinical use in breast cancer. The European Organization for Research and Treatment of Cancer (EORTC) has validated this prognostic data derived from an analysis of more than 8,000 breast cancer patients. In breast cancer, uPA and PAI-1 are predictors for distant metastases. Using a combination of these two components, uPA/PAI-1 (both low and high), is superior to using one. The uPA/PAI-1 can optimally differentiate between high-risk and low-risk patients. Recent observations indicate that high-risk patients who are determined with uPA/PAI-1 will benefit from adjuvant chemotherapy compared to those who only get standard chemotherapy.[5–7]

In lung cancer, increased levels of uPA or suPAR are positively correlated with gender, stage of the tumor, positive nodal status, metastasis, and recurrence of the disease. A study stated that uPA mRNA and uPA protein are predictive factors for disease-free and life expectancy.[8] However, the uPA system has not been widely studied in lung cancer. This study aimed to evaluate the differences in the uPA system in lung cancer patients before and after chemotherapy.

METHODS

This research was an observational analytical study with a cross-sectional design. Subjects were outpatient and inpatient pulmonary clinics patients at Dr. Saiful Anwar Hospital in Malang, Indonesia, in 2013. The consecutive sampling method was applied to meet 30 subjects. The subjects were divided into two groups, a group of lung cancer patients who had not received (before receiving) chemotherapy (n=17) and a group of lung cancer patients who had received (after receiving) chemotherapy for 4 or 6 cycles (n=13).

According to the Helsinki declaration, all protocols were performed and approved by the Institutional Ethics Committee of Faculty of Medicine, Universitas Brawijaya (No. 547/EC/KEPK/12/2013). Written informed consent was obtained from all the subjects for being included in this study.

Inclusion criteria were lung cancer patients aged 40-70 years, male or female, diagnosed with stage III-IV non-small cell lung cancer (NSCLC) who had not received chemotherapy and had received chemotherapy for 4 or 6 cycles, and patients with small cell lung cancer (SCLC) diagnosed in the limited or extensive stage of the disease. Exclusion criteria, on the other hand, were lung cancer patients who did not have malignant histological findings or lung cancer patients who had other comorbidities such as infection, diabetes mellitus, or cardiovascular disease.

Venous blood samples were taken to measure levels of serum uPA, suPAR, and PAI-1. These levels were measured by enzyme-linked immunosorbent assay (ELISA) using the human uPA ELISA kit and human PAI-1 ELISA kit (Assaypro, St. Charles, MO, USA), as well as the human suPAR ELISA kit (Wuhan Elabscience Co., Ltd., Wuhan, China). All samples were measured in duplicate. The data is shown as median (minimum-maximum). Differences between groups were analyzed using the Mann-Whitney test with SPSS Statistics version 22 (IBM Corp.). Only probability values of $P<0.05$ were considered statistically significant.

RESULTS

In this study, up to the prescribed time limit, we only obtained 17 lung cancer patients before and 13 lung cancer patients after chemotherapy. Table 1 shows the characteristics of subjects.

Based on subject characteristics, it was found that the number of males was more than females in groups before and after chemotherapy (82.00% and 53.85%, respectively). The largest age group was 51–60 years old in both before and after chemotherapy groups (47.05% and 53.85%, respectively). Most of the patients were active smokers in groups before and after chemotherapy (76.47% and 46.15%, respectively).

The most common complaint was shortness of breath in groups before and after chemotherapy (64.70% and 61.54%, respectively). Additional complaints often found in groups before and after chemotherapy were coughing (100% and 69.23%, respectively) and weight loss (35.29% and 30.77%, respectively).

Table 1. Characteristics of Patients

Characteristics of Patients		Before Receiving Chemotherapy (n=17)	After Receiving Chemotherapy (n=13)
Gender	Male	14 (82%)	7 (53.85%)
	Female	3 (18%)	6 (46.15%)
Age group	<20 years	0	0
	21–30 years	1 (5.88%)	1 (7.69%)
	31–40 years	2 (11.76%)	1 (7.69%)
	41–50 years	2 (11.76%)	2 (15.38%)
	51–60 years	8 (47.05%)	7 (53.85%)
	>60 years	4 (23.53%)	2 (15.38%)
Smoking	Yes	13 (76.47%)	6 (46.15%)
	No	3 (17.65%)	3 (23.08%)
	Passive	1 (5.88%)	4 (30.77%)
Laboratory examination	CEA levels (ng/mL)	12.48	6.52
	p=0.408*	(1.42–829.10)	(0.51–731.50)
Chest X-ray	Tumor	6 (35.29%)	5 (38.46%)
	Pleural effusion	4 (23.53%)	3 (23.07%)
	Tumor + effusion	3 (17.65%)	2 (15.38%)
	Tumor + atelectasis	2(11.76%)	1 (7.69%)
	Tumor + effusion + atelectasis	2 (11.76%)	2 (15.38%)
Histopathology	Small cell carcinoma	1 (5.88%)	2 (15.38%)
	Non-small cell carcinoma		
	- Adenocarcinoma	7 (41.17%)	4 (30.77%)
	- Epidermoid carcinoma	6 (35.29%)	2 (15.38%)
	Adeno-epidermoid carcinoma	3 (17.65%)	5 (38.46%)
Staging	Small cell carcinoma		
	- *Extended*	1 (5.88%)	2 (15.38%)
	Non-small cell carcinoma		
	- IIIA	2 (11.76%)	0
	- IIIB	2 (11.76%)	0
	- IV	12 (70.59%)	11 (84.62%)

Note: *$P>0.05$ indicates no significant difference between groups (Mann-Whitney test).

The carcinoembryonic antigen (CEA) measurement showed that the median level of CEA was 12.48 (1.42–829.10) ng/ml in the group before chemotherapy and 6.52 (0.51–731.50) ng/ml in the group after chemotherapy. Radiological images of chest X-rays found the mass in groups before and after chemotherapy (35.29% and 38.46%, respectively), while the rest were found to be effusion or atelectasis. The most common histopathological type in the group before chemotherapy was adenocarcinoma (41.17%), whereas in the group after chemotherapy were adenoepidermoid carcinoma (38.46%) and adenocarcinoma (30.77%).

Table 2. The Levels of uPA, suPAR, and PAI-1 Based on Groups

Parameter (ng/mL)	Groups (Before/After Receiving Chemo-therapy)	n	Median (Minimum-Maximum)	*P*
uPA	Before	17	1.23 (0.56–2.85)	0.183
	After	13	1.06 (0.47–1.72)	
suPAR	Before	17	3.65 (1.66–7.79)	0.035*
	After	13	2.89 (1.88–5.54)	
PAI-1	Before	17	33.31 (0.49–646.70)	0.010*
	After	13	1.69 (0.01–47.18)	

Note: *P<0.05 indicates a significant difference between groups (Mann-Whitney test).

The serum uPA, suPAR, and PAI-1 levels in patients before and after chemotherapy are presented in Table 2. The serum suPAR and PAI-1 levels were significantly (P<0.05) decreased in the group after chemotherapy compared to the group before chemotherapy. The serum uPA level was also decreased after chemotherapy compared to before, although not statistically significant (P>0.05).

The serum uPA, suPAR, and PAI-1 levels based on tumor staging in patients before chemotherapy are presented in Table 3. The serum uPA, suPAR, and PAI-1 levels were not significantly (P>0.05) different in patients with stage III or IV of the disease before chemotherapy.

Table 3. The Levels of uPA, suPAR, and PAI-1 Based on Tumor Staging in Patients Before chemotherapy

Parameter (ng/mL)	Tumor Staging	n	Median (Minimum-Maximum)	*P*
uPA	III	4	1.41 (0.93–1.88)	0.955
	IV	13	1.23 (0.56–2.85)	
suPAR	III	4	3.88 (1.66–5.74)	0.734
	IV	13	3.33 (2.61–7.79)	
PAI-1	III	4	63.95 (33.31–646.70)	0.089
	IV	13	7.99 (0.49–95.44)	

Note: P>0.05 indicates no significant difference between groups (Mann-Whitney test).

In lung cancer patients before chemotherapy, the highest serum uPA and suPAR levels were found in adenocarcinoma cell types. The highest serum PAI-1 level was found in adenoepidermoid cell types, as listed in Table 4.

The serum uPA, suPAR, and PAI-1 levels based on chemotherapy response in patients after chemotherapy are presented in Table 5. The serum uPA, suPAR, and PAI-1 levels were not significantly (p>0.05) different in patients with stable or progressive diseases after chemotherapy.

Table 4. The Levels of uPA, suPAR, and PAI-1 Based on Histopathology Results in Patients Before chemotherapy

Parameter (ng/mL)	Histopathology	n	Median (Minimum-Maximum)
uPA	Small cell carcinoma	1	1.07 (1.07–1.07)
	Adenocarcinoma	7	1.68 (0.56–2.85)
	Epidermoid carcinoma	6	1.23 (0.93–1.88)
	Adenoepidermoid carcinoma	3	1.14 (0.60–1.60)
suPAR	Small cell carcinoma	1	2.79 (2.79–2.79)
	Adenocarcinoma	7	4.95 (2.70–7.79)
	Epidermoid carcinoma	6	3.49 (1.66–5.78)
	Adenoepidermoid carcinoma	3	3.13 (3.02–5.14)
PAI-1	Small cell carcinoma	1	49.73 (49.73–49.73)
	Adenocarcinoma	7	12.48 (2.59–646.70)
	Epidermoid carcinoma	6	20.04 (4.03–81.16)
	Adenoepidermoid carcinoma	3	67.45 (0.49–95.44)

Table 5. The Levels of uPA, suPAR, and PAI-1 Based on Chemotherapy Response

Parameter (ng/mL)	Chemotherapy Response	n	Median (Minimum-Maximum)	*P*
uPA	Stable Disease	8	1.14 (0.92–1.72)	0.770
	Progressive Disease	5	1.06 (0.47–1.61)	
suPAR	Stable Disease	8	2.88 (1.88–5.54)	0.884
	Progressive Disease	5	2.91 (2.43–3.41)	
PAI-1	Stable Disease	8	1.65 (0.20–47.18)	0.558
	Progressive Disease	5	28.31 (0.01–37.27)	

Note: P>0.05 indicates no significant difference between groups (Mann-Whitney test).

DISCUSSION

It was shown that the number of male patients was higher than that of females. This is consistent with the data from WHO (2014), which states that the incidences of lung cancer in Indonesia are 25,322 in males and 9,374 in females.[9] In Northeastern India, data from 2008 to 2012 indicates that the male: female ratio of lung cancer is 1.09:1.00.[10] In the United States, age-adjusted incidence rates of lung and bronchus cancers in 2014 are 59.36 and 47.25 per 100,000 in men and women, respectively.[11] Whereas global data in 2012 shows that the estimated number of lung cancer cases is 1,242 million in males and 583 thousand in females.[1] According to the previous study, the highest age-standardized rates of lung cancer among men are found in Central and Eastern Europe (53.5 per 100,000), Eastern Asia (50.4), Micronesia (47.5), and Southern Europe (46.4). The highest age-standardized rates among women are found in Northern America (33.8 per 100,000), Northern Europe (23.7), Micronesia (22.9), Australia/New Zealand (21.7), and Western Europe (20).[12]

The distribution of patients by age group showed that most were aged 51–60 years in groups before and after chemotherapy. However, in Northeastern India, lung cancer most commonly occurs over the age of 60 years, based on data from 2008 to 2012.[10] Moreover, in the United States, lung and bronchus cancers in 2014 most occur over the age of 65 years and increase with age.[11]

Based on smoking status, the result shows that most patients in groups before and after chemotherapy were active smokers. The cause-effect relationship between tobacco smoking and the incidence of lung cancer has been proven ecologically and clinically in many studies. From a global perspective, the trend of increasing tobacco consumption is followed by the trend of increasing lung cancer mortality rates, especially in developing countries.[13] In Indonesia, lung cancer is the leading cause of smoking-attributable mortality. Cancer due to smoking burdened the Indonesian economy by USD 1,309 million in 2013, consisting of USD 1,280 million for men and USD 29.5 million for women.[14]

In both groups, the chief complaint most commonly found was shortness of breath. Additional complaints in the group before chemotherapy were coughing, weight loss, and chest pain. In the group after chemotherapy, there were additional complaints of coughing, weight loss, and hemoptysis.

Shortness of breath is a common complaint in patients with lung cancer. A study found shortness of breath in about 60% of patients. Shortness of breath is caused by airway obstruction, post-obstructive pneumonitis or atelectasis, pleural effusion, pericardial effusion, and as a complication of chemotherapy or radiotherapy such as pneumonitis. A previous study found 65–75% of lung cancer patients suffered from coughing, even more than 25% with a productive cough. Hemoptysis is found in 6–35% of patients, and as many as 3% of patients experience hemoptysis, which causes death. Chest pain is also common and varies from pain at the tumor's location or more severe pain due to the invasion of the chest wall or mediastinum. Other causes of chest pain are pulmonary embolism and post-obstructive pneumonia.[15]

The median level of CEA in the group before chemotherapy was higher than that of the group after chemotherapy. The CEA is used as a marker for pulmonary, colorectal, gastrointestinal, and breast carcinoma. A study revealed that abnormal serum CEA levels are strongly correlated with increased whole-body metastatic potential in advanced NSCLC.[16]

Radiological images of chest X-rays found the mass in groups before and after chemotherapy. There were also pleural effusion and atelectasis. This is consistent with the TNM system in lung cancer, which describes T: primary tumors including atelectasis, N: metastases to lymph nodes, and M: metastases to other organs, including the pleura.[17]

The most common histopathological type in the group before chemotherapy was adenocarcinoma, whereas in the group after chemotherapy were adenoepidermoid carcinoma and adenocarcinoma. This is in line with data from 2010 to 2014 in the

United States, in which the most common type of NSCLC is adenocarcinoma (46.6%), followed by squamous and transitional cell carcinoma (23.2%).[11] The most prevalent kind, epidermoid or squamous carcinoma, is gradually declining, whereas adenocarcinoma is increasing.[18]

In this study, most lung cancer patients were in stage IV. This shows that patients tend to visit doctors when there are respiratory and systemic complaints caused by tumor mass pressure or the process of lung malignancy itself. Symptoms of lung cancer initially tend to be less specific, and generally, coughing, which is the most common symptom, is only considered a normal cough. Data shows that about three-quarters of patients with lung cancer will present with symptoms, and most of them have advanced stages of the tumor at the time of diagnosis. Early-stage detection is rare and usually incidental.[19]

In this study, serum suPAR and PAI-1 levels of the group before chemotherapy were significantly higher than those after chemotherapy. This is consistent with the literature that suPAR is released by tumor cells, and the level of suPAR in the blood of cancer patients will increase. The suPAR plays an essential role in urokinase-mediated plasminogen activation, which will cause tumor invasion and metastasis.[20] Meanwhile, the lower level of suPAR in the group after chemotherapy can occur due to decreased tumor cells activity such as development, implantation, angiogenesis, inflammation, and metastasis. Moreover, several previous studies have shown that PAI-1 levels will increase significantly in malignancy compared to normal tissue and also be associated with patient prognosis.[21]

The highest serum uPA and suPAR levels were found in adenocarcinoma cell types and the highest serum PAI-1 level in adenoepidermoid cell types. However, the levels of uPA, suPAR, and PAI-1 based on staging did not show significant differences between stage III and IV patients. A study found that uPAR levels are significantly ($p < 0.01$) higher in NSCLC patients with stage I, II, and IIIa TNM compared to stage IIIb and IV TNM.[22] A study showed that PAI-1 levels in NSCLC are higher than SCLC. In this study, unfortunately, there were no subjects with stages I and II.[23] Therefore, the measurement of uPA, suPAR, and PAI-1 levels in this study has not been able to predict lung cancer progression.

Moreover, the insignificance of statistical analysis results in this study may occur because patients with stage III lung cancer who were diagnosed had undergone biochemical processes for damage that cannot be proven by medical support. Due to cost limitations, a complete examination was not performed on all patients to exclude distant metastases, such as a head CT scan, bone scan, etc. The difference in the number of subjects, namely four people for stage III compared to 13 people for stage IV, can also affect statistical analysis results.

Based on the chemotherapy response, this study found no significantly different results between serum uPA, suPAR, and PAI-1 levels in stable and progressive diseases. However, only chemotherapy responses of stable and progressive diseases were in the group, so they could not be compared with complete and partial responses. Therefore, the measurement of uPA, suPAR and PAI-1 levels in this study has not evaluated the chemotherapy response. Furthermore, there were no significant differences in the levels of uPA, suPAR, and PAI-1 in patients with stable and progressive diseases.

CONCLUSION

This study revealed that suPAR and PAI-1 levels were decreased in lung cancer patients who had received chemotherapy. This can occur because tumor cell activity decreases.

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The Role of Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), and D-Dimer in Predicting the Outcome of Confirmed COVID-19 patients

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Abstract

Background: *Cytokine storm or hyperinflammation condition in COVID-19 patients could result in fatal outcomes. Inflammation could also result in coagulation disorders. The Neutrophil-Lymphocyte Ratio (NLR) and Platelet-lymphocyte ratio (PLR) have been known as inflammation markers in several diseases. D-dimer value can be used to assess a patient's coagulation status. Further study on thromboinflammation biomarkers in COVID-19 patients is needed. Therefore, we conducted a study to assess the association between NLR, PLR, and d-dimer on the clinical outcome of confirmed COVID-19 patients at Persahabatan Central Hospital.*

Methods*: Observational cohort retrospective analysis was conducted on 214 medical records of confirmed COVID-19 patients who meet the inclusion criteria in Persahabatan Central Hospital from March to July 2020.*

Results*: The mean patient's age in this study is 54.35 years, dominated by male patients (60.7%). Most of the patients had normal nutritional status (54.7%). The proportion of patients with comorbidities is 65.4%. The most common comorbid is hypertension, followed by diabetes mellitus. 76.1% of patients have severe-critically ill disease, followed by moderate (20.1%) and mild disease (3.7%) The length of hospitalization median were 12 days. Sixty patients (28%) have died during hospitalization. The median of initial value of NLR, PLR, and d-dimer is 5.75 (0.68–81.5), 243.5 (44.7–1607), and 1140 (190–141300) respectively. We found significant associations between NLR (P=0.0001), PLR (P=0.013) and d-dimer (P=0.032) on clinical outcome.*

Conclusion*: Initial value of NLR, PLR, and D-dimer of confirmed COVID-19 patients at Persahabatan Central Hospital were associated with clinical outcome.* ***(J Respirol Indones 2021; 41(4): 236–44)***

Keywords: *coronavirus disease 2019; neutrophil lymphocyte ratio; platelet lymphocyte ratio; D-dimer; mortality.*

Hubungan Nilai Rasio Netrofil Limfosit, Rasio Platelet Limfosit dan D-dimer dengan Luaran Tatalaksana Pasien COVID-19 Terkonfirmasi di RSUP Persahabatan

Abstrak

Latar belakang: *Badai sitokin atau kondisi hiperinflamasi pada pasien dengan COVID-19 dapat berakibat fatal pada pasien. Infalmasi dapat menyebabkan gangguan kogulasi. Rasio neutrofil limfosit (RNL) dan rasio platelet limfosit (RPL) telah diketahui dapat menjadi penanda inflamasi pada beberapa penyakit. Status koagulasi asien dapat dilihat dari parameter nilai D-dimer. Peran penandahayati yang dapat menggambarkan keadaan trombоinflamasi pada pasien COVID-19 tersebut perlu ditelaah lebih lanjut.*

Metode: *Analisis observasional kohort retrospektif terhadap pasien COVID-19 terkonfirmasi yang dirawat di RSUP Persahabatan secara total sampling hingga diperoleh 214 rekam medis yang memenuhi kriteria inklusi dari bulan Maret sampai Juli 2020.*

Hasil: *Rerata usia pasien pada penelitian ini adalah 54,35 tahun, didominasi oleh laki-laki sebanyak 60,7%. Status gizi pasien paling banyak adalah normal sebesar 54,7%. Proporsi pasien yang memiliki komorbid sebanyak 65,4%. Komorbid yang paling banyak adalah hipertensi, kedua adalah diabetes melitus. Derajat penyakit paling banyak adalah berat-kritis sebanyak 76,1%, diikuti sedang 20,1%, ringan 3,7%. Median lama rawat adalah 12 hari. Pasien meninggal sebanyak 60 orang (28%). Nilai median RNL, RPL dan D-dimer awal pasien adalah 5,75 (0,68–81,5), 243,5 (44,7–1607) dan 1140 (190–141300), secara berurutan. Terdapat hubungan antara nilai RNL (P=0,000), RPL (P=0,013) dan D-dimer (P=0,032) terhadap luaran pasien.*

Kesimpulan: *Nilai RNL, RPL dan D-dimer awal perawatan pasien COVID-19 terkonfirmasi di RSUP Persahabatan berhubungan dengan luaran tatalaksana pasien.* ***(J Respirol Indones 2021; 41(4): 236–44)***

Kata kunci: *coronavirus disease 2019; rasio netrofil limfosit; rasio platelet limfosit; D-dimer; mortalitas*

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INTRODUCTION

The world has been facing a global pandemic since late 2019. COVID-19 is a viral infection presumed to originate from animals in an animal market in Wuhan, China.[1] After less than one year, the disease has spread from China to every country. On July 28th 2020, it was documented that 16.341.920 confirmed COVID-19 cases around the world, and 650.805 patients have died from it. In Indonesia, the authors' country, up to 100.303 cases have been confirmed, and up to 4.838 patients have died.[2] This number keeps growing as the infection keeps growing and the number of cases fluctuates.

The aetiology of this disease is severe-acute respiratory syndrome corona virus-2 (SARS-CoV-2).[1] The clinical manifestation of COVID-19 varies from mild symptoms like coughing to life-threatening symptoms leading to respiratory failure, muscular pain, and eventually death.[3,4] The severe manifestations are more commonly found in patients with comorbidities such as hypertension, diabetes mellitus, cardiovascular and cerebrovascular disease.[3]

SARS-CoV-2 infection leads to systemic inflammation, the release of pro-inflammatory cytokines, and migration of pro-inflammatory macrophages and granulocytes into the inflamed tissue, leading to massive tissue destruction.[5] Lymphopenia found in patients with COVID-19 indicates dysregulation of the immune system affecting lymphocytes.[6] This dysregulation also causes platelet numbers changes, as it has been found that platelets also play an essential role as an immune modulator.[7] The combination of systemic inflammation and immune dysregulation results in a hypercoagulable state, leading to increased complications of arterial and venous thromboembolism.[8]

This hyper-inflammation and immunological parameter changes raise a significant issue in patients with confirmed COVID-19 infection. Previous studies have reported neutrophil-lymphocyte-ratio (NLR) and platelet-lymphocyte-ratio (PLR) may be used to evaluate immunological and inflammation status in confirmed patients.[9–12] Coagulation status and its complications can be assessed using D-dimer.[13] However, these studies were primarily based in China, which may differ from other countries. Therefore, the author would like to analyse the association between NLR, PLR, and D-dimer levels to predict and the prognosis of patients with early COVID-19 infection in order to provide a better and more effective treatment.

METHODS

We performed a cohort retrospective clinical study on the clinical manifestation and laboratory results of all patients with confirmed COVID-19 in Persahabatan Central Hospital from October to November 2020 that met the inclusion and exclusion criteria. The patients involved met the inclusion criteria of (1) confirmed COVID-19 cases based on RT-PCR examination; (2) patients had completed hospitalisation from March to June 2020. Patients who met exclusion criteria were excluded. Exclusion criteria were: (1) incomplete required data (2) patients who did not complete hospitalization due to personal reasons; (3) pregnant patients; (4) patients with Human Immunodeficiency Virus (HIV) infection; (5) patients with Dengue Haemorrhagic Fever (DHF) infection; and (6) patients with chronic hepatitis infection.

Data collected includes COVID-19 RT-PCR confirmation, length of hospitalisation, treatment outcome, age, gender, nutritional status, disease severity, comorbidity, haemoglobin level, leukocyte count, thrombocyte, lymphocyte count, albumin, NLR, PLR, and D-dimer level in an early stage of hospitalisation. The data involved originated from the medical records of Persahabatan Central Hospital.

Data extracted from medical records was recorded and filed in an excel database and analysed using SPSS version 20.0 software. We grouped the patients into patients who finished hospitalisation and patients who died during hospitalisation. We compared patients' age, haemoglobin, leukocyte, platelet, neutrophil count, lymphocyte count, albumin, NLR, PLR, and d-dimer between those who finished

the hospitalisation group and patients who died during the hospitalisation group using the unpaired T-test, Mann-Whitney, and Chi-Square tests. Each variable's optimal cut-off values were analysed using receiver operator curve (ROC) analysis with a confidence interval of 95%.

RESULTS

Clinical characteristics and initial laboratory parameters of study subjects are provided in Table 1. Of the 425 subjects of confirmed COVID-19 patients hospitalised at Persahabatan Central Hospital from March to June 2020, 211 subjects were excluded for being pregnant, having HIV, DHF, chronic hepatitis B infection, request to move to another hospital, and incomplete data. Only 214 subjects were included. 130 (60.7%) of the confirmed COVID-19 subjects were male, and the average age was 54.35 years old, with 24 years old as the minimum and 83 years old as the maximum. The majority of patients (54.7%) had normal nutritional status, 4.2% had below-normal nutritional status, and 41.1% had above-normal nutritional status.

Comorbidities were found in 65.4% of total study subjects, with hypertension (33.2%) as the most common comorbidity, followed by Type-2 Diabetes Mellitus (32%), and cardiac disease (12.6%). Other comorbidities, including cerebrovascular disease (CVD), pulmonary tuberculosis, malignancy, vertigo, severe head trauma, and femoral fracture, were also recorded. The length of hospitalisation's median is 12 days, with one day as the minimum and 40 days as the maximum. Sixty patients (28%) died during hospitalisation, while the rest were discharged.

The median of haemoglobin was 13.4 (7.8–17.9), the median of leukocyte was 9,030 (2,450–28,870), the median of platelet was 265,500 (57,000–880,000), the median of neutrophil count was 77.8 (34.4–97.8), the median of lymphocyte count was 13.65 (1.2–54.6). The median of albumin was 3.5 (1.9–4.9), the median of NLR was 5.75 (0.68–81.5), the median of PLR was 243.5 (44.7–1,607), and the median of D-dimer was 1,140 (190–141,3000).

Bivariate analysis of each variable on patients' outcomes is provided in Table 2. The analysis showed a significantly high frequency of deaths during hospitalisation found in patients over 50 years old. The length of hospitalisation's median in patients who died was 7 (1–40) days, which was significantly different from those who finished hospitalisation with a median of 14 (2–37) days (P=0.0001). The leukocyte (P=0.001), neutrophil percentage (P=0.0001), lymphocyte percentage (P=0.0001), albumin (P=0.0001), NLR (P=0.0001), PLR (P=0.013), and D-dimer (P=0.32) were also significantly different among those who died and those who finished hospitalization.

Disease severity was classified as mild, moderate, and severe. Nutritional status was assessed based on the WHO classification of body mass index (BMI). Based on the presence of comorbidities, subjects were grouped into those with no comorbidity, those who had 1 comorbidity, or had >1 comorbidity. We compared the mortality rates of male and female patients and discovered that 36 male patients died compared to 24 female patients, but the difference was not statistically significant. Initial disease severity was related to the patients' outcome (P=0.0001). Patients who were initially presented with severe disease were more likely to die than those with mild and moderate disease. No patients with mild diseases were reported to die.

This study used the receiver operator curve (ROC) to predict treatment outcome based on significant variables, as shown in figure 1 and 2. The figure showed that the area under the curve (AUC) of NLR, PLR, d-dimer, neutrophil, and leukocyte were better compared to albumin, lymphocyte, and length of hospitalisation. Based on AUC analysis from SPSS software, we found that the AUC of NLR was 0.704 (CI 95%: 0.628–0.779); the AUC of PLR was 0.610 (CI 95%: 0.509–0.680); the neutrophil count was 0.725 (CI95%: 0.651–0.798); and the leukocyte count was 0.649 (CI95%: 0.565–0.733). The optimal cut-off value and its respective sensitivity and specificity are provided in Table 4.

Table 1. Clinical Characteristics of Study Subjects

Variable	Frequency	Percentage	Mean
Gender			
Male	130	60.7	
Female	84	39.3	
Age (Year)			54.35 ± 13.55
Nutritional Status			
Malnourished	9	4.2	
Normal	117	54.7	
Pre-obsed	69	32.2	
Grade I Obesity	12	5.6	
Grade II Obesity	6	2.8	
Grade III Obesity	1	0.5	
Presence of comorbidities			
No comorbid	74	34.6	
1 comorbid	91	42.5	
2 comorbid	40	18.7	
3 comorbid	7	3.3	
4 comorbid	2	0.9	
Disease severity			
Mild	8	3.7	
Moderate	43	20.1	
Severe-critically ill	163	76.1	
Clinical outcome			
Finished hospitalization	154	72	
Died during hospitalization	60	28	
Length of hospitalization (day)			12 (1–40)
Types of comorbidities			
Hypertension	71	33.2	
Diabetes Melitus	68	32	
Congestive Heart Failure	14	6.5	
Coronary Artery Disease	12	5.6	
Cerebrovascular Disease	11	5.14	
Tuberculosis	5	2.34	
History of Tuberculosis	5	2,34	
Appendicitis	3	1.4	
Malignancy	3	1.4	
Asthma	2	1	
Arythmia	1	0.5	
COPD	1	0.5	
Severe head trauma	1	0.5	
Femoral fracture	1	0.5	
Obstructive Ileus	1	0.5	
Takayasu arteritis	1	0.5	
Thoracotomy	1	0.5	
Renal transplant	1	0.5	
Vertigo	1	0.5	

Table 2. Comparison of age, length of hospitalization and laboratory parameter on clinical outcome.

Variable	Clinical outcome		*P*
	Finished hospitalization	Died during hospitalization	
Age (Year)			
Mean	52.85 ± 14.22	58.2 ± 10.85	**0.004**[a*]
<50 years old	61 (80.3%)	15 (19.7%)	**0.045** ‡
≥50 years old	93 (67.4%)	45 (32.6%)	
Gender			0.889 ‡
Female	60 (71.4)	24 (28.6)	
Male	94 (72.3)	36 (27.7)	
Disease Severity			**0.0001** ‡
Mild	8(100)	0	
Moderate	42 (97.7)	1 (2.3)	
Severe-critically ill	104 (63.8)	59 (36.2)	
Nutritional Status			0.166 ‡
Malnourished	7 (77.8)	2 (22.2)	
Normal	78 (66.7)	39 (33.3)	
Pre-obese and Obese	69 (78.4)	19 (21.6)	
Presence of Comorbidity			0.258 ‡
No comorbidity	58 (78.4)	16 (21.6)	
1 comorbidity	64 (70.3)	27 (29.7)	
> 1 comorbidity	32 (65.3)	17 (34.7)	
Length of hospitalization (days)	14 (2–37)	7 (1–40)	**0,0001** §
Haemoglobin	13.4 (7.8–16.6)	13.25 (8.9–17.9)	0.796§
Leukocyte	8,670 (2,450–28,870)	10,730 (3,870–24,180)	**0.001**§
Thrombocyte	271,000 (57,000–880,000)	250,500(119,000–564,000)	0.309§
Neutrophil (%)	73.8 (34.4–97.8)	85.1 (53.9–94.1)	**0.0001**[*]
Lymphocyte (%)	15.65 (1.2–54.6)	8.75 (2.7–39.2)	**0.0001**§
Albumin	3.6 (2.1–4.9)	3.4 (1.9–3.9)	**0.0001**§
NLR	4.715 (0.68–81.5)	9.955 (1.38–34.6)	**0.0001**§
PLR	217.2 (44.7-1,607)	275.5 (77–651.6)	**0.013**§
D-dimer	1,055 (190–35,200)	1,185 (260–141,300)	**0.032**§

Note: *M T-Test; ‡ Chi square; § Mann-Whitney

Table 3. Association of length of hospitalization and laboratory parameters

Variable	Association between length of hospitalization (days)			
	Finish hospitalization (n=154)		Died during hospitalization (n=60)	
	Correlation coefficient	*P*	Correlation coefficient	P-value
Age (years)	0.131	0.105[a]	0.063	0.635[*]
Haemoglobin	-0.052	0.525[a]	0.170	0.193[*]
Leukocyte	0.056	0.492[a]	-0.089	0.498[*]
Thrombocyte	0.001	0.994[a]	0.153	0.244[*]
Neutrophl percentage	**0.313**	**0.000[a]**	-0.346	**0.007**[*]
Lymphocyte percentage	**-0.274**	**0.001[a]**	0.285	**0.027**[*]
Albumin	**-0.254**	**0.001[a]**	-0.109	0.406[*]
NLR	**0.269**	**0.001[a]**	-0.288	**0.026**[*]
PLR	**0.226**	**0.005[a]**	-0.142	0.278[*]
D-dimer	-0.012	0.886[a]	-0.011	0.933[*]

Note: *Spearman Correlation

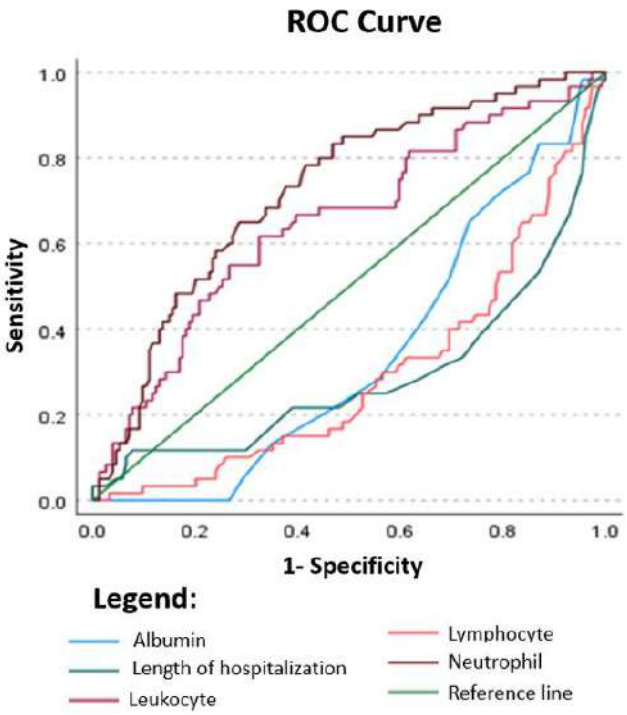

Figure 1. ROC Curve of Albumin, Length of hospitalization, leukocyte, lymphocyte, and neutrophil in predicting clinical outcome. The ROC curve shows how neutrophil and leukocyte count could be used to predict clinical outcome. Cut-off value of each variable are provided in Table 1.

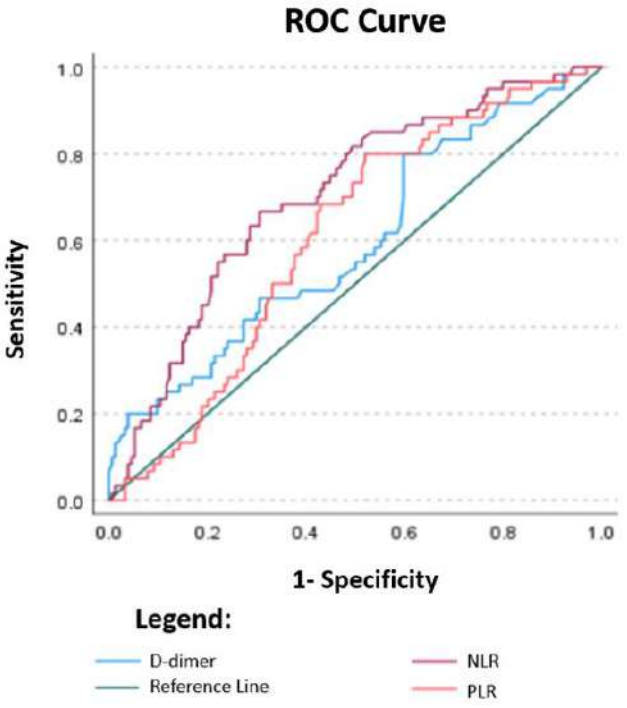

Figure 2. ROC Curve of D-dimer, NLR, and PLR in predicting clinical outcome. ROC curve shows how D-dimer, NLR, and PLR can be used to predict clinical outcome. Cut-off value provided in Table 1.

Table 4. Cut-off value of NLR, PLR, d-dimer, leukocyte, and neutrophil in predicting clinical outcome

Variable	Cut-off Value	Sensitivity	Specificity
NLR	7,035	66,7%	69,5%
PLR	243,5	68,3%	57,1%
D-dimer	1960	46,7%	69,5%
Leukocyte	9595	61,7%	67,5%
Neutrophil	81,95	65%	71,4%

DISCUSSION

It has been more than one year now since the first case of COVID-19 was reported in Wuhan, China.[1] The disease has spread worldwide, causing many deaths and morbidity among all ages. In July 2020, more than 4,500 people died because of this disease in Indonesia, and the number keeps on growing every day.[2] This disease causes systemic inflammation and immune dysregulation, leading to severe tissue destruction and poor outcome.[5] Previous studies performed in China show that several laboratory biomarkers may be used to predict mortality outcomes among patients.[7] However, there was no data from other countries outside of China regarding the result. Therefore, we performed analysis on several laboratory biomarkers on patients' outcomes to evaluate those biomarkers' ability to predict outcomes in the Indonesian population.

Bivariate analysis showed the significant role of age in determining patients' outcome. Like in the previous studies by Zhou et al. and Wu et al.[14,15] We found that the median length of stay of patients who died during hospitalisation was shorter (7 days) than those who finished hospitalisation (14 days). These findings may be explained by the rapid clinical deterioration in that group. This result was like Zhou et al. with a median of 7 days compared to 12 days in those who finished hospitalization.[14]

On laboratory parameters, we found that leukocyte count, neutrophil percentage, lymphocyte percentage are significantly different among the two groups with *P*=0.001, *P*=0.0001, and *P*=0.0001, respectively. We did not find a significant difference in haemoglobin and platelet count between the two groups. A study by Yan et al. also shows similar results, except for the lower platelet value found in patients who died during hospitalisation.[16]

Our study's median of albumin is significantly lower in the group of patients who died during hospitalisation (3.4 [1.9–3.9] compared to patients who finished treatment (3.6 [2.1–4.9] with *P*=0.0001. Several studies have reported similar results by Zhou et al., Yan et al., and Huang et al.[14,16,17] Huang reported that hypoalbuminemia less than 3.5 g/mL could be used as an independent factor to predict death. Albumin is also related to other inflammatory markers such as C-reactive protein (CRP), leukocytes, and NLR. Hypoalbuminemia in COVID-19 may be explained by inflammation-induced capillary permeability elevation leading to albumin shift to the interstitial space.[17] Hypoalbuminemia may also happen because albumin is a negative acute-phase protein that usually decreases during inflammation.[18]

Our study found that the initial value of NLR, PLR, and d-dimer are related to patient outcome with *P*=0.0001; *P*=0.013; and *P*=0.032 respectively. Similar results reported by Yan et al. that report initial high NLR values are related to poor outcomes. The NLR value is an independent risk factor that can be used to predict mortality from all causes during hospitalisation.[16] Qu et al. reported that peak PLR value is an independent factor contributing to disease progression and severe COVID-19 while initial PLR results do not.[19] Zhang et al. reported that an initial d-dimer value above 2,000 g/mL could effectively predict hospital mortality.[20] These results may be explained by the elevation of neutrophil and platelet counts and the decrease in lymphocyte counts.

We discovered no difference in treatment outcome based on gender, nutritional status, or comorbidity. Patients with severe-critically ill disease have significantly higher mortality than moderate and mild disease, similar results as the previous study by Zhou.[14] Our findings differ from Petrilli et al. They reported that BMI >40 was associated with severe disease.[21] They stated that obesity may induce chronic inflammation and increase ACE-2 protein, leading to increased risk of respiratory distress.[22] The lack of an association between nutritional status in our study may be explained as most subjects involved in the study have normal nutritional status.

Bivariate analysis on patients' age, gender, disease severity, and comorbidity presence were not related to the length of hospitalisation. Liu et al. previously reported that age, gender, and comorbidity were not associated with the length of hospitalisation, while disease severity was significantly associated with disease severity. The majority of our subjects were severe to critically ill patients, whereas the majority of Liu's subjects were moderate cases.[23]

In the group of patients who finished hospitalisation, we found a significant relationship between neutrophil, lymphocyte, albumin NLR, and PLR on length of hospitalisation with a low correlation coefficient of 0.313, -0.274, -0.254, 0.269, and 0.226, respectively. While in the group of patients who died during hospitalisation, we found significant relations only between neutrophil, lymphocyte, and NLR on length of hospitalisation with a correlation coefficient of-0.346, 0.285, and 0.288, respectively. Liu et al., previously reported that lymphocyte count was related to length of hospitalisation but not leukocyte, neutrophil, and D-dimer[23], while Yan et al. reported that NLR above 11.75 was related to a longer length of hospitalisation compared to those with NLR below 11.75 (*P*<0.001).[16]

In our study, the applicable cut-off of initial NLR, PLR, D-dimer, leukocyte, and neutrophil count were observed using the ROC curve, giving the results of 7.035, 243.5, 1960, 9595, and 81.95, respectively. However, the cut-off value above has low sensitivity and specificity. Yan et al., who also studied the use of NLR as a prognostic and predictive factor in COVID-19 patients, reported an NLR cut-off value of 11.75 and an AUC of 0.945 (CI 95%: 0.917–0.973) with 97.5% sensitivity and 78.1% specificity. Higher subjects included in the Yan et al. study may explain this difference.[16] Ye et al. also reported a cut-off value for initial NLR of 7.13 with an AUC of 0.86 (CI 95%: 0.73–0.87) with 349 subjects.[24] Zhang et al. reported the optimal cut-off-value of D-dimer to predict in-hospital mortality was 2,000 with an AUC of 0.89, 92.3% sensitivity, and 83.3% sensitivity.[20] We have not found a previous study reporting the cut-off value of PLR to predict mortality in COVID-19 patients.

Several limitations existed in our study. First, our study's design was an observational retrospective on one healthcare centre that highly relies on medical records to gain complete data. Second, most of our subjects are severely-critically ill symptomatic patients. Therefore, our study results may not represent all patients with COVID-19, especially those with mild or asymptomatic infections. In conclusion, initial NLR, PLR, and D-dimer in confirmed COVID-19 patients in Persahabatan Central Hospital are related to treatment outcome. However, further research with more significant subjects may be needed to ensure NLR, PLR, and D-dimer's association with treatment outcome.

CONCLUSION

Initial NLR, PLR, and D-dimer values may predict treatment outcome in confirmed COVID-19 patients.

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Gender Disparities in Their Effects on Characteristics and Prognostics of Lung Cancer Patients in Pulmonary Ward of Dr. M Djamil Hospital, Padang

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Abstract

Background: *Lung cancer incidence in female tends to increase in many countries. Various studies have reported the characteristics of lung cancer in female are different from male. The purpose of this study was to determine the effect of gender on characteristics of lung cancer at Dr. M Djamil Hospital, Padang.*

Methods: *A retrospective analytic study of lung cancer patients treated in the Pulmonary Ward of Dr. M. Djamil Hospital Padang from January 1, 2004 to December 31, 2017, with recognized cancer cell types. Data were grouped according to gender.*

Results: *This study found that 451 lung cancer patients, male-dominant 77.8%. Female were younger than male (52.97±12.79 years vs. 57.81±11.23 years; P=0.0001). Most of male (94.5%) were smokers and former smokers, while 93.9% of female were non-smokers (P=0.0001). Most female were having prior history of tuberculosis (TB) (21.2% vs 11.0%; P=0.008) and also prior history of other organs cancer (10.1% vs 3.4%; P=0.007) than in male. Squamous cells were highest in males (41.1%), while females had adenocarcinoma (55.0%); with P=0.008. Advanced stage in female more than male (91.8% vs 82.7%; P=0.027). The mean life expectancy of female was longer than male, respectively 8.7±1.56 and 7.29±0.64 months; (P=0.95).*

Conclusion: *There are differences in the epidemiology of lung cancer between male and female in Dr. M. Djamil Hospital Padang in the form of age, cell type and staging. Non-smokers, a previous history of TB and a history of cancer in other organs were more dominant in female.* ***(J Respirol Indones 2021; 41(4): 245–51)***

Key word: *lung cancer; gender; epidemiology*

Perbedaan *Gender* dalam Pengaruhnya pada Karakteristik dan Progonostik Pasien Kanker Paru di Bagian Paru RSUP Dr. M Djamil Padang

Abstrak

Latar belakang: *Kejadian kanker paru pada perempuan cenderung meningkat pada banyak negara. Berbagai penelitian melaporkan karakteristik kanker paru pada perempuan berbeda dengan laki-laki. Penelitian ini bertujuan untuk mengetahui pengaruh jenis kelamin terhadap karakteristik kanker paru di RSUP Dr. M. Djamil Padang.*

Metode: *Penelitian analitik retrospektif terhadap pasien kanker paru yang dirawat di Bangsal Paru RSUP Dr. M. Djamil Padang dari 1 Januari 2004 sampai 31 Desember 2017 dengan jenis sel sudah diketahui. Data dikelompokkan menurut jenis kelamin.*

Hasil: *Penelitian ini mendapatkan 451 orang pasien kanker paru, 77,8% diantaranya laki-laki. Usia perempuan lebih muda dari laki-laki (52,97±12,79 tahun vs 57,81±11,23 tahun; P=0,0001). Sebagian besar laki-laki (94,5%) adalah perokok dan bekas perokok, sedangkan 93,9% perempuan bukan perokok (P=0,0001). Riwayat TB sebelumnya pada perempuan lebih banyak dari laki-laki (21,2% vs 11,0%; P=0,008) dan juga riwayat kanker pada organ lain (10,1% vs 3,4%; P=0,007) dibandingkan pada laki-laki. Sel skuamosa terbanyak pada laki-laki (41,1%), sedangkan perempuan adeno karsinoma (55,0%); dengan P=0,008. Staging lanjut pada perempuan lebih banyak dibandingkan laki-laki (91,8% vs 82,7%; P=0,027). Rerata harapan hidup perempuan lebih panjang dibandingkan laki-laki, masing-masing 8,74±1,56 dan 7,29±0,64 bulan; (P=0,95).*

Kesimpulan: *Terdapat perbedaan epidemiologi kanker paru antara laki-laki dan perempuan di RSUP Dr. M. Djamil Padang berupa umur, jenis sel dan staging. Bukan perokok, riwayat TB sebelumya dan riwayat kanker pada organ lain lebih dominan pada perempuan.* ***(J Respirol Indones 2021; 41(4): 245–51)***

Kata kunci: *kanker paru; jenis kelamin; epidemiologi*

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INTRODUCTION

Reports from various countries show changes in the proportion of lung cancer in male and female in the last two decades. The incidence of lung cancer in male in the United States began to decline since 1982; in 2008–2013, the decline in incidence reached 2.9%. Whereas in female, the incidence of lung cancer only decreased in 2006 after previously continuing to increase. The decrease in the incidence of lung cancer in female in 2006–2013 was only 1.4%. Differences in lung cancer incidence patterns between male and female are caused by differences in smoking history in both sexes. The peak prevalence of smoking in female is less than 20 years later than in male.[1,2]

Smoking is not the only affluent factors of lung cancer gender disparities. Several other factors have also been reported to control lung cancer, including exposure to environmental fumes such as ecological cigarette smoke, workplace exposures and indoor smoke. Genetic mutations, hormonal factors and infections have also been reported to affect these differences. In addition, there are differences in life expectancy for each gender. Various studies show that the 5-year life expectancy of female is higher than that of male. Radzikowska et al. found that the relative risk for death in males was higher (RR = 1.15) than females and was statistically significant.[3,4]

The tendencies of lung cancer being treated in the Pulmonary Ward of Dr. M. Djamil Padang needs to be researched. In addition, complete data are needed on the differences in epidemiology and risk factors for lung cancer in both sexes at RSUP Dr. M Djamil Padang.

METHOD

This study is a retrospective analysis of lung cancer patients whose histopathologically diagnosed at the Pulmonary Ward, Dr. M. Djamil Padang, from January 1, 2004, to December 31, 2017. Metastatic lung tumors were not included in the study.

Data collected in the form of morbidity, age, risk factors, cell type, staging and life expectancy are grouped by sex. The risk factors studied were smoking, history of TB, history of cancer in other organs, and family history of cancer. Categorical data are expressed in terms of number and percentage in each category. Continuous data with normal distribution are expressed in mean and SD, continuous data with non-normal distribution is described in median and percentile. Differences between male and female with continuous data were assessed using t-test if the data were normally distributed, and Mann-Withney if not normally distributed. Differences in categorical data were evaluated using the Pearson Chi-Square; if they did not meet the requirements, they were assessed using the Fisher's Exact test. The difference was declared statistically significant when $P<0.05$. Life expectancy was assessed using the Kaplan-Meier curve.

RESULT

Lung cancer patients treated in the Pulmonary Ward, Dr. M. Djamil Padang, histopathologically diagnosed from January 1, 2004, to December 31, 2017, were 451 people. Male dominant (77.8%). The trend of lung cancer incidence in male and female from year to year is relatively unstable (Figure 1). The lowest incidence of lung cancer in male was in 2011 as many as 9 cases (64.3%), while in female, the lowest incidence was in 2008 as many as 3 cases (11.1%). The lowest overall incidence of lung cancer was found in 2011 with 14 points and gradually increased. This is due to broken scope for bronchoscopy, so patients were referred to Jakarta. Incidence trends for both genders were gradually increased every year, but the increase in cases in female is relatively stable.

The average age of male lung cancer patients treated at the Pulmonary Ward, Dr. M. Djamil Padang 57.81±11.23 years, while female are 52.97±12.79 years. The youngest age of the patient is male, 20 years old, female 25 years old, while the oldest age male is 85 years old and female is 83

years old. Based on the Pearson Chi-Square analysis, it was found that the age difference between male and female was significantly different, with *P*=0.0001 (Table 1).

The risk factors that were significantly different between male and female lung cancer were smoking, prior history of TB and cancer in other organs. The number of smokers and ex-smokers were higher in male (94.5%), while 93.9% in female are non-smokers. Pearson chi-square analysis found a significant difference between smoking risk factors in the male and female groups with p=0.00. Prior history of TB in female was more common in female than male (21.2% vs. 11.0%; p=0.008). In addition, female were more likely to have a history of cancer in other organs than male (10.1% vs. 3.4%; p=0.013).

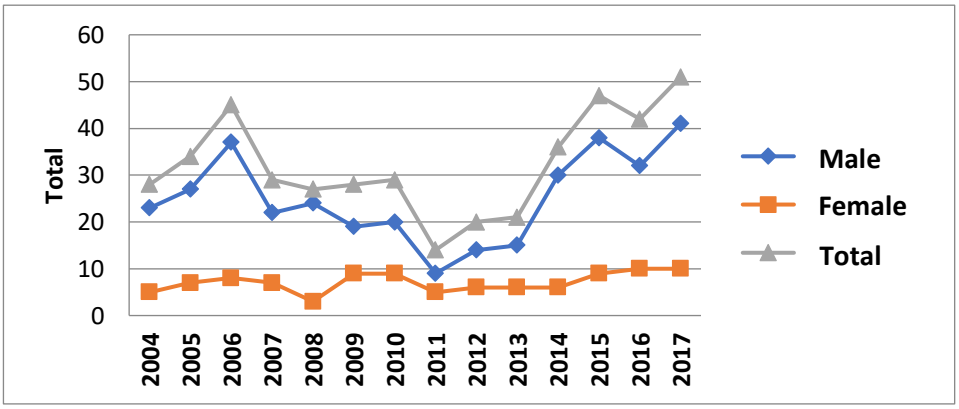

Figure 1. Trends in lung cancer by gender treated in the Pulmonary Ward, RSUP Dr. M. Djamil Padang 2004–2017

Table 1. Differences in the epidemiology and risk factors of lung cancer by sex (N=451)

Risk factors	Male N (%)	Female N (%)	*P*
Age (Mean ± SD)	57,81 ± 11,23	52,97 ± 2,79	0,0001*
Smoking History			
Non smokers	19 (5,5)	92 (93,9)	
Smokers	258 (74,8)	6 (6,1)	0,0001[f]
Ex-smokers	69 (19,7)	0 (0)	
TB History			
There is	38 (11,0)	21 (21,2)	0,008[f]
There is no	309 (89,0)	78 (78,8)	
History of cancer in other organs			
There is	12 (3,4)	10 (10,1)	0,013[λ]
There is no	337 (96,6)	89 (89.9)	
History of cancer in the family			
There is	4 (1,1)	2 (2,0)	0,527[λ]
There is no	344 (98,9)	97 (98,0)	
Cell type			
Small cell	16 (4,6)	1 (1,0)	
Adenocarsinoma	123 (35,1)	55 (55,0)	
Squamous cells	144 (41,1)	31 (31,0)	0,008[f]
Big cell	22 (6,3)	6 (6,0)	
Mix**	17 (4,9)	1 (1,0)	
Not a small cell***	28 (8,0)	6 (6,0)	
Staging			
Early stage (I & II)	59 (17,3)	8 (8,2)	0,027[f]
Advanced stage (III & IV)	283 (82,7)	90 (91,8)	
Total	351 (77,8)	100 (22,2)	

Note: *P*<0,05; * *t-test*; [f]*Pearson chi-square*; [λ]*Fisher's Exact test*

The most common cell type in male was squamous cell (41.1%), while in female it was adenocarcinoma (55.0%). Based on statistical analysis with Pearson Chi-Square, there was a significant difference with *P*<0.05. More advanced stages in both sexes (84.8%). Advanced stage in female was much more (91.8%) than male (82.7%), with *P*<0.05.

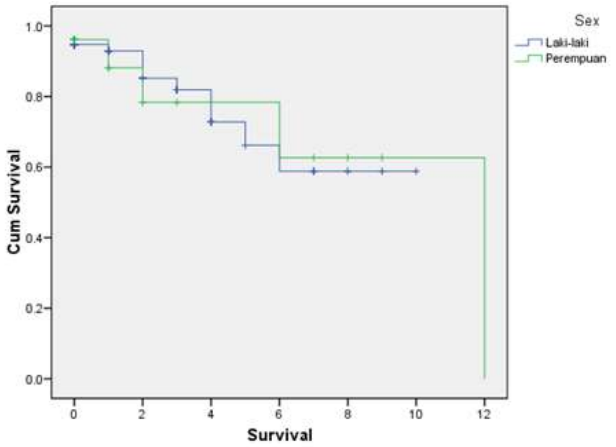

Figure 2. Kaplan-Meier curve for life expectancy of lung cancer patients

The average life expectancy of female (8.74±1.56 months) is longer than that of male (7.29±0.64 months). However, the Log Rank test showed that there was no statistically significant difference (*P*=0.95).

DISCUSSION

The number of people with lung cancer in male is more than in female with a 3.5: 1. Data from Ramdhani et al. in 2008–2012 obtained relatively the same results with a balance of male to female 3.1:1.[5] The number of male patients, both male and female, tend to increase from 2011, but the increase in cases in female is relatively slower than male. Chen et al.'s research in China found an increased incidence of lung cancer, but the increased incidence in female was more significant than male (2.34% vs. 1.30%; *P*<0.05).[6] Statistical data from Siegel et al. on cancer in the United States until 2017 get different results. The number of male sufferers tends to decrease twice as fast as female, while the decline in female is relatively slow. Changes in lung cancer trends in male and female in the United States are associated with changes in smoking habits. The habit of smoking large amounts of smoking in female is late and carried out at an older age than male, and is slower to quit.[1] A study by Costa et al. in Brazil found that both male and female were more smokers and ex-smokers, but the number was higher in males compared to females (87.1% vs. 71.1%), female non-smoker only 28.9%.[7]

The habit of smoking in Indonesia is currently on the rise with the second-largest cigarette consumption globally after China; it is estimated that 316,075 cigarettes were sold to the public in Indonesia in 2016. This number decreased slightly in 2019 to 301,144 cigarettes. It is estimated that 36.3% of adults smoked daily in Indonesia in 2013, with a smoking prevalence of 66% in male and 6.7% in female. The percentage of teenage smokers aged 13–15 years in Indonesia were also high, 35.5% for boys and 3.4% for girls. The number of smokers continues to increase every year, in 2014 an increase of 1.1% compared to 2007.[8–10] This is thought to have caused an increase in the number of lung cancer patients in male in this study, where 74.8% of male with lung cancer were smokers, and 19.7% were ex-smokers so that the total male lung cancer patients associated with smoking was 94.5%. Different results were found in female, where 93.9% of female with lung cancer were not smokers.

Lung cancer in non-smokers is estimated to occur in 10–25% of lung cancer patients globally, more commonly found in female, with the predominant cell type being adenocarcinoma. Exposure to environmental cigarette smoke, especially in female and exposure to carcinogens in the workplace, especially in male, are two alternative risk factors.[10] A meta-analysis study by Sheng et al. found a significant relationship between exposure to environmental cigarette smoke and the incidence of lung cancer in non-smokers in China. The results of this study showed the odds ratio (OR) of the population with exposure to environmental cigarette smoke was 1.64 (95% CI: 1.34–2.01) compared to the unexposed population, male (OR: 1.62; 95% CI: 1,16–2,28), in female (OR=1.57; 95% CI: 1.43–1.72).[11] Study from Ermawati et al. found

that exposure to cigarette smoke from parents is a significant risk factor in female who have lung cancer treated at RSUP M. Djamil Padang and RSUD Solok (OR=13.46, 95% CI: 4.04–44.82; *P*=0.001).[12]

The mean age of female lung cancer patients was younger than male (52.97 years vs. 57.81 years, p<0.05). Based on data from the Surveillance, Epidemiology, and End Results Program (SEER) from 1975 to 2008, the median age of female lung cancer patients in the United States (52.3 years) is younger than male (75.2 years).[13] Study by Radzikowska et al. in 2002 also found female with lung cancer younger than male (60.02 vs. 62.18 years; *P*<0.001). Patients aged <50 years were more common in female (23.3% vs 12%; *P*<0.001).[4]

The same thing was also found in Japan by Funakoshi et al. The comparison between male and female aged <50 years who had lung cancer was smaller than those aged >50 years (1.99 vs. 2.89; *P*=0.003). This shows that female with lung cancer are found at a younger age.[14] The age difference between female and male in this study can be related to the results of Ermawati et al. which that female have been exposed to environmental cigarette smoke from an early age from their parents.[12] Research by Lee et al. in Taiwan has shown that exposure to environmental cigarette smoke in childhood can be a risk factor for lung cancer in adulthood as much as 1.8 times (95% CI: 1.2–2.9) in non-smokers.[15]

Other risk factors that were significantly different in female with lung cancer than male in this study were a previous history of TB (*P*=0.008) and a history of cancer in other organs (*P*=0.013). Study from Yu et al. demonstrated that the incidence of lung cancer increased 11 times in TB patients, with a hazard ratio of 4.37 (95% CI: 3.56–5.36) for the TB cohort after adjustment for demographic variables. The hazard ratio became 3.32 (95% CI: 2.70–4.09) after adjustment for other risk factors such as COPD, other cancers associated with smoking, etc.[16] Chronic inflammatory processes and fibrosis due to TB can induce genetic mutations. Various hypotheses of the role of TB in causing lung cancer have been proposed by experts, including variations in vascular morphology, the process of lymphocytosis, the formation of immune system mediators such as interleukins (IL). Induction of necrosis and apoptosis or reactivation of TB, especially in immunocompromised patients, can increase IL-17 and Tumor Necrosis-alpha (TNF-α), which can reduce p53 activity or increase B-cell lymphoma 2 (Bcl-2) expression, reduce B-cell Lymphoma associated x (Bax-T) and cause inhibition of caspase-3 expression, resulting in mitochondrial expression, decreased cytochrome oxidase.[17]

Data in the United States found about 880,300 people from 11 million cancer patients who survived until January 1, 2005, were diagnosed with more than one cancer called multiple primary cancer. Lung cancer is among the ten most common cancer sites, both in male and female, with an observation/expectation ratio (O/E ratio) for female being more significant than male (1.53 vs. 1.32). The causes of multiple primary cancers are grouped into three categories, namely familial cancer syndromes and other genetic susceptibility factors, concurrent risk factors such as smoking and the effects of previous cancer treatment. Specifically for smoking-related cancers, the O/E ratio in female for lung cancer ranged from 1.17 to 7.01 according to primary cancer, while in male, it was only 0.97 to 3.82.[18]

The most common cell type in female were adenocarcinoma (55%), While most men got squamous cell carcinoma (41.1%) with p<0.001. Study by Sagerup et el. In 2010 showed that squamous cell types were still dominant in male. In 1998–2002 were relatively the same between adenocarcinoma and squamous cells. But since 2003–2007, the number of adenocarcinomas was dominant in male. The cell type in female since 1988 has been dominated by adenocarcinoma.[19] This change in lung cancer cell types is associated with changes in smoking patterns. Study by Muhas et el. in 2018 showed that squamous cell type was dominant in male smokers (63.25%), while adenocarcinoma type was prevalent in non-smoker

female (66.67%).[20] This was also found in this study, where 74.8% of male are smokers, while 93.9% of female are non-smokers.

Female's life expectancy was longer than male's (8.74±1.56 months vs. 7.29±0.64 months, *P*=0.95). A study by Radkiewicz et al. in 2019 obtained the same results where male with non-small cell lung cancer had a poorer prognosis than female, both in the type of adenocarcinoma and squamous cell.[21]

CONCLUSION

This study shows that gender disparities affluent by various risk factors such as history of smoking and prior TB infection. And this could affect the prognostic of lung cancer patients at M Djamil Hospital Padang (history of smoking and TB) and prognostic of lung cancer patients at M Djamil Hospital, Padang

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Inflammatory Markers upon Admission as Predictors of Outcome in COVID-19 Patients

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Abstract

Background: *Coronavirus disease 2019 (COVID-19) may cause dysregulation of the immune system, leading to hyperinflammation. Inflammatory markers can be used to predict in-hospital mortality in COVID-19 patients. This research was aimed to investigate the association between the levels of various inflammatory markers and mortality in COVID-19 patients.*
Methods: *This study was conducted at Persahabatan National Respiratory Referral Hospital, Indonesia. Blood tests were performed upon admission, measuring the C-reactive protein, PCT, leukocyte, differential counts, and platelet count. The outcome measured was the mortality of hospitalized COVID-19 patients. Statistical analysis methods included the Mann–Whitney U test, receiver operating characteristic (ROC) analysis, and area under the curve (AUC) test.*
Results: *Total 110 patients were included, and the laboratory values were analyzed to compare survivors and non-survivors. The non-survivor group had significantly higher leukocyte count, lower lymphocyte count, higher CRP and PCT levels, higher neutrophil-to-lymphocyte ratio (NLR), higher platelet-to-lymphocyte ratio (PLR), and lower lymphocyte-to-CRP ratio. As predictors of mortality, AUC analysis revealed that PCT, CRP, NLR, and PLR had AUCs of 0.867, 0.82, 0.791, and 0.746, respectively.*
Conclusions: *Routine and affordable inflammatory markers tested on admission may be useful as predictors of in-hospital mortality in COVID-19 patients requiring hospitalization.* ***(J Respirol Indones 2021; 41(4): 252–9)***
Keywords: *biomarkers; COVID-19; mortality; prognosis*

Penanda Inflamasi saat Masuk Sebagai Prediktor Luaran pada Pasien COVID-19

Abstrak

Latar Belakang: *Coronavirus Disease 2019 (COVID-19) dapat menyebabkan disregulasi sistem imun yang berujung pada hiperinflamasi. Penanda inflamasi dapat digunakan untuk memprediksi mortalitas dan kesintasan pada pasien COVID-19. Penelitian ini bertujuan untuk menyelidiki hubungan antara berbagai penanda inflamasi dengan mortalitas pada pasien COVID-19.*
Metode: *Penelitian ini dilakukan di Rumah Sakit Persahabatan, Indonesia. Uji laboratorium pada sampel darah yang meliputi C-reactive protein (CRP), procalcitonin (PCT), jumlah dan hitung jenis leukosit, dan jumlah trombosit diukur pada saat masuk rawat. Luaran yang dievaluasi adalah kematian pada pasien rawat inap dengan COVID-19. Analisis statistik meliputi uji Mann-Whitney U, analisis karakteristik operasi penerima (ROC), dan uji area di bawah kurva (AUC).*
Hasil: *Data laboratorium dan luaran dari 110 pasien yang dirawat di RS Persahabatan dengan COVID-19 dianalis. Kelompok non-survivor memiliki jumlah leukosit yang lebih tinggi secara signifikan, jumlah limfosit yang lebih rendah, tingkat CRP dan PCT yang lebih tinggi, rasio Neutrofil-ke-Limfosit (NLR) yang lebih tinggi, serta Rasio Platelet-Limfosit (PLR), dan rasio Limfosit / CRP yang lebih rendah. Sebagai prediktor mortalitas, analisis AUC menunjukkan bahwa PCT, CRP, NLR, dan PLR masing-masing memiliki AUC 0,867, 0,82, 0,791, dan 0,746.*
Kesimpulan: *Penanda inflamasi rutin dan terjangkau yang diuji selama masuk mungkin berguna sebagai prediktor kematian di rumah sakit pada pasien COVID-19 yang membutuhkan rawat inap.* ***(J Respirol Indones 2021; 41(4): 252–9)***
Kata kunci: *penanda inflamasi; COVID-19; mortalitas; prognosis*

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously called the novel coronavirus (2019-nCoV). It was first identified following an increase in respiratory illness with an unknown cause.[1,2] The disease spread rapidly throughout multiple countries and was declared a public health emergency of international concern by the World Health Organization (WHO) on 30 January 2020. The WHO escalate the status to be a global pandemic on 11 March 2020. The first two cases of COVID-19 in Indonesia were reported on 2 March 2020, and the number has been increasing since then. As of 23 February 2021, there have been more than 117 million confirmed cases of COVID-19 globally causing disruption in normal healthcare routine.

The mortality rate of COVID-19 is approximately 2–7% and varies Among the countries.[3] Approximately 20% of patients with COVID-19 develop severe symptoms, including acute respiratory distress syndrome requiring hospitalization.[4] As the number of patients with COVID-19 increases, an imbalance between demand and availability of medical assistance may occur.[5–7] This may explain why the mortality rate remains relatively low in developed countries and gradually increase in overburdened countries. Worsen situation emerges urgent need prioritizing healthcare resources to save more lives, for example deciding patient to get advance care in Intensive Care Unit (ICU). Above all, the foremost goal is to keep a low mortality.[8,9]

Along with substantial evidence that COVID-19 may cause dysregulation of the immune system, allows the development of hyperinflammation. Severe cases of COVID-19 tend to have lower lymphocyte counts, higher leukocyte counts, and higher neutrophil-to-lymphocyte ratios (NLR).[10] The NLR is a well-known biomarker of systemic inflammation and infection. Higher NLR values have been associated with poor prognosis in inflammatory diseases, such as sepsis and cancer.[11,12] In COVID-19, the NLR has been suggested as a predictor of poor prognosis. This study aimed to investigate the association between several inflammatory markers tested upon admission and mortality rates in patients hospitalized with severe COVID-19.

METHODS

This was a retrospective cohort study conducted at the Persahabatan National Respiratory Referral Hospital in Jakarta, Indonesia, which is one of the major hospitals responsible for COVID-19 management, assigned by the government. A total sampling method was used. All hospitalized patients aged 18 years and older with confirmed COVID-19 between March and April 2020 were included in this study. The diagnosis of COVID-19 was based on WHO guidelines and confirmed by positive results of SARS-CoV-2 RNA. A total of 110 patients with COVID-19 who had a definite outcome (survivors vs. non-survivors) were included. Outcomes were measured at the time of death or discharge. The patient was discharged after at least 14 days of observation and two consecutive negative reverse transcription polymerase chain reaction (RT-PCR) tests.

Collected data including demographic data (age and sex) as well as laboratory findings (white blood cells [WBCs], neutrophils, lymphocytes, monocytes, platelets, C-reactive protein [CRP], and procalcitonin [PCT]). Using these data, we calculated the NLR, platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-CRP ratio (LCR). All data were extracted from electronic medical records using a standardized data collection form.

Blood samples were obtained within 24 hours after admission to perform routine laboratory tests, such as complete blood count, electrolytes, serum biochemical tests, and coagulation profiles. All measurements were performed within 1 hour after blood sampling. Complete blood count was analyzed using the Sysmex XN-2000 hematology analyzer. The CRP assay was performed using the Abbott Architect c8000. The PCT assay was performed using the Abbot Architect i2000.

Data analysis was conducted using IBM SPSS Statistics for Windows, version 20.0. Descriptive analysis was performed using frequencies and percentages for categorical variables and median (minimum–maximum) for quantitative variables. Bivariate analysis of the associations between various inflammatory markers and in-hospital mortality was performed. Normally distributed data were analyzed as independent samples using the independent sample t-test, while skewed distribution data were analyzed using the Mann–Whitney U test. Comparison of categorical variables between survivors and non-survivors were performed using the chi-square test. The optimal cutoff points for various inflammatory markers were evaluated using receiver operator characteristic (ROC) curves. To minimize observer bias, personnel directly involved in patient care were not involved in the statistical analysis.

This study was approved by the Ethics Committee of the Persahabatan National Respiratory Referral Hospital on 30 March 2020, in Jakarta, Indonesia.

RESULTS

A total of 110 hospitalized patients aged 28–84 years were included in this study. The overall mortality rate was 58.2%. No statistically significant difference in mortality was observed between men and women. The mean age was significantly higher in the non-survivor group (*P*=0.035).

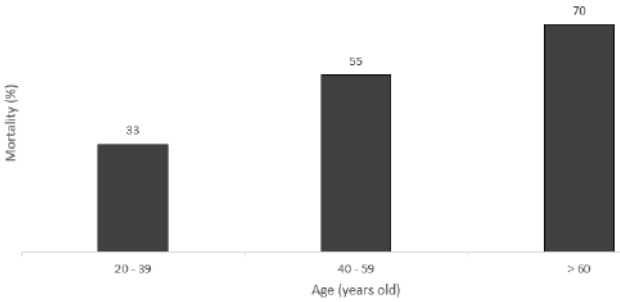

Figure 1. Mortality rate in different age groups (%).

We further divided the subjects into the following three age groups: 20–39, 40–59, and >60 years (Figure 1). Mortality was higher in the older age groups than in the younger, as shown in Figure 1. Differences in the mean values of inflammatory markers between COVID-19 survivors and non-survivors were significant for leukocyte count, neutrophil count, lymphocyte count, CRP, PCT, NLR, PLR, and LCR (Table 1).

For all inflammatory markers described in Table 1, we evaluated their predictive values for mortality using ROC curves (Figure 2). We excluded patients who did not have all inflammatory markers tested on admission. A total of 94 patients were included in the ROC analysis.

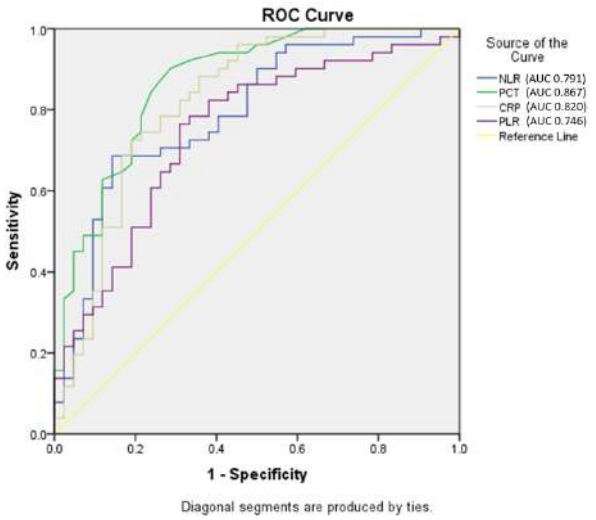

Figure 2. Performance of various inflammatory markers in predicting mortality in COVID-19 patients

These results demonstrated the great predictive capacity of PCT, CRP, NLR, and PLR as possible clinical predictors of mortality in hospitalized COVID-19 patients (Table 2). The optimum cutoff values of various inflammatory markers for the prediction of mortality as well as their sensitivity and specificity are summarized in Table 3.

The predictive capacity of the LCR was evaluated using an area under the curve (AUC) analysis. The LCR AUC as a predictor of good outcome was 0.852 (*P*<0.001; 95% confidence interval [CI]: 0.772–0.932) (Figure 3).

The optimal cutoff point of LCR for the prediction of good outcome was set at 0.086, and the corresponding calculations for sensitivity and specificity as well as the positive and negative predictive values were 81.4%, 77.8%, 84%, and 74.74%, respectively.

Table 1. Characteristics of subjects

Variable	Non-survivor, n (%)	Survivor, n (%)	*P*	RR (95% CI)
Age (years ± SD)	58,11±12,058	52,76±14,054		
Young adult (20–39)	5 (4,5%)	10 (9.1%)		
Adult (40–59)	28 (25,5%)	23 (20.9%)	0,035	
Elderly (>60)	31 (28,2%)	13 (11.8%)		
Gender				
Male	46 (60,5%)	30 (39,5%)	0,456	1.143 (0.793–1.647)
Female	18 (53%)	16 (47%)		
Laboratory findings				
Leucocyte (10^3/µL)	10,74 (3,54–24,18)	6.99 (3.21–17.06)	<0,001	
Neutrophil (%)	86,75 (51,20–95,60)	75,30 (36,40–94,70)	<0,001	
Lymphocyte (%)	7,75 (1,00–39,30)	17,25 (3,20–51,50)	<0,001	
Monocyte (%)	5,80 (1,00–16,10)	6,50 (1,10–14,40)	0,111	
Platelet (10^3/µL)	241,50 (100,00–564,00)	262,00 (43,00–451,00)	0,533	
CRP (mg/L)	164,20 (22,50–449,80)	49,70 (1,50–348,90)	<0,001	
Procalcitonin (ng/mL)	0,29 (0,05–17,66)	0,06 (0,01–1,15)	<0,001	
NLR	11,27 (1,30–94,10)	4,42 (0,71–29,59)	<0,001	
PLR	29,24 (3,42–198,00)	15,34 (3,61–85,00)	<0,001	
LCR	0,04 (0,01–0,73)	0,28 (0,01–14,53)	<0,001	

Note: RR=relative risk; NLR=neutrophil-to-lymphocyte ratio; PLR=platelet-to-lymphocyte ratio; LCR=lymphocyte-to-CRP ratio

Table 2. AUCs of inflammatory markers for predicting mortality in severe, hospitalized COVID-19 patients

Variable	Area under the curve	*P*	95% CI
Neutrophil-to-lymphocyte ratio (NLR)	0.791	<0.001	0.698–0.884
Platelet-to-lymphocyte ratio (PLR)	0,746	<0,001	0,645–0,847
Procalcitonin	0,867	<0,001	0,793–0,941
C-reactive protein	0,820	<0,001	0,730–0,911

Table 3. The cutoff points of PCT, CRP, NLR, and PLR for predicting mortality in severe and critical COVID-19 patients

Cutoff Points	Sensitivity	Specificity	PPV[a]	NPV[b]
Procalcitonin ≥0.155 ng/mL	76.5%	78.6%	82.35%	72.34%
C-reactive protein ≥94,750	80,4%	69%	75,86%	74,36%
Neutrophile/ lymphocyte ratio ≥7,08	70,6%	71,4%	76,36%	60,00%
Platelet/lymphocyte ratio ≥ 19,57	76,5%	69%	75,41%	63,27%

Note: [a]PPV positive predictive value; [b]NPV negative predictive value

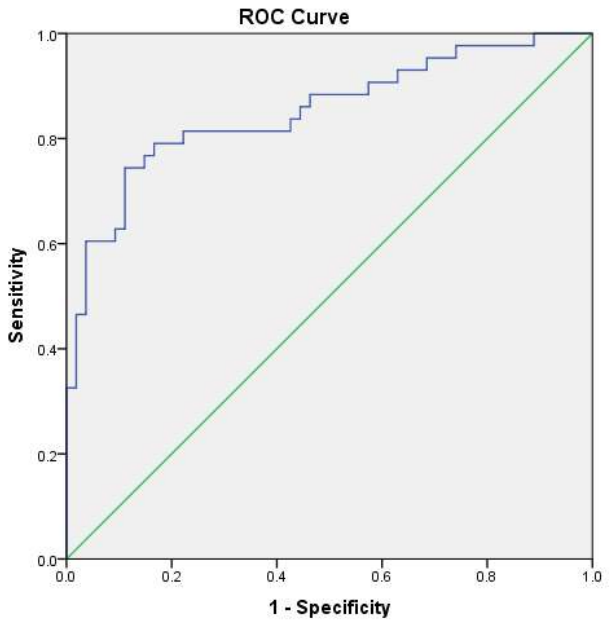

Figure 3. Performance of lymphocyte-to-CRP ratio in predicting good outcome in COVI1D-19 patients with an AUC of 0.852

DISCUSSION

As clinicians in a developing country, we often face the dilemma of deciding which patients would be given the limited health resources, for example, ICU bed, ventilator or high flow oxygen therapy. The particular significance in this study is the fact that we only analyzed inflammatory markers that are affordable and readily available in most hospitals. More importantly, these markers are routinely assessed for every patient during admission, rendering them ideal for screening COVID-19 patients with a higher mortality rate.

In this study, the mortality rate was higher than that reported in other studies. This can be attributed to the fact that the Persahabatan National Respiratory Referral Hospital was a COVID-19

referral hospital; therefore, only patients with severe and critical COVID-19 were hospitalized. This analysis only included patients who were hospitalized and had a final outcome on the day of data analysis. Ongoing treatment patients without final outcome (survival or death) were not included in this study.

This study revealed that older patients had higher mortality rates than younger patients. Increased mortality among elderly might have been caused by the impairment of the immune system characterized by the low-grade and chronic systemic inflammatory state associated with aging.[13] Older patient also tend to have more comorbidities, such as diabetes and hypertension.[14] Diabetes is a chronic inflammatory state disease characterized by multiple metabolic abnormalities that potentially affect the body's response to pathogens. Insulin resistance and the resulting hyperglycemia promote the synthesis of pro-inflammatory cytokines and oxidative stress, which may worsen outcomes in patients with COVID-19.[15,16] Hypertension has also been shown to increase the mortality of patients with COVID-19 through the involvement of vascular damage, although the exact mechanism is still largely unknown.[17]

Based on an analysis of 110 patients with COVID-19, we found that leukocyte and neutrophil counts increased significantly, whereas lymphocytes significantly decreased in non-survivors when compared to those in survivors. According to a study by Qin et al.(10), the decreased lymphocyte subsets are regulatory cells and CD4+ cells, which have vital role in suppressing inflammation. This condition may lead to a hyperinflammatory immune response in patients with severe COVID-19. Well-coordinated immune responses are important in defending against viral infections. However, when the immune system is dysregulated, excessive inflammation may occur, resulting in injury and even death. An increased NLR also suggests that an excessive innate immune response, unbalanced by a dysregulated adaptive immune response, may be the cause of higher severity in COVID-19. The innate immune system plays a major role in the development of sepsis and systemic inflammatory response syndrome (SIRS).[18]

In normal and healthy population, reference ranges have not been established yet; however, several studies suggest the normal NLR value within healthy population within healthy population is approximately 1–3.[19] In line with this study, Yang et al. revealed that increased NLR was associated with poor outcome and resulted in similar AUC value. Yang et al. used 3.3 as the cutoff value to differentiate patients with good and poor outcomes. This yielded higher sensitivity (88%) but lower specificity (63.6%).[20] In this study, the optimal threshold for normal and increased NLR was 7.08, which yielded 70.6% sensitivity and 71.4% specificity.

An increase in CRP level was also observed in non-survivors. The increase in CRP level was positively correlated with COVID-19 severity. Another study demonstrated that the CRP level was higher in critically ill COVID-19 patients than in severe patients, and in severe patients than in moderate patients. It was also revealed that CRP levels were positively correlated with the size of lung lesions. These findings support the assumption that mortality is higher in patients with wider lung lesions.[21] This increase in CRP is also consistent with findings from another study by Yan et al.[22] in which machine learning was used to select inflammatory markers with the highest value in predicting mortality. According to Yan's study, inflammatory markers can be used to predict mortality up to 7 days before the outcome. In this study, we demonstrated that inflammatory-marker testing on hospital admission can accurately predict mortality, regardless of the duration from admission to outcome.

We also examined the LCR as a predictor of good outcome. Similar to NLR, LCR is a marker that reflects systemic inflammatory responses.[23] LCR has been used as a prognostic predictor in several diseases. Lower levels of LCR have been shown to indicate poor prognosis in patients with colorectal and gastric cancers.[24,25] A recent meta-analysis demonstrated that lower LCR was associated with poor prognosis in patients with COVID-19.[26] In this study, a higher LCR was associated with better

outcome. As shown in a previous study, regulatory and CD4+ lymphocyte cells were decreased in COVID-19 patients.[10] These two lymphocyte subsets play an important role in maintaining a normal inflammatory response. On the other hand, CRP has long been known as a marker for systemic inflammation.[27] Therefore, this may indicate that dysregulation of the immune response in patients with high LCR is less severe thus resulting lower mortality.

However, in this study, the strongest predictor was PCT. Procalcitonin is routinely tested in patients with pneumonia and other critical conditions to determine whether a patient has a concomitant bacterial infection leading to sepsis. In COVID-19, bacterial infection, indicated by an increase in PCT, may be the strongest predictor of mortality in patients with COVID-19.[28] However, PCT levels may also be elevated in the absence of bacterial infection, typically during tissue injury. Currently, we know that COVID-19 may induce coagulopathy, resulting in wide tissue injury. The elevated PCT in COVID-19 patients may reflect this condition. The cutoff for poor prognosis in this study (0.155 ng/mL) was similar to the well-established cutoff for elevated PCT (0.15–0.2 ng/mL).[29,30]

Through these results, we may predict which patient have poorer prognosis. In the clinical setting during pandemic, the decision made using this newfound knowledge may goes both ways. In the setting of overwhelming number of patients, typical in disaster situation, clinician may prioritize patient with better odds of survival. However, in healthcare center with adequate medical resources, clinician should prioritize patient with more severe COVID-19.

The limitation of this study is the lack reporting of different antibiotic use during hospitalization. Due to limited data, we also Did not foresee comorbidities and bacterial coinfection as potential confounding factors in predicting mortality. Further studies to assess the efficacy of antibiotic administration and the role of comorbidity in increasing mortality in patients with COVID-19 are paramount. Another limitation of this study is that it was conducted in national respiratory referral hospital during the first phase of COVID-19 pandemic. The patients referred to this hospital were relatively in more severe condition compared to other hospital. Therefore, the result of this study may not be applicable in community setting That have generally milder symptoms.

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CONCLUSION

Routine and affordable inflammatory markers tested on admission may be useful as predictors of mortality in COVID-19 patients requiring hospitalization and help clinician prioritize patient according to the availability of medical resources. This screening method can be used both in referral healthcare center and peripheral hospital. The markers reviewed in this study, especially peripheral blood sampling, is routinely checked. Procalcitonin gave the best prediction, however it may not be available in rural hospital.

This study does not include several important variables such as antibiotic use, the presence of concomitant bacterial infection, and comorbidity due to constraint of resources during the early days of pandemic. The result of this study may not accurately reflect the pandemic situation in the current days. On the other hand, this study may also prove that continuous research is needed to accurately assess the ever-changing COVID-19 situation. We encourage fellow researcher to further investigate this subject of interest.

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Correlation between Measurement of Lung Diffusion Capacity Using Single Breath Methods (D_{LCO}-SB) and COPD Group in Persahabatan Hospital Jakarta

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Abstract

Background: *This was a preliminary study to measure D_{LCO}-SB on COPD patients in Persahabatan Hospital to understand the prevalence of D_{LCO} reduction among COPD patients.*

Methods: *This was a cross sectional study of COPD patients who attended COPD-Asthma clinic in Persahabatan Hospital Jakarta. Spirometry and D_{LCO} -SB were performed consecutively during May–July 2015. Comorbidities were also recorded.*

Results: *Spirometry and D_{LCO} -SB measurements were conducted on 65 COPD subjects of which 10.8% subjects were in COPD Group A, 29.2% Group B, 32.3% Group C and 27.7% Group D. The mean age was 64.15; mean FEV_1% was 46.05%, mean D_{LCO} measured was 19.42 ml/min/mmHg and the mean D_{LCO} % was 72.00%. The proportion of D_{LCO} decline among COPD patients was 56.92%. There were significant correlations between COPD group, GOLD COPD grade, FEV_1, BMI and comorbidities with the D_{LCO} value results. There were no significant correlation between D_{LCO} value with sex, age, smoking history, Brinkmann Index, obstructive-restrictive criteria, comorbidities and length of COPD period.*

Conclusion: *The proportion of D_{LCO} decline among COPD patients was 56.92%. There were significant correlations between COPD group, GOLD COPD grade, FEV1, BMI and previous TB history with the results of D_{LCO}.* ***(J Respirol Indones 2021; 41(4): 260–71)***

Keywords: *spirometry, diffusion capacity of the lung for carbon monoxide (D_{LCO}), COPD, comorbidities*.

Hubungan antara Pemeriksaan Kapasitas Difusi Paru terhadap Karbon monoksida Metode Napas Tunggal (D_{LCO}-SB) dan Grup PPOK di RSUP Persahabatan Jakarta

Abstrak

Latar belakang: *Penelitian ini merupakan studi awal untuk mengukur D_{LCO} -SB pada pasien PPOK di RSUP Persahabatan Jakarta yang bertujuan mengetahui prevalens penurunan D_{LCO} pada pasien PPOK.*

Metode: *Penelitian ini menggunakan desain potong lintang pada pasien PPOK yang berkunjung ke Poliklinik Asma-PPOK RSUP Persahabatan Jakarta. Dilakukan uji spirometri dan D_{LCO} -SB pada pasien PPOK yang diambil secara berurutan antara bulan Mei-Juli 2015. Komorbiditas juga dicatat.*

Hasil: *Uji spirometri dan D_{LCO} -SB dilakukan pada 65 subjek yang terdiri dari 10,8% pasien PPOK Grup A, 29,2% Grup B, 2,3% Grup C dan 27,7% Grup Ddidapatkan rerata usia 64,15 tahun, rerata VEP_1% 46,05%, rerata nilai D_{LCO} 19,42 ml/menit/mmHg dan rerata D_{LCO} % sebesar 72,00%. Proporsi penurunan D_{LCO} pasien PPOK adalah 56,92%. Terdapat hubungan bermakna antara grup PPOK, derajat GOLD PPOK, VEP_1, IMT dan komorbiditas dengan nilai hasil uji D_{LCO}. Tidak terdapat hubungan bermakna antara nilai D_{LCO} dengan jenis kelamin, umur, riwayat merokok, Indeks Brinkmann, kriteria obstruksi-restriksi, komorbid dan lama terdiagnosis PPOK.*

Kesimpulan: *Proporsi penurunan nilai DLCO pada pasien PPOK adalah 56,92%. Terdapat hubungan bermakna antara grup PPOK, derajat GOLD PPOK, VEP_1, IMT dan riwayat TB dengan hasil uji D_{LCO}.* ***(J Respirol Indones 2021; 41(4): 260–71)***

Kata kunci: *spirometri, kapasitas difusi paru (D_{LCO}), PPOK, komorbiditas.*

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the non-communicable diseases which is a public health problem in Indonesia and was predicted to be the third cause of death in the world by 2020. Patients of COPD increase every year and as a cause, among other things, increased life expectancy and high exposure to risk factors. The host factor associated with the incidence of COPD cases is the increasing number of smokers (especially at young age) and also outdoor and indoor air pollution at work.[1,2]

Patients with moderate to severe COPD in Asia in 2006 had reached 56.6 million cases with a prevalence of 6.3%. The prevalence ranged from 3.5 to 6.7% as in China with COPD cases reaching 38.16 million, Japan had 5.014 million and Vietnam had 2.068 million cases. In Indonesia it was estimated at 4.8 million patients with a prevalence of 5.6%. At Persahabatan Hospital Jakarta, COPD patients increased from 616 in 2000 to 1735 in 2007.[3] These cases will increase in the future in line with the high smoking habits (men over 15 years 60–70%), population growth, increasing mean age of population, high burden industrialization, air pollution (especially in big cities, industrial and mining activities).[1–4]

COPD is a preventable and treatable lung disease, characterized by persistent airflow limitation which is usually progressive and associated with chronic inflammatory and respiratory responses to toxic/dangerous particles or gases. Exacerbations and comorbidities contribute to the severity of the disease.[1]

The characteristics of airway obstruction in COPD are caused by a combination of small airway obstruction (bronchiolitis obstruction) and various parenchymal damage (emphysema) in each individual.[1] Chronic inflammation causes changes in airway structure and narrowing in small airway. Pulmonary parenchymal destruction is also caused by an inflammatory process that results in damage to the wall of alveoli and reduces pulmonary elastic recoil so that these changes limit the ability of the airways to remain open during expiration. Airflow resistance can be assessed with spirometry devices that have been used throughout the world, in addition to be easily obtained and also reproducible in lung function test.[1,2]

Chronic inflammatory response induces parenchymal destruction leading to emphysema and disrupts normal repair mechanism and resilience of lung tissue resulting in small airway fibrosis. These pathological changes induce air trapping and progressive airway obstructions which lead to shortness of breath and typical COPD symptoms. Gas exchange from the alveoli to the capillary blood vessels can be estimated by measuring the capacity of the pulmonary diffusion of carbon monoxide (D_{LCO}). Decrease in D_{LCO} values can be due to the surface area of the alveolar-capillary gas exchange area, pulmonary capillary blood volume, membrane thickness and hemodynamic conditions such as cardiac output and hemoglobin levels. D_{LCO} is an examination to evaluate the severity of pulmonary fibrosis and pulmonary emphysema.[1,5]

Air trapping or residual volume deteriorates from the beginning of the COPD diagnosis so that the airway obstruction further worsens the pulmonary static hyperinflation. These changes can be measured by a body plethysmograph, or by measuring lung volume using helium dilution method but the accuracy is still below the body plethysmograph. D_{LCO} test with a single breath method provides information about the functional effects of emphysema in COPD and assists to explain the condition of patients with shortness of breath that is not in accordance with the degree of airway obstruction.[1,6–8]

This test is carried out to assess the estimated gas diffusion from the alveoli to pulmonary capillary vessels. Studies abroad found that D_{LCO} values were reduced in COPD patients and associated with decreased alveolar-capillary surfaces due to progression of pulmonary emphysema.[9,10] Deesomchok, et al.[10] obtained that 20% of grade 1 COPD patients had decreased D_{LCO} values below 70% of predictive value. Sin, et al.[10] found that 50% of grade 3 and 4 COPD patients had significant

decrease in D_{LCO} values. Another study found a significant positive correlation between the value of the first second forced expiratory volume (FEV_1) and D_{LCO} value. However, there were still no data about D_{LCO} test in COPD patients in Indonesia.[9–11]

This study aimed to determine the correlation between the D_{LCO} values using single breath method with the degree of COPD patients according to GOLD 2014.

METHOD

This cross-sectional study was conducted at Asthma-COPD Clinic of Persahabatan Hospital Jakarta during May to July 2015. Study subjects were all stable COPD patients who visited the Asthma-COPD Clinic in Persahabatan Hospital from May to July 2015. Primary data were obtained from interviews based on questionnaires while secondary data were gained from medical records of study subjects.

The sample size in this study was calculated based on the formula for cross sectional study. It was obtained as much as 60 subjects using consecutive sampling. Inclusion criteria were all stable COPD patients who visited the Asthma-COPD Clinic at the time of the study, and willing to sign informed consent after the full explanation of the study procedure. The exclusion criteria were COPD patients with comorbidities (such as diabetes mellitus (DM), interstitial lung disease (ILD), history of asthma, lung cancer and human immunodeficiency virus (HIV) infection) based on medical record data and COPD patients who were unable to complete spirometry examination and measurement of pulmonary diffusion capacity.

Study subjects will be interviewed and performed physical examination, spirometry and D_{LCO} test, examined for dyspnea score based on mMRC dyspnea score and COPD Assessment Test (CAT) and filled out study worksheet.

The research data were processed descriptively to see the frequency distribution of all observed variables, and bivariate analysis to see the correlation of each independent variable with the dependent variable observed followed by multivariate analysis if the requirements were fulfilled.

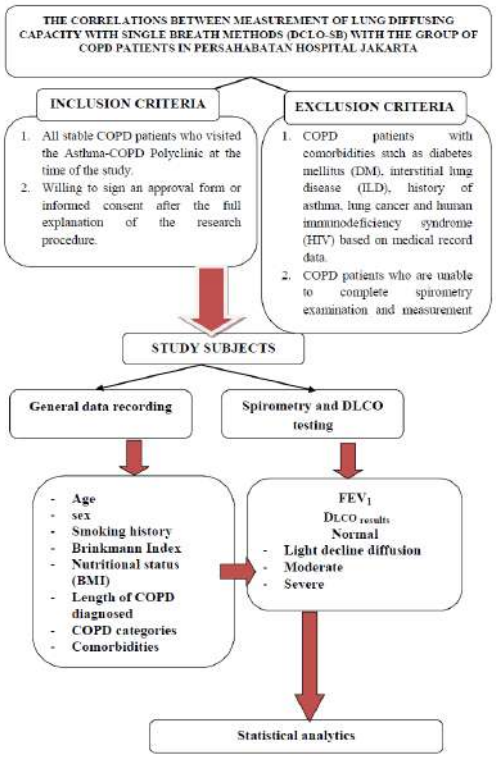

Figure 1. Study Pathway

RESULTS

The results of this study were primary data obtained from interviews, physical examination, spirometry examination and D_{LCO} test. A total of 65 subjects were consecutively collected and interviewed then spirometry and D_{LCO} tests were carried out.

Subjects consisted of 60 (92.3%) men and 5 (7.7%) women. Most subjects (39 subjects) were in the age range of 60-79 years. The highest level of education in the subjects was 27 (41.5%). There were 25 subjects who were still employed (38.5%) while those unemployed were 40 subjects (61.5%). Subjects who had smoking history were 56 subjects (86.2%) and 9 were non-smokers (13.8%). There were 55 subjects (84.6%) with moderate Brinkmann Index (BI) and 10 subjects (15.4%) with mild BI. Subjects diagnosed as COPD within less than or equal to 5 years were 57 subjects (87.7%) and who were more than 5 years were 8 subjects (12.3%). Based on the distribution of COPD group, the

subjects of COPD group A were 7 subjects (10.8%), group B of 19 subjects (29.2%), group C of 21 subjects (32.3%) and group D of 18 subjects (27.7%). If divided into COPD groups according to the latest GOLD criteria, group A-B COPD were 26 subjects (40%) and group C-D COPD were 39 subjects (60%). A total of 40 subjects (61.5%) with normal and lowest BMI were 2 subjects with obese. A total of 47 (27.3%) subjects had comorbidities while 18 (27.7%) subjects were without comorbidities. Subjects with former TB were 24 subjects (36.9%) and those without TB history were 41 subjects (63.1%). The characteristics distribution of subjects based on COPD groups spreaded mainly in COPD groups B, C and D. The complete subject characteristics can be seen in Table 1.

Table 1. Subject characteristic base on COPD group

Subject Characteristic	COPD Group				Total	%
	Group A	Group B	Group C	Group D		
Age						
40–59 years old	3	4	11	5	23	35.4
60–90 years old	4	15	10	13	42	64.6
Percents	10.8%	29.2%	32.3%	27.7%	100%	
Sex						
Male	7	18	18	17	60	92.3
Female	0	1	3	1	5	7.7
Education level						
Uneducated	1	2	0	1	4	6.2
Primary School	0	1	6	4	11	16.9
Junior High School	1	4	3	3	11	16.9
Senior High School	3	8	9	7	27	41.5
D3/S1 degree	2	4	3	3	12	18.5
Employment						
Employed	4	6	10	5	25	38.5
Unemployed	3	13	11	13	40	61.5
Smoking history						
Smokers	6	17	17	16	59	90.8
Non-smokers	1	2	4	2	6	9.2
BI (Brinkmann Index)						
Mild	1	2	4	3	10	15.4
Moderate	3	7	8	9	27	41.5
Severe	3	10	9	6	28	43.1
Length of time diagnosed as COPD						
0–5 years	6	14	20	17	57	87.7
≥5 years	1	5	1	1	8	12.3
BMI						
Malnutrition	1	1	5	5	12	18.5
Normal	6	13	9	10	38	58.4
Overweight	0	5	5	2	12	18.5
Obese	0	0	2	1	3	4.6
Spirometry test						
Obstructive	7	19	15	14	55	84.6
Mixed	0	0	6	4	10	15.4
Comorbidities						
Yes	3	12	16	16	47	72.3
No	4	7	5	2	18	27.7
TB history						
Yes	1	3	11	8	24	36.9
No	6	16	10	10	41	63.1
Total	7	19	21	18	65	100

Table 2. Mean value of spirometry and D_{LCO} test

Variable	Minimum	Maximum	Mean	SD
Age (year)	45	89	64.15	9.222
BMI (kg/m^2)	14	39	22.13	4.636
FEV_1(ml)	580	3160	1243.23	534.933
FEV_1 %	23	97	46.05	17.22682
FVC (ml)	1150	4520	2402.15	633.109
FVC %	34	98	68.23	14.90362
FEV_1/FVC%	35	104	66.40	16.28439
PEF (l/second)	1.61	9.82	4.31	1.50810
PEF %	25	109	59.61	19.48384
FEF_{25-75}	0.14	1.74	0.47	0.36140
FEF_{25-75} %	4	74	22.89	16.45555
D_{LCO} (ml/min/mmHg)	8.90	36.40	19.42	8.30442
D_{LCO}%	34	137	72.00	29.41817
VA(L)	2.58	7.43	4.49	1.15171
VA %	57	137	92.97	18.49828
KCO (ml/min/mmHg/L)	2.13	8.70	4.39	1.39650
KCO%	39	164	82.40	25.11586

Table 3. D_{LCO} value interpretations based on Degree of COPD and COPD group.

COPD Group	D_{LCO} Result (n)				Total	%
	Normal	Mild	Moderate	Severe		
COPD Group						
Group A	5	1	0	1	7	10.8
Group B	11	5	2	1	19	29.2
Group C	5	6	9	1	21	32.3
Group D	7	3	7	1	18	27.7
COPD degree						
GOLD 1	3	0	0	0	3	4.6
GOLD 2	13	6	4	2	25	38.5
GOLD 3	9	7	8	1	25	38.5
GOLD 4	3	2	6	1	12	18.5
Total	28 (43.07)	15 (23.07)	18 (27.69)	4 (6.15)	65	100

The mean age of the study subjects was 64.15 years (45–89). Mean BMI was 22.13 kg/m^2 (14–39). The mean FEV1% predictive value was 46.05% (23–97). The mean value of FEV_1/FVC was 66.40% (35–104). The mean D_{LCO} in ml/minute/mmHg was 19.42 (8.90-49.50). The mean D_{LCO}% predictive value was 72.00% (34–137). The mean value of KCO (D_{LCO}/VA) was 4.39 ml/minute/mmHg/L (2.13–8.70). The mean KCO% predicted was 82.4% (39–164). The characteristics of spirometry and D_{LCO} test results can be observed in Table 2.

Based on the interpretation of the D_{LCO} test according to the COPD degree of the latest GOLD criteria, the proportion of patients with D_{LCO} impairment was 37/65 (56.9%) while 28/65 (43.1%) had normal D_{LCO} values. Complete explanations were shown in Table 3.

If assessed by the degree of COPD according to spirometry criteria, in GOLD 1–2 COPD 16/28 subjects (57.1%) had normal D_{LCO} values, 6/28 subjects (21.4%) had mild decrease and 6/28 subjects (21.4%) had moderate decrease. Whereas in GOLD 3–4 COPD there were 12/28 subjects (42.9%) with normal D_{LCO} values, 6/28 subjects (21.4%) with mild decrease and 6/28 subjects (21.4%) with severe decrease. D_{LCO} The proportion of decreased D_{LCO} in group A-B were 10/26 subjects (38.5%) while in group C-D 27/39 subjects (69.2%). Bivariate analysis with chi-square test obtained *P* value of 0.014 (P<0.05). There was a significant correlation between COPD groups and decreased D_{LCO} values. The higher the COPD group (C-D) the greater the D_{LCO} decreased. More complete data are shown in Table 4.

Table 4. COPD group correlation with D_{LCO} results

COPD group	D_{LCO} results (n)		Total	%	*P*
	Normal	Decline			
Group A+B	16	10	26	40	0.014*
Group C+D	12	27	39	60	
Total	28	37	65	100	

Note: ***Chi-square test*

If the criteria of COPD group were divided into 4 main variables, which were GOLD degree based on spirometry, exacerbation history per year, breathlessness scale according to mMRC and CAT, it was found that spirometry had a significant correlation with decreased D_{LCO} (*P*=0.046) using bivariate analysis of Chi-square test. The proportion of D_{LCO} reduction in GOLD 1–2 was 12/28 subjects (42.9%) while in GOLD 3–4 was 25/37 subjects (67.6%) Higher degree of COPD had a decline in D_{LCO} value.

Table 5. Correlation of spirometry GOLD degree, CAT score, exacerbation and mMRC scale to D_{LCO} results

Categories	D_{LCO} results		Total	%	*P*
	Normal	Decline			
COPD degree					
GOLD 1–2	16	12	28	43.1	0.046*
GOLD 3–4	12	25	37	56.9	
mMRC scale					
mMRC 0–1	21	29	50	76.9	0.749*
mMRC ≥2	7	8	15	23.1	
Exacerbation history					
0–1 per year	24	35	59	90.8	0.221*
≥2 per year	4	2	6	9.2	
CAT score					
<10	9	19	28	43.1	0.121*
≥10	19	18	3	56.9	
Total	28	37	65	100	

Note: **Chi-square test*

When the FEV_1 value was divided into 2 categories; FEV_1 <1500 ml and ≥1500ml, in subjects with FEV_1 <1500 ml (49 subjects), the prevalence of D_{LCO} was about 33/49 subjects (67.3%) while insubjects with FEV_1 <1500 ml (16 subjects), the prevalence of D_{LCO} was about 4/16 subjects (25%). There was a significant correlation between the FEV_1 value and the D_{LCO} results. Subjects with FEV_1 <1500 ml experienced decrease in D_{LCO} values with *P* value of 0.004. The lower the FEV_1 value, the lower the D_{LCO} value.

Table 6. Correlation of FEV_1 values and DLCO results

FEV_1	D_{LCO} results (n)		Total	%	*P*
	Normal	Decline			
<1500 ml	16	33	49	75,4	0,004*
≥1500 ml	12	4	16	24,6	
Total	28	37	65	100	

Note: **Chi-square test*

Table 7. Factors that influenced the D_{LCO} results

Categories	D_{LCO} results		Total	*P*
	Normal	Decline		
Age group				
40–59 years	13	10	23	0.123*
60–90 years	15	27	42	
Sex				
Male	27	33	60	0.278*
Female	1	4	5	
Smoking History				
Smokers	24	32	56	0.602*
Non-smokers	4	5	9	
Brinkmann Index				
Mild	5	5	10	0.631*
Moderate-severe	23	32	55	
Obstruction Categories				
Obstructive	26	29	55	0.176*
Obstructive-restrictive	2	8	10	
Length of time diagnosed as COPD				
0–5 years	22	35	57	0.052*
≥5 years	6	2	8	
BMI				
Non-obese	16	34	50	**0.001***
Obese	12	3	15	
Comorbidities				
Yes	17	30	47	0.069*
No	11	7	18	
Total	28	37	65	

Note: **Chi-square test*

Of the several factors which affected the D_{LCO} values (sex, age, smoking history, BI, BMI, comorbidities, obstruction and length of COPD period), only BMI had a significant correlation with decreased D_{LCO} value (*P*<0.001).

It was found that 24 subjects (36.9%) were former TB and 41 subjects (63.1%) were not. COPD subjects with former TB experienced a decrease in D_{LCO} values compared with no TB history (*P*=0.037).

Table 8. Correlation of TB history with D_{LCO} results

TB history	D_{LCO} results (n)		Total	%	*P*
	Normal	Decline			
Yes	6	18	24	36.9	0.037*
No	22	19	41	63.1	
Total	28	37	65	100	

Note: **Chi-square test*

From bivariate analysis we found 5 variables with statistically significant correlation with decreased D_{LCO}, namely: FEV_1 value, COPD spirometry degree, COPD group, BMI and comorbidities. Afterward, we conducted a multivariate analysis using binary logistic regression method and received 2 variables with strong correlation to the D_{LCO} reduction, they were BMI with *P* value of 0.002 and FEV_1 with *P* value of 0.015.

Tabel 9. Multivariate Analysis (Binary logistic regression)

Variables	CI 95%	*P*
COPD group	0.362–2.291	0.240
COPD Degree	0.109–9.463	0.663
BMI	0.018–0.405	0.001
FEV_1	0.104–0.942	0.015
TB history	0.107–0.945	0.683

DISCUSSION

Subjects that was found the most in this study were in COPD group C (32.3%), followed by group B (29.2%). COPD patients often present with disturbing complaints so that patients start to look for treatment. Our study obtained subjects according to GOLD degree as GOLD 1 of 3 subjects (4.6%), GOLD 2 of 25 subjects (38.5%), GOLD 3 of 25 subjects (38.5%) and GOLD 4 of 12 subjects (18.5%). However, Boutou, et al. in their study that examined 604 COPD patients found GOLD 1 of 2.3%, GOLD 2 of 17%, GOLD 3 of 28.4% and GOLD 4 of 52.2%.[12]

Subjects in this study were 92.3% men and 7.7% women with mean age of 64 years, similar with study of Zhang, et al. in China on subjects with stable COPD that obtained mean age of 64 years among 89% men and 11% women.[13] Chugh, et al. in India gained a lower mean age of 61.50 years.[14] It was slightly different from previous local studies by Hanif and Hastuti with mean age of 67 years.[15,16] Miniati, et al. in Italy discovered mean age of 66 years among COPD patients. The highest age group in this study was more than 60 years, 64.4% of which was distributed in group B, C and D.[17] This was higher than study of Hanif that found 57.7% subjects in the age group >65 years.[15]

Moreover, Hastuti got higher subjects in the age group above 65 (71.1%).[16] This showed an increase in life expectancy and survival of COPD patients along with the quality improvement of the available health services. When viewed from the education level, secondary education (Junior High School and Senior High School) was the highest level of education (58.4%), the same result was observed in study by Hanif (57.8%) and Hastuti (57.9%).[15,16]

The number of patients diagnosed as COPD within 0–5 year reached 85.7%, this was because there were still many patients who routinely visited for regular control in the COPD clinic while those diagnosed above 5 years were 12.3%. This number was far less considering that COPD was progressively slow so that the COPD degree became heavier resulting in morbidity and mortality due to illness or other causes.

A total of 86.2% subjects had a previous smoking history. It was lower than study from Hanif (94.4%) and Hastuti (96%).[15,16] This stated that smoking was still the main cause of COPD in Indonesia. Only 13.8% of subjects who had no history of smoking in their lives were likely to become passive smokers or suffered from occupational COPD, related to the exposure to biomass. The severe BI in this study was 43.1%, almost similar to Hastuti (49.3%). Different result was seen in study from Hanif (56.71%). Miniati, et al. found an average BI index of 55%. These results supported smoking as a major risk factor for COPD.[17]

The mean BMI in this study was 22.13 kg/m^2 which was almost identical to study from Hanif that was 22 kg/m^2 and Hastuti 21 kg/m^2.[15,16] Andrianopoulous, et al. and Cassanova, et al. received higher result of 25.6 kg/m^2 and 28 kg/m^2, respectively.[18,19] These results indicated that the nutritional status of COPD patients in Europe was better than developing countries such as in Indonesia. In this study most subjects had normal BMI (61.5%), higher than Hanif (47.9%) and Hastuti (39.3%).[15,16]

We obtained 47 subjects (72.3%) with comorbidities which included mainly cardiovascular comorbidities (hypertension, heart failure and

ischemic cardiac history), while COPD subjects with previous TB history were 36.9%. Miniati, et al. also gained the same result of most comorbidity that was cardiovascular in as much as 95% subjects and the rest was other comorbidities. In this study there were 24 subjects (36.9%) with former TB while Miniati, et al. was 5%.[17] This might be due to Indonesia as the fourth highest country in TB cases in the world and the majority of TB patients also had smoking history. This was in contrast to European countries and other developed countries that had relatively small TB cases compared to degenerative and metabolic diseases.

We found mean FEV_1% predictive value of 46.05%, mean FEV_1/FVC of 66.40%, mean D_{LCO} result of 19.42 ml/minute/mmHg, mean D_{LCO}% predictive value of 72.00%, mean value of KCO (D_{LCO}/VA) of 4.39, and mean KCO% prediction of 82.4%. Sin, et al. studied 24 COPD patients in Ankara, Turkey in 2006 and found mean predicted FEV_1% of 43.79%, FVC% predicted value of 59.54%, FEV_1/FVC percent of 56%, D_{LCO} of 11.45 ml/minute/mmHg, D_{LCO}% predicted value of 49.16%, KCO of 3.13 ml/min/mmHg/L and KCO% (D_{LCO}/KCO) of 79.47.[10] Those numbers were lower than our study.

Gonzales-garcia, et al. in Bogota, Colombia on 2004 studied 25 COPD patients, 7 of them were women. They found out those subjects had moderate obstruction (43.3% VEP1) and moderate to severe D_{LCO}% 53.1% as much as 23%, FEV_1% predicted value of 43.3%, FEV_1/FVC of 44.7%, D_{LCO} of 14.68 ml/minute/mmHg, D_{LCO}% predicted value of 53.10, D_{LCO}/VA value of 3.20 ml/min/mmHg/L and predicted D_{LCO}/VA% of 65.7%.[20] Those numbers were also much lower than our study. Study from Boutou, et al. in Greece obtained FEV_1/FVC% prediction of 84.5% and mean D_{LCO}% prediction of 40.8%. The D_{LCO} value of COPD subject in this study was still higher than the results of study in Europe and South America.[12] This might be due to various subjects and there was a tendency to choose a subject that was truly able to complete the examination because the D_{LCO} test equipment could not be placed in clinic for safety reason.

Based on the interpretation of the D_{LCO} test in accordance with the COPD degree based on the latest GOLD criteria, the proportion of patients with a decrease in D_{LCO} values were 37 subjects (56.9%) while with normal D_{LCO} values were 28 subjects (43.1%). If the subjects were assessed by the degree of COPD according to spirometry criteria, in GOLD 1–2 COPD there were 16/28 subjects (57.1%) with normal D_{LCO} values and 12/28 subjects (42.8%) with decreased D_{LCO} values. Nevertheless, in GOLD 3–4 COPD there were 12/37 subjects (32.4%) with normal D_{LCO} values and 25/37 subjects (67.6%) with decreased D_{LCO}. The decreased D_{LCO} values in group A-B were observed in 10/26 subjects (38.5%) while in group C-D 27/39 subjects (69.2%). There was a significant correlation between COPD groups and decreased D_{LCO} values. There was a tendency of D_{LCO} value to decline in higher COPD group (C-D) with a *P* value of 0.014.

Foreign studies stated that D_{LCO} values decreased in COPD patients due to reduced alveolar-capillary surface caused by the development of pulmonary emphysema. Deesomchok, et al. discovered that 20% of patients with COPD grade 1 had decline in D_{LCO} values below 70% predictive value.[9] Fujimoto, et al. in 2011 found that COPD patients with emphysematous phenotype in inspiratory capacity and low D_{LCO} values showed greater dynamic hyperinflation compared to COPD patients with nonemphysematous phenotype.[21]

The decrease in pulmonary elastic recoil and alveolar bond due to alveolar destruction contributed significantly to the collapse of the alveoli and early airway closure during expiration (dynamic hyperinflation). Sariaydin, et al. stated that D_{LCO} values were reduced in emphysema patients in addition to the loss of alveolar-capillary surface area and heavy obstruction of the airway.[22] Sin, et al. in 2006 revealed that among 24 COPD patients, as many as 79% was proven to have parenchymal emphysema and about 50% had a decrease in D_{LCO} value.[10] Reduced D_{LCO} values might have a direct linkage to the loss of surface area of the alveolar capillary membrane due to emphysema. To assess

the level of emphysema, it was strongly recommended to conduct a High-Resolution Computed Tomography (HRCT) examination to determine the extent of the emphysema, and a D_{LCO} examination to confirm how much impairment in pulmonary diffusion capacity.

Of the four components that were elements to determine the distribution of COPD based on the group, the one that had a significant correlation with the D_{LCO} value was the degree of COPD based on spirometry with a *P* value of 0.046. The higher the degree of COPD, the more the tendency of decreased D_{LCO} value. Tanabe, et al. conducted a longitudinal study on the impact of COPD exacerbations on emphysema which resulted in exacerbations that caused the development of pulmonary emphysema in COPD patients. Emphysema progressiveness was also associated with a significant reduction in D_{LCO} values and should be evaluated as one of the considerations for COPD management.[23]

Lee. et al. in 2011 obtained 126 of 197 COPD patients were detected with emphysema while the rest 71 were non-emphysematous. They also found that COPD patients with emphysema had lower survival rates and higher rate of pulmonary loss.[24] Brusasco, et al. found that decline of D_{LCO} increased according to the degree of COPD. The D_{LCO} value started to decrease dramatically in GOLD 3–4. Decrease in D_{LCO} value compared to alveolar volume (D_{LCO}/VA) were seen in degree 1 because of early increase in VA and a tendency to increase to GOLD 4.[25]

In this study there was a significant correlation between the FEV_1 value and the D_{LCO} results. FEV_1 <1500 ml had more probability to have a decline in D_{LCO} values with *P* value of 0.004. The lower the FEV_1 value, the lower the D_{LCO} value. According to Brusasco, et al. the decreased D_{LCO} values in COPD patients usually occured after a decrease in FEV_1, so if D_{LCO} impairment was found to be severe but spirometry exhibited mild obstruction, another cause of D_{LCO} impairment should be considered.[25] Cystic fibrosis and alpha-1 antitrypsin enzyme deficiency should be considered in children and young adults with low obstruction and D_{LCO} values. This pattern was also seen in adult patients with bronchiolitis obliterans, bronchiectasis and lymphangioleiomyomatosis. The rate of decline in FEV_1 values could be predicted by the degree of obstruction and airway hyper reactivity. There was a little evidence that a decrease in D_{LCO} predictive values intensified mortality and morbidity in COPD patients (from baseline FEV_1 and airway hyper reactivity).[7,25]

Factors which influenced the results of D_{LCO} were: age, sex, smoking history, Brinkmann Index, obstruction category, duration of diagnosis of COPD, BMI category and comorbidities. After statistical analysis among factors which influenced D_{LCO}, BMI had a significant correlation with a decrease in D_{LCO} (*P*=0.001). The lower the BMI, the higher the risk of decrease in D_{LCO} value. Casanova, et al. revealed that the lower the BMI, the higher the risk of developing pulmonary hyperinflation which developed into emphysema.[3] The more severe the emphysema, the lower the D_{LCO} value. The age group of 60-90 years had a predisposition to decrease in D_{LCO} although it was not statistically significant (*P*=0.123). This could be due to the relatively small number of study subjects. Male sex was the majority subject in this study after statistic test pointed out a non-significant result and it was not related to a decrease in D_{LCO} value (*P*=0.278). From various studies, gender also did not have a significant correlation to the decline in D_{LCO} value.

In this study 57.1% of subjects with a history of smoking experienced a decrease in D_{LCO} values. It was statistically not found to be significant (*P*=0.075) but it clinically revealed that COPD patients with a smoking history would tend to experience a decrease in D_{LCO} values compared to those who did not smoke as smoking was the main risk factor for COPD. McCormack and colleagues stated that active smokers had lower D_{LCO} values which were more significant than non-smokers.[27] An important factor to be integrated into clinical interpretations such as when D_{LCO} went back to normal partially after quitting smoking, was to estimate the degree of D_{LCO} disorder due to

asbestos exposure. Decreased D_{LCO} in active smokers was not always associated with emphysema and could be affected by an increase in carboxyhemoglobin levels. However, the shortcoming in this study did not include hemoglobin examination as one of the factors which could influence the D_{LCO} results.

According to study from Mohammed, et al. in Iraq, it was observed that spirometry values such as FVC, FEV_1, FEV_1/FVC%, PEFR and D_{LCO} were found to be lower on smokers compared to non-smokers.[27] Han, et al. asserted that interference with diffusion capacity was a free predictor of emphysema tendency on radiological examination.[28] Patients with COPD usually present with comorbidities including cardiovascular, metabolic syndrome, osteoporosis, depression, reduction and periodic skeletal muscle dysfunction. The low long-term D_{LCO} value in active smokers with obstruction disorders is always associated with emphysema. D_{LCO} is an important index in assessing the anatomical degree of emphysema in smokers with airway obstruction. Low D_{LCO} values are highly correlated with the low mean lung density on CT-scans and in accordance with the anatomical degree of emphysema. Smokers with airway obstruction but normal D_{LCO} values usually have chronic bronchitis without emphysema. Patients with airway obstruction due to asthma can have normal or high D_{LCO} values.

We obtained 23 subjects (35.4%) with no TB history and 24 subjects (36.9%) who were former TB. Patients with comorbidities including TB experienced a higher decrease in D_{LCO} values compared to those without (*P*=0.047). Nevertheless, it could be questioned whether the subject possessed history of extensive TB lesions that might affect the results of D_{LCO}. Unfortunately, in this study there were no chest X-ray (CXR) examination to see the extent of TB lesions. However, spirometry in 7/24 (29.2%) COPD patients with former TB indicated obstruction and restriction. This evidenced that TB was one of the factors that worsened the decline in diffusion capacity among COPD patients in Indonesia.

Allwood, et al. from Cape Town, South Africa in 2014 examined the mechanism of airway obstruction in Tuberculosis-associated obstructive pulmonary disease (TOPD). They performed interview, spirometry, plethysmography, D_{LCO} tests as well as thoracic CT-scan on 196 subjects. They obtained 31 subjects (30.1%) without a history of TB, former probable TB of 39 subjects (33.32%), former definitive TB of 39 subjects (37.8%).[29] Subjects with a history of former definitive TB had a 16.3% lower D_{LCO} value (95%CI: -26.3–(-6.3%); *P*=0.002) than subjects without a history of TB. We also found that subjects with former TB had 6.5% higher experience of air trapping (*P*=0.014), 0.33% higher value of fibrosis score (*P*=0.007) and 3.5% higher emphysema score (*P*=0.038) than those without history of TB.

The mechanism of obstruction and decreased diffusion capacity in TOPD is narrowing of the airway due to bronchiolitis, bronchiectasis or persistent inflammation in consequence of the healing process of TB. Decreased elastic recoil corresponds to pre-existing emphysema. The term TOPD can be used as a separate clinical phenotype for COPD. COPD patients with a history of TB should be considered as one of the clinical phenotypes of COPD characterized by lower D_{LCO} values and more air trapping confirmed by pulmonary examination and CT scan.[29]

Of the 5 variables that correlated significantly with the decrease in D_{LCO} values when bivariate analysis was performed (FEV_1, COPD spirometry degree, COPD group, BMI and TB history), we conducted a multivariate analysis using binary logistic regression and obtained those variables which had strong correlation with D_{LCO} value reduction were BMI and FEV_1 with P values of 0.002 and 0.015, respectively.

There were some limitations in our study, included the subjects who were dominated mostly by male, no radiological examinations (CXR and/or thoracic CT scan) were performed, and no Hb level examination were carried out due to the limited funding.Further study is needed using homogenous

samples, control group as a comparison, CXR or thoracic CT examination, and Hb level examination.

CONCLUSION

The proportion of decreasing D_{LCO} values in COPD patients was 37/65 subjects (56.9%). The mean D_{LCO} value in COPD patients was 19.42 ml/minute/mmHg while the mean D_{LCO}% prediction was 72.00%, the mean FEV1% predictive value was 46.05%, the average FEV1/ FVC value was 66.40%. No significant relationship was found between demographic characteristics (sex and age) stable COPD patients with D_{LCO} test results. There is a tendency to decrease the value of D_{LCO} with the higher degree of COPD. There is a meaningful relationship between FEV_1 values and D_{LCO} values. VEP1 <1500 ml then the D_{LCO} value will decrease.

There is a significant relationship between BMI (nutritional status) and the value of D_{LCO}. the lower the IMT, the more D_{LCO} values will decrease. There is a tendency to decrease D_{LCO} values in COPD subjects with a history of smoking. There is no relationship between the duration of diagnosis of COPD and the value of D_{LCO}. Subjects with COPD with a history of former TB will have lower D_{LCO} values than COPD patients without prior TB history.

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Neutrophil To Lymphocyte Ratio as A Marker of COVID-19 Disease Severity in Banda Aceh

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Abstract

Background: *Patients with severe COVID-19 always coincide with high mortality rate, meanwhile, inflammatory immunity parameters in COVID-19 infection such as Neutrophil to Lymphocyte Ratio (NLR) reflect the infection progress. These are used by clinicians for early identification of patients at high risk or to determine when it is a serious disease. This study aims to determine the effectiveness of NLR as a marker of COVID-19 pneumonia severity.*

Method: *This study was conducted using a retrospective cross-sectional analytical design at the Regional General Hospital of DR. Zainoel Abidin Banda Aceh from June to September 2020. Patients' demographic characteristics, comorbidities, clinical manifestations of COVID-19 infection, chest x rays, examination of blood samples at admissions such as leukocytes, lymphocytes, neutrophils and NLR were extracted from medical record data. The patients were divided into four groups according to the disease severity, namely mild, moderate, severe and critical.*

Result: *A total of 105 medical records were collected for COVID19 patients, meanwhile, 51 to 70 years was the largest age group (60.8%) with twice male than female. Moreover, fever, cough, shortness of breath and weakness are the most common symptoms found in treated patients while almost two-thirds of the patients have bilateral pneumonia. Generally, the levels of leukocytes, neutrophils, NLR were found to increase while the levels of lymphocytes decreased, in addition, more than half of the COVID19 patients were severe. There was a strong relationship between an increase in NLR levels and COVID-19 disease severity (α: 0.05; P=0.001)*

Conclusion: *Based on the results, NLR is applicable as an early inflammatory marker which reflects severe and critical COVID19 infection and also suitable as an objective basis for early identification and management of severe COVID-19 pneumonia.* ***(J Respirol Indones 2021; 41(4): 272–8)***

Keywords: *Neutrophyl Limfosit Ratio, Severity, COVID19*

Neutrophil To Lymphocyte Ratio sebagai Marker Derajat Keparahan COVID-19 di Banda Aceh

Abstrak

Latar belakang: *Penderita COVID-19 berat selalu memiliki tingkat mortalitas yang tinggi, sementara itu parameter imunitas inflamatorik pada infeksi COVID-19 seperti Rasio Neutrofil Limfosit (RNL) mencerminkan progresivitas infeksi. Hal ini digunakan oleh klinisi sebagai identifikasi awal pada pasien dengan risiko tinggi atau untuk menentukan tingkat keseriusan penyakit. Penelitian ini bertujuan untuk mengetahui efektivitas RNL sebagai penanda tingkat keparahan pneumonia COVID-19.*

Metode: *Penelitian ini menggunakan desain analitik potong-lintang retrospektif di Rumah Sakit Umum Daerah Dr. Zainoel Abidin Banda Aceh pada bulan Juni hingga September 2020. Karakteristik demografi pasien, komorbiditas, manifestasi klinis infeksi COVID-19, rontgen dada, pemeriksaan sampel darah pada saat rawat inap seperti leukosit, limfosit, neutrofil dan RNL didapatkan dari data rekam medis. Pasien dibagi menjadi empat kelompok sesuai dengan tingkat keparahan penyakitnya, yaitu ringan, sedang, berat dan kritis.*

Hasil: *Sebanyak 105 rekam medis pasien COVID19 dikumpulkan, dimana kelompok umur terbesar adalah 51-70 tahun (60,8%) dengan jumlah laki-laki dua kali lebih banyak dibandingkan perempuan. Selain itu, demam, batuk, sesak napas dan kelemahan adalah gejala yang paling umum ditemukan pada pasien yang dirawat, sementara hampir dua pertiga pasien menderita pneumonia bilateral. Secara umum kadar leukosit, neutrofil, RNL ditemukan meningkat sedangkan kadar limfosit menurun, selain itu, lebih dari separuh penderita COVID19 tergolong parah. Terdapat hubungan yang kuat antara peningkatan kadar RNL dan keparahan penyakit COVID-19 (α: 0,05; P=0,001).*

Kesimpulan: *Berdasarkan hasil penelitian, RNL dapat digunakan sebagai penanda awal inflamasi yang mencerminkan infeksi COVID19 yang parah dan kritis serta cocok digunakan sebagai dasar yang objektif untuk identifikasi awal dan manajemen pneumonia COVID-19 berat.* ***(J Respirol Indones 2021; 41(4): 272–8)***

Keywords: *Neutrophyl Limfosit Ratio, Severity, COVID19*

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INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with increasing morbidity and mortality in Indonesia.[1] The Reverse Transcription Polymerase Chain Reaction (RT-PCR) examination is the standard for diagnosing this disease. However, the tests are very limited, expensive, rare, and difficult to perform as the tests are generally carried out in the provincial capital laboratories and there is no established World Health Organization (WHO) algorithm to clearly determine COVID-19 cases.[2] Therefore, most clinicians make an initial diagnosis based on clinical, laboratory and radiological data.[3] When the initial outbreak occurred in China, it was difficult to identify patients suspected of being infected with COVID-19, therefore, initial diagnosis and management were based on simple clinical data.[4]

Several studies have indicated the role of inflammation in the development of viral pneumonia such as COVID-19. White blood cells or leukocytes differential count, especially neutrophils and lymphocytes, neutrophils-to-lymphocytes ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are systemic inflammation markers.[5] Neutrophils are the first leukocytes which migrate from the blood to injured or infected sites to kill pathogens through cytotoxic mechanisms.[6]

Besides, in inflammatory conditions, neutrophils extracellular traps (NETs) is formed actively from neutrophils to trap and kill pathogens.[6] Therefore, the complete blood count (CBC), especially neutrophils and lymphocytes are inexpensive clinical indicator markers of inflammation with fast circulation time and are simultaneously specific and sensitive.[7] Neutrophils increased with bacterial infection and lymphocytes are reduced during viremia. The serial assessment of the two parameters are of great help in assessing COVID-19 infection.[8]

The NLR is a simple blood test that is easily applied in daily clinical practice. It is cost effective and useful as an assessment and consideration for treating patients.[9] Meanwhile, the NLR value is very important for the treatment of inflammation and also used as a predictive value of mortality in COVID-19 patients.[10] It also provides an objective side for identification in severe COVID-19 patients. Furthermore, increased NLR is used as an early warning sign of severe COVID-19 symptoms and as an independent prognostic marker.[11] NLR is a biomarker of widespread inflammatory conditions, which is used to reflect disease severity.[12]

Most of the NLR studies have been reported in China, Europe, and in South Asian, while very few studies in Indonesia.[7,11] Therefore, this study aims to determine the effectiveness of NLR on COVID-19 severity.

METHOD

This study used a retrospective cross-sectional method by taking medical records of confirmed COVID-19 patients that received treatment at the Respiratory Intensive Care Unit (RICU) as well as New-emerging and Re-emerging Infectious Diseases (PINERE) at the Regional General Hospital, DR. Zainoel Abidin, Banda Aceh, from June to September 2020. This study was reviewed and approved by the Institutional Review Board of the School of Medicine, Syiah Kuala University, Banda Aceh (297/EA/FK-RSUDZA/2020) together with the National Health Research and Development Ethics Commission (KEPPKN) of the Indonesian ministry of health (#1171012P).

Demographics data (gender, age and occupation), comorbid (hypertension, diabetes mellitus (DM), coronary heart disease), lung diseases (asthma or chronic obstructive pulmonary disease (COPD)), and clinical symptoms were collected and recorded on the data collection form. In addition, during hospital admission, an evaluation of the data from chest X-ray examination and laboratory tests of blood samples was also carried out according to standard operating procedures. In this study, the NLR was used as a marker of inflammation which results from the distribution of total neutrophils to lymphocytes.[13]

Disease severity is divided into four categories, namely mild, moderate, severe, and critical based on WHO guidelines.[14]

$$NLR = \frac{Absolute\ Number\ of\ Neutrophil}{Absolute\ Number\ of Lymphocyte}$$

Exploratory statistical analysis was performed to assess potential patient characteristic variables including demographics, clinical symptoms, laboratory results and chest X-rays. For statistical analysis, the NLR values were divided into two categories, namely low and high. The value is low when NLR level is less than 13.51 and high when it is greater than 13.51. To test the effect of NLR levels and COVID-19 severity, the Spearman test was used. The significance for all data analyzed was α = 0.05. All statistical analysis were carried out using the Statistical Package for Social Sciences (SPSS) for Windows version 25.0 (IBM SPSS Inc., USA).

RESULT

A total of 105 medical records for COVID-19 patients were collected. The 51 to 70 years age group was the most predominant age group found (60.8%). Based on gender, the male treated patients were twice as much as the females. Most of the occupations are government and private employees that are usually active and have indoor activities, which allows a greater possibility for work-related transmission. Fever, cough, shortness of breath and weakness are the most common symptoms found in treated patients. Almost two-thirds of the patients have bilateral pneumonia, meanwhile, patients treated without pneumonia symptoms or had normal x-ray results were only 6 to 7 out of 100. The most common comorbids are DM and hypertension. The complete demographic characteristics of the study are shown in Table 1.

The treated patients had a systolic pressure of 131 to 132 mmHg and a diastolic pressure of 78 to 79 mmHg. Generally, patients suffered from tachypnoea with a frequency range of breaths between 18 and 36 times per minute. Although the patient's body temperature was still within normal, the average was almost 37°C. The average oxygen saturation was 88 to 89% indicating that the patient had mild hypoxemia. The levels of leukocytes, neutrophils and NLR were found to increase while the levels of lymphocytes decreased (Table 2).

Table 1. Demographic characteristics of the study

Characteristics	Number	Percentage
Age		
21-40 years	6	5.7
41-60 years	62	59
61- >70 years	37	35.3
Gender		
Male	72	68.6
Female	33	31.4
Occupation		
Civil servants	51	62.8
Private employees	35	33.4
Unemployed	16	15.2
Clinical manifestations		
Fever	88	83.8
Cough	87	82.9
Shortness of breath	77	73.3
Weakness	59	56.2
Nausea	19	18.1
Sore throat	18	17.1
Headache	17	16.2
Anosmia	11	10.5
Chest X-ray		
Normal	7	6.7
Pneumonia	29	27.6
Bilateral pneumonia	69	65.7
Comorbid		
DM	51	48.6
Hypertension	30	28.6
Obesity	18	17.1
COPD	7	6,7
Coronary Artery Disease	6	5.7
Chronic Kidney Disease	4	3.8
Chronic Heart Failure	1	1.0
The severity of COVID-19		
Mild	7	6.7
Moderate	18	17.1
Severe	42	40.0
Critical	38	36.2

Table. 2 Vital signs and laboratory of COVID-19 patients

Parameter	Variable	n	Min.	Max.	Mean	SD
Vital signs	Systolic	105	83.00	188.00	131.68	19.97
	Diastolic	105	48.00	110.00	78.38	10.88
	Heart rate	105	61.00	138.00	95.09	13.16
	Respiratory rate	105	18.00	36.00	26.61	5.01
	Temperature	105	35.70	38.80	36.91	0.52
	O_2 saturation (without O_2 supplementation)	105	60.00	99.00	88.54	7.54
Laboratory	Hemoglobin	105	4.20	18.00	13.09	2.39
	Leukocytes	105	1.100	34.400	11.465	6.071.28
	Segment neutrophils	105	43.00	97.00	82.75	10.84
	Lymphocytes	105	2.00	41.00	11.07	8.94
	NLR	105	1.05	48.50	13.51	10.90

Table 3. Relationship between NLR levels based on the severity of COVID-19

NLR levels	Severity								Total		*P*	r
	Mild		Moderate		Severe		Critical					
	n	%	n	%	n	%	n	%	n	%		
Low	7	11.3	18	29.0	27	43.5	10	16.1	62	59	0.001	0.69
High	0	0	0	0	15	34.9	28	65.1	43	42		
Total	7	6.7	18	17.1	42	40	38	36.2	105	100		

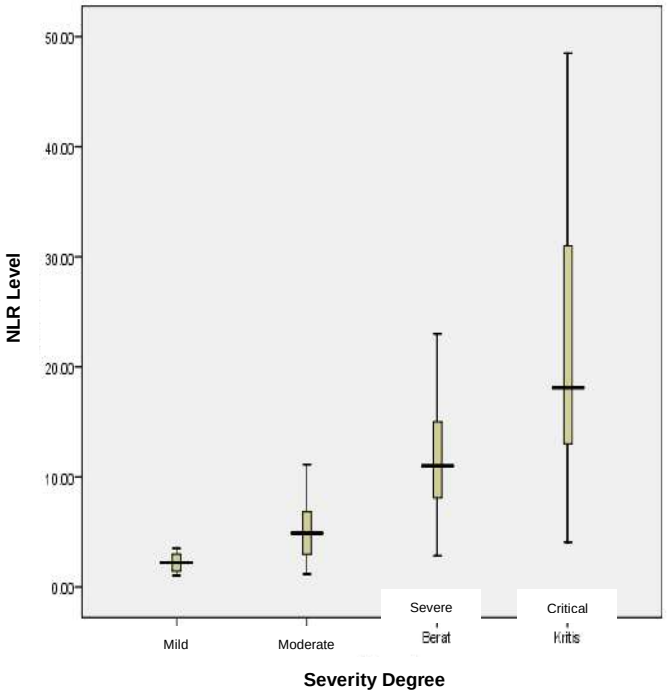

Figure 1. Boxplot diagram of NLR levels and the severity of COVID-19

There is a strong relationship between the increase in NLR levels and the COVID-19 severity based on the Spearman test at a Confidence Interval of 95% and α = 0.05 with a p-value of 0.001 (Table 3). This is shown in the Boxplot Diagram indicating a strong relationship, where the higher the NLR level, the higher the severity of COVID-19 (Figure 1).

DISCUSSION

A number of studies have shown that males are more susceptible to infection than females, and are more hospitalized for Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and COVID-19 infections.[15–17] Several mechanisms that cause males more susceptible to infection with COVID-19 include sex hormone and gene X-related activity which plays a role in modulating the innate and adaptive immune response modulation when infected with the virus.[18]

Besides, the main route of infection with SARS-CoV-2 is through the Angiotensin-converting enzyme 2 (ACE2) receptor, therefore, the biological differences in the receptors greatly affect the susceptibility of disease transmission. A previous study showed that males have higher amounts of ACE2 expression in the circulation and lungs than females.[15] This is in accordance with the results of this study where males were mostly infected with COVID-19 and received treatment in hospital.

Neutrophils are natural immune cells that play a role in the immune system. During the initial infection with pathogenic microorganisms, the cells tend to rapidly converge chemotactically at the infection site and act in the body's defense and immune regulation.[19] Therefore, when the body's

neutrophils significantly reduced, the body's immunity is compromised and the infection risk increases significantly.[20] Lymphocytes are the main effector cells of the human immune response, hence the number of lymphocytes in the body is closely related to the immune and the defense system against pathogenic microorganisms which correlates negatively with the degree of inflammation.[21] Moreover, NLR contains two types of leukocyte subtypes that reflect the body's neutrophil balance, namely lymphocyte count level and degree of systemic inflammation.[22] The NLR reflects a better balance between the inflammatory severity and immune status, therefore, it is considered as an important marker of the systemic inflammatory response.[23]

Based on this, researchers speculated that severe COVID-19 infection causes significant systemic inflammation and NLR plays a role in reflecting the infection severity. Clinical observations showed that some patients with mild disease developed into severe disease with a high mortality risk within a short period of time. This sudden disease severity is due to the rapid onset of acute respiratory distress syndrome (ARDS) and subsequent multi-organ dysfunction that associated with a "cytokine release storm".[7]

In 2003, infection with the SARS-CoV virus was also found to cause ARDS and multiple organ failure, resulting to a very high mortality rate. The fundamental pathology of this event is the discovery of a persistent inflammation storm.[24] Meanwhile, SARS-CoV-2 virus is very similar to the SARS-CoV virus as it belongs to the -CoV coronavirus family.[25]

Based on the close similarity between the two viruses, the clinical condition of a COVID-19 patient that changes from mild to critical is due to a storm of inflammatory factors.[25] Imran et al. showed that NLR was an independent risk factor for severe COVID-19 pneumonia in a severe group.[7] Furthermore, Li et al. showed that some of the proinflammatory cytokines such as interleukin (IL)-2, IL-7, IL-10, granulocyte colony-stimulating factor (GSCF), interferon gamma-induced protein 10 (IP10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein 1 alpha (MIP1A) and tumor necrosis factor (TNF) had elevated plasma in patients with severe COVID-19 pneumonia.[26] This certainly occurs due to the inflammatory response in the patient's body, which is in accordance with the results of this study.

Briefly, this study performed a retrospective analysis of common clinical parameters that are easily obtained from the laboratory. This study showed that there was a significant relationship between NLR and the COVID-19 severity. The severe group tended to have a significant higher NLR.

This study has certain limitations, such as being carried out in only one central place. For more accurate, precise and a broader generalization of results, the study needs to be conducted in several places to provide better validation of the results. The authors are grateful to the entire medical team involved in collecting data for this study. There is no conflict of interest in this study.

CONCLUSION

NLR is applicable as an early warning signal for the severity of COVID-19 infection and also provides an objective basis for early detection and management of severe COVID-19 pneumonia. This marker is very important, especially in remote areas where diagnostic tests are limited, which often creates difficulties in diagnosing COVID-19.

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Specific Levels of Calcidiol, Calcitriol, Cathelicidin and Interferon Gamma in Diabetic Patients with TB Infection in Jakarta: Case-Control Study

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Abstract

Background: *Vitamin D plays a role in regulating the immune system via Vitamin D receptors, expressed by T-helper cells (Th). Cathelicidin LL-37 is an antimicrobial peptide that acts as the primary barrier against the M. tuberculosis bacterial infection, which is induced by calcitriol, the active form of Vitamin D3. Interferon gamma (*IFN-γ*) is a cytokine released by Th-1 cells, and is essential for the elimination of M. tuberculosis. This study aims to determine the state of, and correlation between, calcidiol, calcitriol, cathelicidin and IFN-γ levels, as well as other clinical factors among patients with Type 2 Diabetes Mellitus (T2DM) with active TB coinfection. Further analysis is also performed to differentiate between T2DM patients with active tuberculosis, latent TB and without TB infection.*

Methods: *This study using a case-control design, with a sample size of 102 T2DM patients, which are divided into 3 categories of TB infection status; active TB, latent TB and without TB coinfection. Screening for active and latent TB coinfections using Interferon Gamma Release Assay (IGRA) test, Quantiferon TB Gold Plus, GeneXpert MTB/Rif examination of the sputum and Chest X-ray. Serum calcidiol and calcitriol levels were measured using the Liquid Chromatography Double Mass Spectrometry (LC-MS/MS), whereas Cathelicidin LL-37 levels were measured using the Enzyme-linked Immunosorbent Assay (ELISA). TB specific IFN-γ levels were obtained through the IGRA test, which measured IFN-γ from CD-4 (TB1) and CD-8 (TB2) cells.*

Results: *Nearly all T2DM patients had abnormal serum calcidiol levels. Patients with an active TB infection exhibited the lowest serum calcidiol levels and were Vitamin D deficient, compared to patients with latent TB infection or without TB infections (P=0.004). T2DM patients with active TB also had high levels of calcitriol cathelicidin LL-37 and IFN-γ (TB2), compared to the other groups. Calcidiol was shown to have a negative correlation with HbA1C, calcitriol and specific IFN-γ (TB2-nil) levels in T2DM patients with active TB. Significant differences in serum calcidiol were found between T2DM patients with different smoking habits, however no significant difference was found in correlation to body mass index.*

Conclusion: *T2DM patients have lower levels of Vitamin D on average, hence require supplementation due to cases of active TB coinfection. Increases in calcitriol, cathelicidin LL-37 and specific IFN-γ can be used as potential diagnostic biomarkers of M. tuberculosis infection in T2DM patients.* ***(J Respirol Indones 2021; 41(4): 279–87)***

Keywords: *vitamin D, IFN-γ, tuberculosis, DM type 2*

Kadar Spesifik Calcidiol, Calcitriol, Cathelicidin dan Interferon Gamma pada Penderita Diabetes dengan Infeksi TB di Jakarta: Studi Kasus-Kontrol

Abstrak

Latar belakang: *Vitamin D berperan dalam pengaturan sistem imun melalui reseptor Vitamin D yang diekspresikan oleh sel T-helper (Th). Cathelicidin LL-37 adalah peptida antimikroba yang bertindak sebagai penghalang utama terhadap infeksi bakteri M. tuberculosis, yang diinduksi oleh calcitriol, bentuk aktif Vitamin D3. Interferon gamma (IFN-γ) adalah sitokin yang dilepaskan oleh sel Th-1, dan penting untuk eliminasi M. tuberculosis. Penelitian ini bertujuan untuk mengetahui keadaan, dan hubungan antara kadar kalsidiol, kalsitriol, cathelicidin dan IFN-γ, serta faktor klinis lain pada pasien Diabetes Mellitus Tipe 2 (DMT2) dengan koinfeksi TB aktif. Analisis lebih lanjut juga dilakukan untuk membedakan antara pasien DMT2 dengan TB aktif, TB laten dan tanpa infeksi TB.*

Metode: *Penelitian ini menggunakan desain case-control, dengan jumlah sampel 102 pasien DMT2, yang terbagi dalam 3 kategori status infeksi TB; TB aktif, TB laten dan tanpa koinfeksi TB. Skrining untuk koinfeksi TB aktif dan laten menggunakan tes Interferon Gamma Release Assay (IGRA), Quantiferon TB Gold Plus, pemeriksaan sputum GeneXpert MTB/Rif dan rontgen dada. Kadar kalsidiol dan kalsitriol serum diukur menggunakan Liquid Chromatography Double Mass Spectrometry (LC-MS/MS), sedangkan kadar Cathelicidin LL-37 diukur menggunakan Enzyme-linked Immunosorbent Assay (ELISA). Kadar IFN-γ spesifik TB diperoleh melalui uji IGRA, yang mengukur IFN- dari sel CD-4 (TB1) dan CD-8 (TB2).*

Hasil: *Hampir semua pasien DMT2 memiliki kadar serum calcidiol yang abnormal. Pasien dengan infeksi TB aktif menunjukkan kadar kalsidiol serum terendah dan kekurangan vitamin D, dibandingkan dengan pasien dengan infeksi TB laten atau tanpa infeksi TB (P=0,004). Pasien DMT2 dengan TB aktif juga memiliki kadar calcitriol cathelicidin LL-37 dan IFN-γ (TB2) yang tinggi dibandingkan dengan kelompok lain. Kalsidiol terbukti memiliki korelasi negatif dengan kadar HbA1C, kalsitriol dan IFN-γ (TB2-nil) spesifik pada pasien DMT2 dengan TB aktif. Perbedaan signifikan dalam serum kalsidiol ditemukan antara pasien DMT2 dengan kebiasaan merokok yang berbeda, namun tidak ada perbedaan signifikan yang ditemukan dalam korelasinya dengan indeks massa tubuh.*

Kesimpulan: *Pasien DMT2 rata-rata memiliki kadar Vitamin D yang lebih rendah, sehingga memerlukan suplementasi karena kasus koinfeksi TB aktif. Peningkatan calcitriol, cathelicidin LL-37 dan IFN-γ spesifik dapat digunakan sebagai biomarker diagnostik potensial infeksi M. tuberculosis pada pasien DMT2.* ***(J Respirol Indones 2021; 41(4): 272–87)***

Keywords: *vitamin D, IFN-γ, tuberkulosis, DM tipe 2*

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INTRODUCTION

Despite the consistent decline in global cases, Tuberculosis (TB) is still a major global health concern. In 2019, around 10 million new cases and 1.6 million deaths due to active TB were recorded. Diabetes mellitus (DM) has been known to increase the risk of contracting TB by at least 3 times, compared to non-diabetic individuals. Several studies have also shown the importance of DM as a risk factor for TB infection.[1,2]

Vitamin D is known to have pleiotropic effects on multiple organs, and plays an important role in innate and adaptive immunity. Calcidiol undergoes hydroxylation in the liver, catalysed by the enzyme 25-hydroxylase. Further hydroxylation by the enzyme 1-alphahydroxylase occurs in the kidneys, forming Calcitriol, the active form of vitamin D.[3] Crowle et al.[4] showed that calcitriol is an essential factor for the antimicrobial activity of human monocytes and macrophages, against *M. tuberculosis* infections. Other studies have also described the function of calcitriol as an immunomodulator in the homeostasis of the immune system, and its ability restrict the growth of *M. tuberculosis* via the induction of Cathelicidin LL-37.[4,5]

Cathelicidin LL-37, and calcitriol induce *autophagy* that acts as the first barrier against the TB infection.[6,7] Calcidiol is the primary form of the vitamin in circulation, and has a longer half-life, which makes it an effective screening marker of Vitamin D3 sufficiency. Previous studies have shown that vitamin D deficiency is correlated to the risk of active TB, as well as failure to achieve glycemic control in T2DM patients.[8,9] Despite the well-established role of vitamin D in the pathogenesis of TB, the correlation between calcidiol, calcitriol, cathelicidin and IFN-γ levels, as well as other clinical factors, among T2DM patients with active TB coinfection, latent TB and no TB infection, remains to be studied.

METHODS

This research was an observational study with a case-control design. The sample size was obtained based on a significance level of 0.05 and power of 0.8. Research subjects included T2DM patients who had visited the endocrinology and pulmonology clinic at Dr. Cipto Mangunkusumo Hospital, Persahabatan Hospital, Harapan Jaya Hospital, and Islam Pondok Kopi Jakarta Hospital. The subjects were selected via consecutive sampling. The subjects included T2DM patients who had been diagnosed with DM for at least 1 year, were not pregnant, did not suffer from liver or kidney disorders, had not been diagnosed with cancer, and were not consuming immunosuppressant drugs.

A total of 102 patients were collected based on the criteria. The research subjects were screened using the IGRA test (Quantiferon TB Gold Plus/QFT Plus), chest x-ray, and GeneXpert MTB/Rif sputum examination. Subjects with a positive IGRA result, but a normal chest x-ray and sputum examination were classified as DM with latent TB, whereas subjects with positive IGRA and sputum examinations were grouped as DM patients with active TB, regardless of chest x-ray results indicative of TB infection. Subjects who tested negative in every screening method were grouped as DM without TB coinfection. Baseline characteristics of the research subjects, such as sex and age, from every group were matched. Serum calcidiol and calcitriol levels were measured using the LC-MS/MS method, Cathelicidin levels were measured using the competitive ELISA method and TB specific IFN-γ levels were obtained from the QFT Plus (TB1 and TB2) results.

In this study, cathelicidin LL-37 levels were measured via the ELISA method from MyBioSource, with a detection threshold of 1.56-100 ng/mL. Calcitriol and calcidiol levels were measured using the LC-MS method, with a limit of detection (LOD) of 1 ppb, via the Agilent LC system 1290, with the Agilent Triple Quad 6460 (LC-MS). Vitamin D status was classified based on the Hollick criteria; normal (>30 ng/mL), insufficiency (20-29.9 ng/mL), deficiency (10-19.9 ng/mL) and severe deficiency (<10 ng/mL), however in this study, the criteria categories are simplified to normal, insufficient and deficiency.

Variables such as T2DM and TB status are analysed by using the Chi Square or Fisher test.

Results from the hypothesis testing wil include p-values, which are considered significant if P<0.05, as well as the corresponding confidence intervals. To study the correlation between calcidiol, calcitriol, cathelicidin and IFN-γ levels, and other clinical factors, and the TB status among T2DM patients, appropriate hypothesis testing will be conducted. Statistical analysis of the data are performed using the SPSS for Windows 20 program. This study had been approved by the Ethical Clearance Committee, Faculty of Medicine, Universitas Indonesia (610/UN2.F1/ETIK/2017), and the Health Reseach Ethics Commission Persahabatan Hospital (41/KEPK-RSUPP/09/20) on the 19 September 2017.

RESULTS

This study was performed on 102 diabetic patients, who were divided into 3 groups, based on their TB status; active TB, latent TB and without TB. Based on the sex, there were more female subjects (52.9%) than male subjects (47.1%). Every group had the same number of female (n=18) and male subjects (n=16). There were no significant differences in the age of the subjects between the groups, since the subjects were matched based on their age. On average, the age of the T2DM subjects without TB was 48.4 years, compared to 49.8 years for the latent TB group and 47.3 years for the active TB group.

Majority of the patients from each group did not have a history of smoking, however there were 8 subjects (23.5%) who were smokers in the group without TB infection, compared to 3 subjects (8.8%) in the latent TB group and 11 subjects (32.4%) in the active TB group. Duration of diabetes was varying among the subject groups. On average, T2DM patients with latent TB had a longer history of diabetes (median = 8.5 years), compared to without TB (median = 5.5 years) and active TB (median = 3 years).

Markers of glycemic control, such as Fasting Blood Glucose (FBG), 2-hour Post Prandial Blood Glucose (PPG) and HbA1c were poor on average. T2DM subjects without TB had a median FBG of 140.5 mg/dL, whereas patients with latent TB and active TB had median values of 140 mg/dL and 229 mg/dL, respectively. Post prandial glucose levels were higher on average for DM patients with active TB coinfections (310.71 mg/dL), followed by latent TB coinfections (229.65 mg/dL) and without TB coinfection (195.76 mg/dL).

Table 1. Characteristics of Research Subjects

Characteristics	DM without TB infection (n=34)	DM with Latent TB (n = 34)	DM with Active TB (n=34)	P
Smoking History				0,19
Smokers	8 (23.5%)	3 (8.8%)	11 (32.4%)	
Ex-smokers	7 (20.6%)	6 (17.6%)	5 (14.7%)	
Non-smokers	19 (55.9%)	25 (73.5%)	18 (52.9%)	
Duration of DM (years)	5.5 (1–18)	8.5 (1-26)	3 (1–21)	0,01
≤5	17 (50.0%)	9 (26.5%)	24 (70.6%)	
6–15	12 (38.7%)	19 (55.9%)	8 (23.5%)	
>15	5 (14.7%)	6 (17.6%)	2 (5.9%)	
FBG (mg/dL)	140.5(84–273)	140 (82–343)	229 (94–403)	<0,001
2hPP(mg/dL)	195.76 ± 58.59	229.65 ± 77.16	310.71 ± 82.59	<0,001
HbA1c (%)	6.9 (5.7–12.9)	8.45 (5.5–12.5)	10.35 (6.4–15.7)	<0,001
< 7	18 (52.9%)	7 (20.6%)	2 (5.9%)	
7–9.9	10 (29.4%)	16 (47.1%)	14 (46.7%)	
≥ 10	6 (17.6%)	11 (32.4%)	18 (52.9%)	
BMI (kg/m^2)	25.66 (18.31–37.78)	25.18 (16.22–36)	23 (15.63–28.44)	0,01
< 18.5	1 (2.9%)	4 (11.8%)	4 (11.8%)	
18.5–22.9	11 (32.4%)	10 (29.4%)	14 (41.2%)	
23.0–24.9	5 (14.7%)	10 (29.4%)	14 (41.2%)	
≥ 25.0	17 (50.0%)	10 (29.4%)	2 (5.9%)	

Similarly, HbA1c levels were lowest in patients without TB (6.9%), followed by latent TB (8.45%) and active TB coinfections (10.35%). Markers of glycemic control were significantly different among the subject groups, with active TB coinfection group displaying the worst glycemic control on average.

On average, calcitriol levels in the active TB group were the highest (53.88 ng/mL), followed by latent TB (51.38 ng/mL) and no TB infection (43.5 ng/mL). The difference between the calcitriol levels between the three groups was not statistically significant (P=0.99).

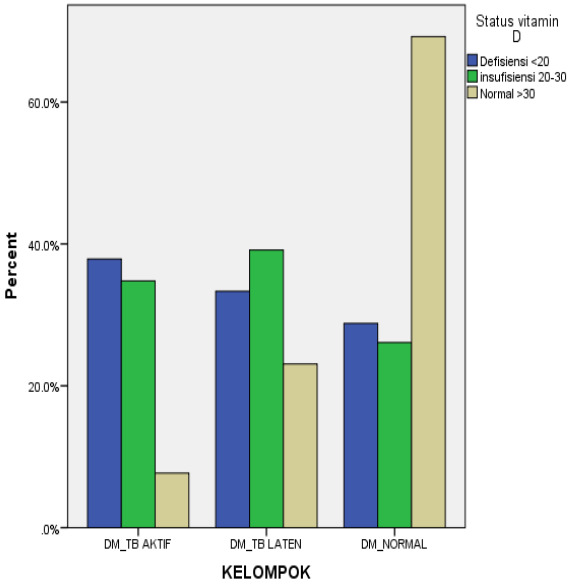

Figure 1. Vitamin D3 (Calcidiol) status in DM patients with active TB, latent TB and without TB infection

Cathelicidin levels in T2DM subjects with active pulmonary TB (49.6 ng/mL) were higher than that of subjects with latent TB (23.49 ng/mL) and without TB infection (10.46 ng/mL) on average, and this difference was statistically significant (P<0.0001).

Levels of specific IFN-γ TB2-Nil were found to be greater than IFN-γ TB1-Nil levels across all subject groups. On average, specific IFN-γ levels were greater in subjects with active TB, compared to the other groups (P<0.0001).

Among the T2DM subjects with active TB, vitamin D levels were found to be negatively correlated to HbA1c (P=0.004; r=0.5), calcitriol (P=0.023; r=0.39) and specific IFN-γ (TB2-Nil) (P=0.04; r=0.36) levels, as illustrated in Figure 2.

Figure 3 shows that latent TB DMT2 subjects had Calcidiol levels only moderately correlated with Calcitriol levels (P=0.006; r=-0.46), and not correlated with specific HbA1c and IFN-γ levels.

No significant correlation was found between Calcidiol levels and the variables assessed in the group of T2DM patients without TB coinfection. Smoking history was significantly associated with Calcidiol levels, with smokers having lower levels (15.09±7.57) on average, compared to former smokers (16.04±9.01) and non-smokers (22.10±12.18).

Median vitamin D-25OH levels among subjects who were obese, overweight, normoweight and underweight were 17.23 ng/mL, 18.65 ng/mL, 15.9 ng/mL and 11.98 ng/mL respectively. No significant differences in vitamin D-25OH levels were found between T2DM subjects across all nutritional statuses (P=0.32).

Vitamin D is an essential nutritional component, which has unique metabolic and physiologic functions, when compared to other vitamins. Vitamin D has shown to have a role in diabetes mellitus and has an impact on the risk of TB infection.

Table 2. Calcidiol, Calcitriol, Catheliciidn LL-37 and IFN-γ levels

Indeks	DM without TB infection	DM TB Latent	DM with Active Tb	P
Calcidiol (ng/mL)	18,61 ± 10,92	17,77 ± 8,53	15 ± 10,14	0,04
Normal (>30 ng/mL)	9 (26,5%)	3 (8,92%)	1	
Insufficiency (20 – 30 ng/mL)	16 (47,05%)	9(26,47%)	8	
Deficiency (< 20 ng/mL)	19 (55,89)	22 (64,7%)	25	
Calcitriol (ng/mL)	43,5 ± 43,5	51,38 ± 49,31	53,88 ± 59	0,99
Cathelicidin LL-37 (ng/mL)				<0,001
IFN-γ (IU/L)	10,46 (0,26–78,01)	23,49 (2,57–53,13)	49,6 (9,3–174,11)	<0,001
IFN-γ (TB1-Nil)	0,03 (0–0,29)	1,4 (0,18–7,89)	1,79 (0,01–10)	
IFN-γ (TB2-Nil)	0,04 (0–0,30)	1,4 (0,22–8,02)	3,7 (0,06–10)	

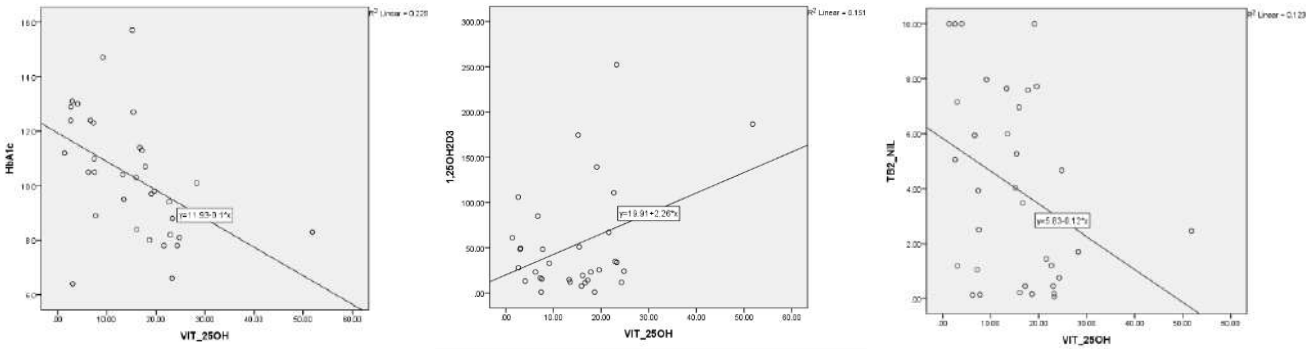

Figure 2. Correlation of vitamin 25OHD3 levels with HbA1c, calcitriol and specific IFN-γ

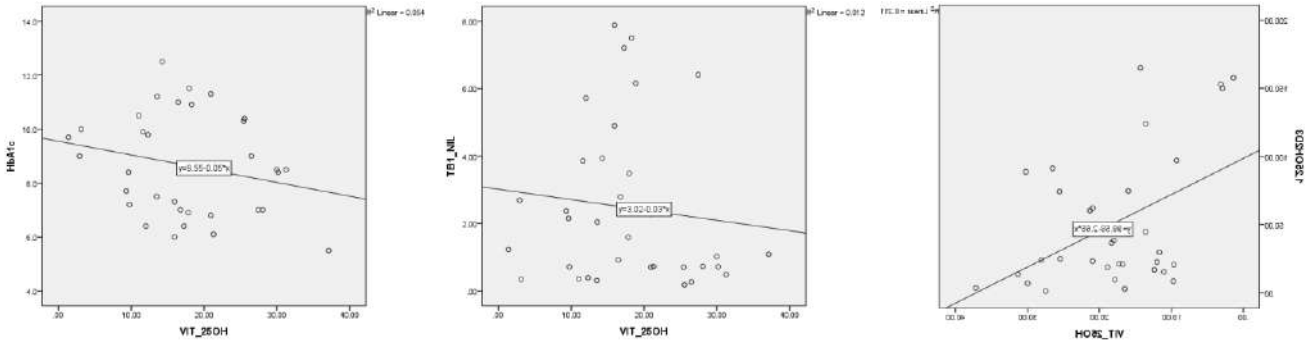

Figure 3. Correlation of vitamin 25OHD3 levels with HbA1c, calcitriol and specific IFN-γ

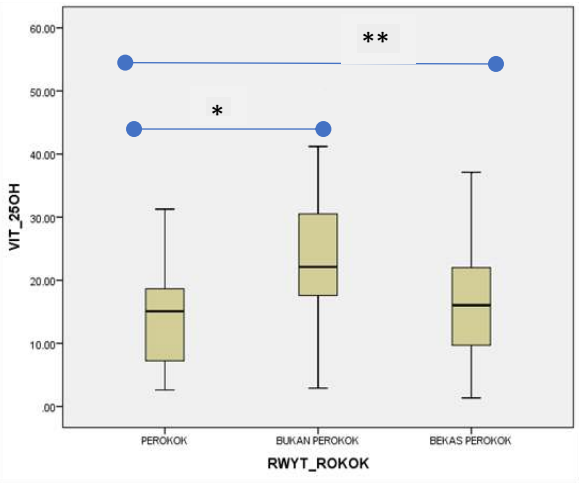

Figure 4. Calcidiol levels in DMT2 subjects based on smoking history

DISCUSSION

Median calcidiol levels across all subject groups are classified as deficient levels of Vitamin D (<20 ng/mL). The median vitamin D levels among T2DM patients without TB coinfection is 18.6 ng/mL, which is similar to levels described by Chaudhary et al.[10] which is 19.42 ng/mL. Average calcidiol levels in T2DM patients with active TB in this study were found to be 115 ng/mL. These results are confirmed by Chaudary et al. who have found average calcidiol levels among similar subjects to be as high as 15.96 ng/mL. However, studies by Zhao et al.[11] and Zhan et al.[12] have recorded average calcidiol levels among T2DM subjects with active TB to be 12.1 ng/mL and 11.36 ng/mL respectively. These results are much lower when compared to healthy subjects with similar baseline characteristics to the subjects in this study.

The difference in average vitamin D levels across various studies may be attributed to differences in testing protocol, geographical variation of the study sites, seasonal changes and genetic or ethnic variation in the study subjects.

The study by Zhao et al.[11] in China, illustrates the impact of seasonal variation and time of data collection on the vitamin D measurements, which led to deficiency in vitamin D among TB patients and T2DM subjects with active TB coinfection. Subjects who were tested in the colder months were found to be more deficient on average, compared to T2DM subjects who were tested in the warmer months. The low Calcidiol levels in T2DM patients with active TB coinfection can also be caused by lower mRNA expression of *Vitamin D Binding Protein* (VDBP), which is in concordance to overall lower albumin levels among active TB patients compared to normal healthy controls.[9,11] The lack of protein formation may

be associated with the general nutritional deficiency seen in cases of TB. Roughly 70-90% of TB patients have shown to have calcidiol levels lower than 20 ng/mL. These results can be attributed to the tendency of patients with chronic lung disease to limit physical activity and exposure to sunlight, due to the overall limited capacity to perform activities. In addition, advanced age leads to greater catabolism of calcidiol, with the simultaneous reduction in synthesis, which leads to lower serum calcidiol levels.[13]

The variation in calcidiol levels may be accredited to polymorphism of the VDR gene. Polymorphism of the *Fok*I on the VDR gene has shown to increase the risk of TB among Asian individuals, as is the case with the polymorphism of the *Tag*I alleles of the VDR gene.

Low vitamin D levels have been long regarded as a significant risk factor for glucose intolerance. Type 2 Diabetes Mellitus has consistently been shown to affect individuals with vitamin D deficiency more often. Available evidence has described the role of vitamin D in insulin secretion, via the presence of VDR on the Beta cells, and vitamin D dependent calcium binding protein on the pancreatic tissue.[14–16]

Low calcidiol levels are found in South and South East Asian regions, where TB and DM cases are common. Other factors that play a role include old age and obesity.[17] Old age is associated with the lack of *7-dehydrocholesterol* within the skin, leading to a reduction in the production of vitamin D3 by 4 times, within individuals aged 60 years compared to 20 year old individuals. This can further be attributed to lower outdoor activities and poor absorption from food.

This study has demonstrated that among individuals with T2DM and active TB coinfection, serum vitamin D levels are negatively correlated to HbA1c, calcitriol and specific IFN-γ levels, which is in concordance with results obtained by Zhao et al.(11)

Vitamin D has an impact on the secretion and sensitivity of insulin, and the chronic inflammation that is the primary mechanism of pathogenesis of T2DM. Results of a meta-analysis have shown that supplementation of Vitamin D, can increase serum Vitamin D 25-OH levels and improve glycemic control in T2DM patients.[18]

Patients with T2DM and active TB coinfection have the highest serum calcitriol levels, followed by latent TB coinfection and patients without TB infection. Currently, limited data is available on the expression of calcitriol in patients with T2DM and TB coinfection. Davies et al.[19] have conducted *ex vivo* studies, which show that the median calcitriol levels in pulmonary TB patients was 35.7 pg/mL prior to treatment, compared to healthy controls which was 28.7 pg/mL. Similar results were obtained by Selvaraj et al.[20] where higher calcitriol levels were found in pulmonary TB patients compared to healthy controls, albeit still within normal limits. Conflicting results were reported by Gao et al.[21] with lower calcitriol levels being reported, compared to healthy controls (365,9 µg/L vs. 464,3 µg/L), which predisposed the patients towards being infected with TB and developing disease.

Abnormal metabolism of vitamin D is a common finding during infections, when the levels of active form of calcitriol increase due to the increase in the extrarenal production of calcitriol. As a result, the increase in calcitriol leads to a decrease in calcidiol levels, due to the increase in vitamin D3 breakdown. Deficiency of calcidiol has been associated with the risk of T2DM onset. Low levels of calcidiol, with an associated increase in calcitriol, can cause insulin resistance and inhibit glucose absorption by adipocytes. Low serum calcidiol levels are also associated with an increase in proinflammatory cytokines among diabetics.[22] Selvaraj et al.[20] have shown that among subjects with pulmonary TB, a decrease in VDR protein levels were found when compared to control groups, due to the downregulation of the VRD gene expression and increase in the synthesis of calcitriol. This decrease is associated with increased risk of TB infection via cathelicidin LL-37 and inflammatory cytokines.

Levels of cathelicidin LL-37 in T2DM patients with active TB coinfection have been found to be different, when compared to T2DM groups with latent or without TB. The difference in cathelicidin LL-37 levels are statistically significant, and is in

concordance with studies by Yamshchikov et al.[23] and Kumar et al.[24]

Cathelicidin LL-37 is considered as an essential component for the control of TB. *In vitro* studies have shown that cathelicidin LL-37 play an important role in the antimicrobial activity of macrophages. Expression of cathelicidin increases to its peak values post infection; the first day post infection, 21 days post infection during the development of protective immunity and 60 days post infection, when the disease becomes progressive, which is evident in animal models by the total number of pathogens and degree of organ damage. High expression of cathelicidin in the macrophage vacuole indicates the greater immunomodulatory effect of cathelicidin, compared to the antimicrobial effect in progressive disease. As a result, an increase in cathelicidin is observed in active TB, compared to latent or without TB, in T2DM patients.[25]

Relatively higher levels of cathelicidin LL-37 in T2DM without TB indicates the multiplication process of *M. tuberculosis* or ongoing inflammatory process.

Multiple studies that have been conducted previously, have shown that specific IFN-γ response by TB2 is associated with an active TB infection and a more severe disease profile. The research conducted by Lee et al.[26] showed that greater CD8+ cell response to QFT Plus tests were found in subjects with active TB, confirmed by culture, compared to latent or subjects without TB. The results of the study are concordant with our findings, which show that specific IFN-γ from TB2 is greater in the T2DM with active pulmonary TB group, compared to the latent TB or without TB groups. Other studies have shown that T2DM subjects with latent TB have a minimal CD8+ response.[27,28]

Latent TB in patients with T2DM express fewer proinflammatory cytokines specific to *M. tuberculosis*, lesser anti-inflammatory activity and weaker Th2 cellular response compared to normoglycemic patients with latent TB. Activation of TB infection increases cytokine levels from CD4+, CD8+ lymphocytes and NK cells. The increase in cytokine levels is indicative of the high *bacterial load* in patients with TB DM coinfection, as a consequence of delay in initial control of *M. tuberculosis* replication. In addition, greater organ damage is also observed as a consequence of weaker cytokine response in latent TB patients.[29]

This study has a few limitations, as the measurements of vitamin D were not taken at the same time period. Furthermore, VDR and CYP27B1 testing was not conducted, which would describe the complete status of vitamin D and its metabolites, as well as polymorphism factors were not studied, which could influence the vitamin D status. The study did not also assess nutritional adequacy and sunlight exposure of the research subjects.

CONCLUSIONS

Based on the results of this study, it can be concluded that lower levels of Vitamin D 25(OH) are in T2DM patients with concurrent TB infection, both active and latent, when compared to without TB infection. Levels of active vitamin D3 and cathelicidin are higher in T2DM patients with active TB, compared to latent or without TB infection. Vitamin D has the potential to be used as adjunctive therapy for TB, as well as prevention of TB infection and reactivation of latent TB. Vitamin D supplementation can improve glycemic control in T2DM patients, and hence reduce the risk of TB infection. Increases in the levels of cathelicidin and IFN-γ can act as potential biomarkers of active TB and latent in T2DM, and in cases without TB.

Limitations of this study include lack of vitamin D measurements during the same time period, as well as lack of assessment of VDR and CYP27B1 status, in order to have a complete assessment of vitamin D status, and its metabolites. Polymorphic factors that affect vitamin D status has also not been studied in this research. Finally, measurements of nutritional adequacy and sunlight exposure on the subjects have not been addressed.

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Immunological Aspects of Latent Tuberculosis Infection in Diabetes Mellitus

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Abstract

The interaction of diabetes mellitus (DM) with tuberculosis (TB) is currently a health concern. Diabetes mellitus is one of the main risk factors for TB infection to become latent TB and / or progress to active TB. Immune mechanisms contribute to this increased risk. The disruption of the mycobacteria recognition process, phagocyte activity and cellular activity will affect the disruption of cytokine and chemokine production. Hyperglycemia that occurs will result in delayed adaptive immune response resulting in reduced Th1, Th2, and Th17 cells as well as the cytokines produced by these cells that play a role in macrophage activation and TB inflammatory response. Understanding of the immune mechanisms that underlie the sensitivity of DM to TB infection, especially latent TB, will facilitate the implementation of strategies in screening and therapy to deal with the double burden of both diseases. The purpose of this literature study focuses on the relationship of DM with latent TB infection in terms of immunology. ***(J Respirol Indones 2021; 41(4): 288–99)***

Keywords*: DM, tuberculosis, laten tuberculosis infection (LTBI), immune mechanism*

Aspek Imunologis Tuberkulosis Laten pada Diabetes Melitus

Abstrak

Interaksi diabetes melitus (DM) dengan tuberkulosis (TB) saat ini menjadi salah satu perhatian dalam kesehatan. Diabetes melitus merupakan salah satu faktor risko utama timbulnya infeksi TB menjadi TB laten maupun berkembang menjadi TB aktif. Mekanisme imun berpengaruh terhadap meningkatnya risiko ini. Terganggunya proses pengenalan mikobakteria, aktivitas fagosit dan aktivitas selular akan berimbas pada terganggunya produksi sitokin dan kemokin. Hiperglikemia yang terjadi akan mengakibatkan terlambatnya respon imun adaptif dan mengakibatkan berkurangnya sel Th1, Th2, dan Th17 serta sitokin yang dihasilkan sel tersebut yang berperan pada aktivasi makrofag dan respons inflamasi TB. Pemahaman terhadap mekanisme imun yang mendasari kepekaan DM terhadap infeksi TB terutama TB laten akan mempermudah penerapan strategi dalam penapisan dan terapi untuk menghadapi beban ganda kedua penyakit. Tujuan studi kepustakaan ini berfokus pada hubungan DM dengan infeksi TB laten yang ditinjau dari sudut imunologi. ***(J Respirol Indones 2021; 41(4): 288–99)***

Kata kunci: *DM, tuberkulosis, infeksi TB laten, mekanisme imun*

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INTRODUCTION

Diabetes mellitus (DM) is one of the non-communicable diseases whose number of cases is increasing. Currently, it is estimated that there are more than 350 million cases of DM in the world; most of them are type 2 DM (DMT2). This number is predicted to continue to increase to 592 million cases in 2035.[1] The number of people with DM in Indonesia has been estimated at more than 5 million, it means that 1 in 40 Indonesian people suffer from diabetes. Based on *Riset Kesehatan Dasar* (Riskesdas) 2018 data, the prevalence of DM in Indonesia increased from 6.9% in 2013 to 8.5% in 2018. World Health Organization (WHO) data shows that 8 out of 10 countries with the highest incidence of DM are also countries with the highest TB sufferers. Indonesia as a country that ranks 2nd in the number of TB sufferers, is also included in the 10 countries with the highest number of people with DM in the world.[1–3]

Diabetes mellitus is known to increase the risk of infection, including TB infection. Several studies have also shown that DM is an important risk factor for TB infection. The cohort studies found that the relative risk of developing active TB in people with DM was 3.1 (95% CI 2.3–4.3), and some case-control studies had an odds ratio (OR) of 1.2-7.8. In general, WHO data shows that DM will increase the risk of TB infection by 3 times greater than the average population.[4,5]

Primary *M.tb* infection will develop into TB disease in 5–10% of individuals, and the remaining 90–95% will develop latent TB infection. In individuals with impaired immune response, both by exogenous and endogenous factors, *M.tb* bacteria remain in the host's body without causing clinical manifestations or what is known as latent TB. Latent TB infection (ITBL) is the largest reservoir for TB bacteria.[4,5] Latent TB is a subclinical *M.tb* infection without clinical signs, bacteriological and radiological manifestations, but positive immunological test results (tuberculin or interferon-gamma release assay). Latent TB infection is important because individuals with latent infection can develop active TB at any time, even years after primary infection. Several studies have found that 2–15% of individuals with ITBL will develop active TB. It will certainly be a source of infection that will disrupt the global TB elimination program in 2050, which WHO has proclaimed. Currently, it is estimated that one-third of the world's population, or 2–3 billion people has latent TB.[4,5] Research conducted by Patra et al. on 72,684 individuals in 14 countries with high TB rates found that DM is one of the factors that lead to TB reactivation in addition to smoking, alcohol consumption, and low body mass index (BMI).[6]

Latent Tuberculosis

TB infection begins when the *M.tb* bacteria is inhaled, which will replicate during a certain period, followed by an immunological process. This process is latent TB, which is an infection characterized by persistent live bacteria in the host's body without evidence of clinical or radiological manifestations of active TB. Currently, the global number of latent TB cannot be calculated with certainty, but it is estimated third of the world's population has been infected with TB (2–3 billion people). It is estimated that 2–15% of these infected individuals have the potential of developing active TB.[7,8]

TB Pathogenesis

The course of TB infection is more complex than that of other pathogenic bacterial infections. TB infection has a more extended incubation period, and clinical outcomes are highly dependent on the host and pathogen. Tuberculosis can infect all organs, but the organ most affected is the lungs (60–75% of all cases) and is also a source of infection transmission, especially from cavities that form in the lungs. Active TB patients transmit *M.tb* bacteria through coughing, which will release droplet nuclei with a size of <5 mμ. These droplet nuclei can survive for several hours in non-flowing air and then be inhaled by other individuals who contact with the patient. Approximately 30–50% of individuals in

household contact with TB patients will develop immune sensitization due to infection.[7,8]

One droplet nuclei contain 1–10 *M.tb* bacilli, which will then enter the lungs. Droplet nuclei can avoid the defense system in the bronchi because of their small size and can penetrate the terminal alveoli, which macrophages and dendritic cells will then phagocytose. *Mycobacterium tuberculosis* can also infect non-phagocytic cells in the alveolar space, such as M cells, alveolar endothelial cells, and type 1 and 2 pneumocytes. In the early stages of infection, *M.tb* is phagocytized by phagocytic cells and then replicates intracellularly and then immune cells that already contain *M.tb* bacteria penetrates the alveolar cell barrier causing systemic spread. Intracellular replication and systemic spread continue to reach pulmonary lymph nodes and other extracellular sites until an adaptive immune response develops. This proves that *M.tb* has an extraordinary ability to evade the body's defense system and survive indefinitely in the host's body.[7,8]

Infected individuals will generally develop an effective cell-mediated immune response within 2–8 weeks after infection that will stop *M.tb* bacteria from replicating. Furthermore, activated T lymphocytes, macrophages, and several other immune cells will form granulomas which are walls of necrotic tissue that continue to expand and prevent the spread of bacilli. *Mycobacterium tuberculosis* is generally eradicated in caseous granuloma tissue. Further development of the disease will be restrained. However, *M.tb* bacteria will not be completely eradicated. In some individuals, these pathogens can develop effective strategies to evade the immune response to produce some bacteria that can survive and persist but do not replicate. It is known as ITBL, as evidenced by the presence of *M.tb* in culture and the finding of *M.tb* DNA in the lung tissue of patients who died not from TB disease, and pathologically, no signs of TB were found. Recent results show that TB infection can persist for up to 30 years or even a lifetime.[7,8] The presence of defects in the immune system will result in the reactivation of dormant *M.tb* bacteria after infection many years ago into active TB (TB disease).

TB Immunopathogenesis

Experts have agreed that the humoral immune system has no role in TB; on the contrary, it is the cellular immune system that plays a role in TB. *Mycobacterium tuberculosis* is one of the intracellular bacteria that are facultative intracellular.[8,9]

One of the characteristics of facultative intracellular bacteria is that they can live and even reproduce in phagocytes. These bacteria find a place to hide, so that circulating antibodies cannot reach it. Types of bacteria, such as *M.tb*, inhibit phagocytosis and the formation of reactive oxygen intermediates (ROI) or the occurrence of respiratory bursts (oxidative). Bacteria can avoid phagosome traps so that they remain free in the cytoplasm and avoid further destruction.[8,9]

Specific Immunity In *M.Tb* Infection

The studies conducted both in experimental animals and in humans have shown a wide-scale immune component in *M.tb* infection. The cells that play a role in addition to macrophages and dendritic cells are CD4+ and CD8+ cells, CDI restricted T cells, γδ-T cells, and cytokines produced by these immune cells. Among the many immune cells that play a role in *M.tb* infection, the most important are CD4+ and IFN-γ. CD4+, CD8+, and NK cells are the main cells that produce IFN-γ. The study of Carusso and Cooper cited by Dutta in mice with CD4+ deficiency showed that the production of IFN-γ by CD4+ early in infection accompanied by macrophage activation was a determining factor in the outcome infection.[10] In addition, CD4+ cells also play a role in defense against *M.tb* infection beyond their ability to produce IFN-γ. Decreased CD4+ count is strongly associated with reactivation of infection in chronic *M.tb* infection.[10] It was shown in the study of Scanga et al. cited by Schwander in *M.tb*-infected mice, and reduced CD4+ counts resulted in worsening of pathological features and increased mortality of mice even though IFN-γ levels remained high as a result of normal CD8+ cell

responses and inducible nitric oxide synthase (iNOS) levels.[11]

CD4+ T lymphocytes have an essential function in controlling infection in granulomas. Apoptosis is one of the important functions through Fas/Fas ligand interactions, production of cytokines (IL-2 and TNF-), inducing other immune cells such as macrophages and DC cells to produce several immunoregulatory cytokines such as IL-10, IL-12, IL-15, and macrophage activation directly via CD40 ligand. CD4+ cells also play an important role for CD8+ cells in carrying out their function as cytotoxic cells mediated by IL-15. CD4+ cells can also control the growth of intracellular *M.tb* via nitric oxide mechanism.[10,11]

CD8+ T lymphocytes also produce IFN-γ and several other cytokines that are also cytotoxic to *M.tb* present in infected macrophages. *Mycobacterium tuberculosis* in macrophages will be killed by CD8+ cells directly with granulysin and ultimately facilitate the control of both acute and chronic infections. A large and excessive number of *M.tb*-specific CD8+ cells in ITBL individuals suggests that CD8+ cells play an important role in latent TB infection and supports the evidence for TB reactivation followed by CD8+ cell depletion, as shown by the Cornel model in latent TB.[10–12]

Immune cells that play a key role in protection against *M.tb* infection are IFN-γ. Research has shown that humans and experimental animals with a defect in the IFN-γ gene receptor will be more susceptible to *M.tb* disease. Interferon-γ is produced mainly by CD4+, CD8+, and NK cells that work synergistically with TNF- to activate macrophages to kill intracellular *M.tb* bacteria. Interferon-γ also increases antigen presentation and recruitment of CD4+ cells and CD8+ cells to kill *M.tb* bacteria and prevents memory T cells' weakening. Interferon IFN-γ also induces more than 200 genes in macrophages, including genes expressing MHC class II and free radicals and nitric oxide production. The main mechanism of the antimicrobial effect of IFN synergizing with TNF-α is the induction of nitric oxide production and other reactive nitrogen intermediates (RNI) by macrophages through iNOS. Some *M.tb* antigens such as lipoprotein 19kD can attenuate IFN responses to macrophages through inhibition of transcription of IFN-γ responsive genes.[10–12]

Tumor necrotizing factor-α is a cytokine other than IFN-γ, which plays an important role in protecting against *M.tb* infection. Tumor necrotizing factor-α is produced by macrophages, DC cells, and T cells. TNF- is produced by infected macrophages and then induces the expression of chemokines, including IL-8, MCP-1, and RANTES, which signal immune cells to migrate to the site of infection *M.tb*. The mice with reduced TNF-α or TNF-α receptors were more susceptible to *M.tb* infection. TNF- initiates migration, and granuloma formation is formed. The weaknesses TNF- response will increase the number of *M.tb*. In resistant strains of *M.tb* (W Beijing family), phenolic glycolipids found in bacterial cell walls can inhibit the release of pro-inflammatory cytokines from macrophages such as IL-6, IL-12 including TNF-α. The IL-12 cytokine is also one of the important cytokines in the immune response to *M.tb*. Interleukin-12 activates CD4 cells to produce TNF-α and IFN-γ. The studies have shown that individuals with impaired IL-12 production have an increased risk of TB.[11,12]

M.Tb Infection Persistency and Reactivation

Three conditions may occur when we look at the natural course of *M.tb* infection, after initial infection, and sensitization. These conditions are influenced by predisposing factors, which will later determine infection and change the proportion in each part of the condition. After infection, there is a critical period in which predisposing factors determine the outcome. In the first group, the primary infection will progress too progressive. It only occurs in a small proportion of the adult population and is more common in the severely immunosuppressed group and infants. In the second group, the primary infection was completely controlled, and reactivation was unlikely. The third group of controls for unstable infection can be slow or even increase due to precipitating factors. It is in this group that reactivation is most likely to occur.

Precipitation factors can make the disease progression; before this occurs, a sub-clinical infection phase occurs first. In this third phase, *M.tb* can be isolated by culture and pathological changes seen from imaging, all of which precede clinical symptoms.[10,12]

M.tb infection is characterized by the inability of the individual to develop a full immune response to eliminate the pathogen. *M.tb* bacillus has several strategies to avoid and manipulate host immune cells so that *M.tb* bacilli are avoided from host immune elimination. The result is that the pathogen can remain in the host cell. Several *M.tb* antigenic factors such as ManLAM and 19-kDa lipoprotein have been known to modulate the antigen presentation pathway and blunt the antimicrobial function of immune cells, including macrophages and other immune cells and RNI and inhibit phagolysosomal maturation. Several studies have been conducted to determine the persistence of *M.tb* bacteria in host cells, but these studies have only been carried out on experimental animals. Several factors have been identified as the cause of *M.tb* persistence, including phospholipases with codes plcA, plcB, plcC and plcD, PhoP and PhoQ proteins, and phosphatase binding proteins PstS1 and PstS2.[10]

Active tuberculosis may develop immediately after exposure and after primary infection or during ITBL. ITBL reactivation is a state where *M.tb* is active again from its dormant period. Several factors that can trigger active disease from an inactive infection include HIV, which is the main factor in reactivation of latent TB, in addition to uncontrolled diabetes, malnutrition, old age, kidney failure, or diseases with the use of immune-suppressing drugs such as cancer and rheumatism. TB reactivation can be found in all body organs that were the site of primary infection PstS2.[12]

Research conducted by Sun et al. cited by Dutta et al.[10] showed that adding a supernatant containing acid-labile and heat-stable resuscitation factor increased the viability of the *M.tb* H37Rv culture. This finding continued with discovering the protein resuscitation-promoting factor (Rpfs), which is thought to be associated with the reactivation of *M.tb* from a previous chronic infection. The *M.tb* genome containing the Rpf gene encoding rpfA–rpfE was shown to stimulate the regrowth of nonreplicating *M.tb* cells in vitro and increase the survival of *M.tb* bacilli in vivo.

Traditionally ITBL is an *M.tb* infection that resides in foci in the granuloma in a non-replicating state and will cause active TB when the immune response is compromised. From the model, it is known that during infection, *M.tb* will grow well in phagosomes. Still, there are some bacteria from necrotic macrophages that escape into the extracellular environment and stop replicating. The cessation of bacterial growth occurs even though a complete immune response has not occurred due to creation of a hypoxic and acidic extracellular environment and the release of bactericidal enzymes from dead macrophages and neutrophils.[10,12]

From the ITBL model, it is also known that foamy macrophages arise during the chronic infection process, which further phagocytizes cellular debris rich in fatty acids and cholesterol originating from cellular membranes. Foamy macrophages are full of non-replicating bacteria. Then the granuloma in the lung is pulled into the bronchial tubes and back to a different location in the lung parenchyma so that the infection process occurs again in the new site. In this dynamic process, reinfection in the upper lobes of the lung leads to the possibility of cavitation. The high oxygen tension in the location supports the rapid growth of extracellular *M.tb* bacilli, and the host immune response can fully control it. The subsequent stronger inflammatory response will lead to tissue destruction, liquefaction, and cavity formation. This dynamic infection process is similar to the development of immune reconstitution inflammatory syndrome (IRIS) in patients with HIV. HIV patients will tolerate the existing *M.tb* bacilli because the host immune response is unable to control the growth of the pathogen, but as the CD4+ cell count increases due to antiretroviral

administration, a granuloma response and active TB rapidly develop. [10,12]

Location of *M.Tb* Basis In Latent TB

In latent TB, it is known that there is a small proportion of *M.tb* bacteria that remain alive which will later be able to reactivate into active TB. However, the exact location or place of the *M.tb* bacillus is still a question. Several studies have concluded that *M.tb* bacteria in latent TB are present in caseous tissue and necrotic granulomas. Rabinowitsch's study cited by Dutta showed that lymph nodes in mesenteric and bronchial origin from patients without active TB containing lime-like tissue were found to cause TB when infected in rabbits; this occurred in 4 out of 5 experimental animals. This study, along with other similar studies, put forward the theory that the spread of *M.tb* bacilli in the lymphatic system is important in the adaptive immune system and is also important as a basis for the pathological spread of infection.[10,12]

Research Hobby et al. cited by Dutta, who performed culture in liquid medium of 85 closed healthy necrotic lesions in 40 treated TB patients found that 78% of these lesions could grow *M.tb*, but the viability of the bacilli was only detected after an extended incubation period of 9-12 weeks.[10]

Latent TB Risk Factors

Individuals with untreated active TB are a source of transmission of new TB infection cases. The source of transmission comes from the respiratory tract of patients with active TB. Controlling the transmission of TB infection from active TB cases is one of the main objectives of the TB eradication program in countries with high TB rates, including Indonesia.

Generally, infected individuals will experience an infectious process limited by the immune system, and *M.tb* bacteria will survive in granuloma caseosa or tubercles. It is estimated that 5% of infected individuals will become ill with TB in the first 2 years after infection. Approximately 10% of infected individuals will develop latent TB, which is reactivation in the first 1 year after infection, and this risk persists for life. This reactivation generally occurs by reactivating TB bacteria that were previously dormant in the primary infection or because of a lesser chance of being infected with TB bacteria again. Overall, approximately 10-15% of these infected individuals will be at risk of developing TB disease at some stage of their life. This risk will increase to 10% per year in HIV-positive individuals and other immunocompromised individuals, including DM.[10,12]

There are two different essential aspects of the risk of TB infection, namely the risk of infection and the risk of progression of infection to TB disease. The risk of infection when exposed to the causative bacteria is mainly regulated by exogenous factors with a combination of intrinsic factors such as the infectious level of the source of transmission, the proximity of contact with the source of transmission and social risk factors and habits such as smoking, alcohol and indoor air pollution.[13]

Factors that increase the progression of infection to TB disease are influenced more by factors that exist in the host itself. Conditions that can alter the immune response, such as HIV, become very important and decisive on this factor. Still, on the population, the impact is highly dependent on the local prevalence in the area, but other factors such as diabetes, smoking habits, malnutrition and indoor air pollution are also factors that have a more significant impact on the population in accelerating the risk of progression of TB infection.[6,13]

Diabetes as a Risk Factor for Latent TB

Several studies have shown that diabetes is one factor that increases the risk of developing active TB. In a systematic review conducted by Jeon and Muray, it was concluded that individuals with DM had a three times greater risk of developing TB than individuals without DM.[11] Epidemiological studies in India and Mexico show DM is present in 22% of TB cases or one-third of all TB cases in these countries. This, of course will have a significant impact on the TB control program.[14,15]

Diabetes mellitus also has an impact on the clinical and course of TB disease. TB patients with DM more often show positive smear results than those without DM, contributing to the spread of TB infection. In addition, TB-DM patients have a higher mortality risk than TB without DM.[5,14] The increased risk of TB infection in people with DM is thought to be due to changes in the immune response. Diabetes mellitus is characterized by hyperglycemia caused by impaired insulin secretion, impaired insulin response or a combination of both. Uncontrolled glycemic levels can lead to compromised immunity, making it easier for patients to be infected with intracellular bacteria, especially *M.tb*.

The etiology of DMT2 includes a complex mix of genetic and environmental factors that lead to insulin resistance and elevated blood glucose and free fatty acids (FFA) levels. Changes in glucose and lipid metabolism in adipocytes and hepatocytes will increase the pro-inflammatory state characterized by an increased population of activated macrophages. Pressure on pancreatic beta cells occurs as a result of metabolic and inflammatory changes that will eventually lead to insulin deficiency and hyperglycemia.[5,16]

The hyperglycemia will result in an impaired immune response to *M.tb*. Research conducted in Japan showed a relationship between glucose intolerance and the incidence of TB. This study is in line with a survey conducted in Africa with the results of the risk for TB in subjects with glucose at 11.1 mmol/L was 2.15 times compared to subjects with glucose at <11.1 mmol/L.[10] Hyperglycemia is known to affect macrophage action. Macrophages themselves are one of the first immune cells to fight mycobacterial infection and are the cells in which mycobacteria thrive during infection.[16]

Hyperglycemia also results in impaired macrophage function in receptor expression associated with antigen presentation and T cell activation. Research conducted by Lopez-Lopez et al. showed that macrophages of diabetic patients infected with H27Rv TB had reduced expression of CD86, CD80, HLA-DR, and molecules associated with antigen presentation and T lymphocyte activation as reduced induction of IL-6, IL-1β, IL-10 and IL-12 before and after infection.[17] Glycemic control is usually measured by the HbA1C level, which indicates glucose concentration in the blood 2 or 3 months before the test.

HbA1C levels recommended by the American Diabetes Association (ADA) are <7% or preprandial capillary glucose levels 83-130 mg/dL and postprandial glucose levels <180 mg/dL. Kumar et al. showed changes in the levels of monocyte activator markers.[18] Almeida et al. demonstrated that high HbA1C levels were associated with the severity of lung damage by *M.tb*, but the mechanism that explains this pathology is still unclear.[19] In in vitro studies, it is known that *M.tb* uses triglycerides from the host as a site of infection in hypoxic conditions.[20] This causes the formation of a fatty acid-rich environment and becomes a source of energy from lipids during *M.tb* infection, as seen in experimental animal granulomas. This concept is consistent with latent TB infection in DM. Lipid accumulation in macrophages will form foam cells (foamy cells) that secrete cytokines. Foamy macrophages contribute to mycobacterial persistence and pathological changes in tissues during TB. High triglyceride levels in DM patients will cause increased levels of oxidized LDL (Ox LDL).[21]

Research conducted by Vrieling et al., shows that macrophages with high levels of Ox-LDL have a high mycobacterial load compared to macrophages that Ox-LDL does not accompany.[21] This evidence reinforces the concept that high Ox-LDL concentrations in DM patients contribute to the progression of TB infection in DM, and dyslipidemia in DM is strongly associated with DM susceptibility to TB infection. Kumar et al. showed that DM patients with latent TB and active TB had decreased levels of adiponectin, adipsin, and/or increased levels of leptin, visfatin and PAI-1.[22] Adiponectin and adipsin were negatively correlated with HBA1C levels, while visfatin, leptin and PAI-1 were positively correlated with HbA1C levels. These changes in systemic adipocyte levels strongly indicate systemic inflammatory changes in adipose tissue in people

with diabetes, thus contributing to the course of TB infection. Resistin is a protein that is considered to play a role in insulin resistance both in humans and in experimental animals. Thus, protein is key to the link between obesity and diabetes. Resistin increases the expression of proinflammatory cytokines such as TNF-α, IL-6, IL-12 and MCP-1, macrophages and hepatic stellate cells through the NF-κβ factor pathway. Research shows that people with diabetes have high resistin levels in serum along with a reduced ability of THP-1 macrophages to produce ROS when fighting *M.tb* infection. TB infection showed a marked increase in resistin levels. This evidence suggests that TB induces changes in resistin production that affect metabolic and immune responses and is derived from deactivated macrophages.[16,22]

Treatment given to DM patients aims to overcome hyperglycemia. The standard drug recommended by the ADA is metformin. Several retrospective studies conducted in Taiwan showed hyperglycemia therapy with metformin was a factor in preventing TB in DM patients (HR 0.552; 95% CI (0.493 to 0.617) and HR 0.84; 95% CI (0.74 to 096)).[23] Metformin works by reducing MMP production 1, 2 and 8. Metformin is associated with a reduced number of mycobacteria in TB patients with DM; however, Lee et al. in Seoul showed that the use of metformin and anti-tuberculosis drug (ATD) in DM-TB patients had no effect on sputum conversion and observed TB recurrence for 1 year after completion of therapy.[23] These results are supported by animal studies which concluded that there was no increase in the efficacy of ATD therapy with the addition of metformin. The evidence above shows that the control of hyperglycemia exerts an influence on the metabolic environment that can reduce susceptibility to TB infection through its mechanism.

Hyperglycemia conditions in the long term accelerate the formation of advanced glycation end products (RAGE) produced by non-enzymatic protein glycation. Increased levels of AGE and FFA will trigger the production of inflammatory mediators and reactive oxygen species (ROS). The increase in ROS is also due to increased glucose metabolism through oxidative phosphorylation. There is a balance of ROS production in healthy individuals with an increase in antioxidant activity, especially that carried out by glutathione, but this is not the case in people with diabetes. Obesity is also thought to influence chronic inflammation due to increased pro-inflammatory cytokines by adipocytes and macrophages in adipose tissue. Excessive production of TNF-α in adipose tissue is associated with inflammatory, metabolic changes, and it is also a cause of insulin resistance. Macrophages that have not been activated will accumulate in adipose tissue, releasing inflammatory mediators such as TNF-α, C-reactive protein (CRP), IL-1β, IL-6, IL-8 and IL-12. Many other mechanisms influence changes in the immune response of DM patients to TB infection that have not been studied extensively, including age, vitamin D levels, and the anti-inflammatory effect of the drugs used.

Natural and Adaptive Immunity Against TB in People with DM

In people with DM, the disruption of the immune process has started during the initial process of introducing *M.tb* by the innate immune cells of the host. Monocytes of diabetes patients experienced a significant decrease in their attachment function and phagocytosis to *M.tb* compared to monocytes of non-DM patients, due to changes in monocytes with DM, especially in the C3 component, which is a complement to *M.tb* phagocytosis events.[13,14] This is also the case, following the study of Martinez et al.[54(39) quoted from 24] which showed a decrease in the phagocytic function of macrophages in rats after being infected by *M.tb* for 2 weeks. A multivariate analysis comparing monocytes of TB DM patients with non-DM TB found an increase in CCR2 and CCL2 (MCP-1) expression, which are CCR2 ligands in DM patients. In addition to the reduced ability to perform phagocytosis, people with diabetes also show reduced gene expression that contributes to the presentation of antigens and antimicrobial peptides.[13,14,22]

The process of phagocytosis and the initial response to prepare for the adaptive immune function is an essential process in the host immune response to limit the growth of *M.tb*. The delay in the phagocytic process that occurs in people with DM facilitates *M.tb* infection and persistence. Research by Restrepo et al. showed that TB patients with DM showed an increase in the number of NK cells found in the blood and bronchoalveolar lavage (BAL) fluid compared to the non-DM TB group.[13] However, the effect of this on the sensitivity of DM patients to TB infection is still unclear.

Dendritic cells are immune cells that play a role in the relationship between natural and adaptive immunity. Migration of dendritic cells to lymph nodes is essential in TB infection. Research has revealed that DM patients with TB infection show lower myeloid and plasmacytoid dendritic cells than normal individuals. However, their contribution to the pathogenesis of TB infection in DM is still unclear, although it is possible that hyperglycemia can affect it.

Neutrophils are immune cells that also play an essential role in the pathogenesis or defense against TB infection. Neutrophils play a role in innate immunity against TB through an oxidative process that kills mycobacteria. Neutrophils are the first immune cells to migrate to the site of infection and will secrete cytokines and chemokines, which in turn induce and activate other immune cells. Hyperglycemia that occurs in DM has been shown to increase integrins' adhesion and expression, reducing the chemotaxis and microbicidal activity of neutrophils. In addition, there is evidence that glycated collagen inhibits neutrophil migration due to the RAGE receptor expressed by neutrophils and other leukocytes.

Natural Killer (NK) cells are also effector cells of innate immunity. During the early stages of infection, NK cells can activate phagocytic cells to the site of infection and rapidly recognize and destroy infected host cells. In addition, NK cells produce several cytokines, including IFN-c, IL-17 and IL-22, which play an essential role in the host defense mechanism against mycobacterial infection. Recent studies have shown that TB DM is characterized by increased expression of type 1 (TNF-) and type 17 (IL-17A and IL-17F) cytokines from NK cells.

Antimicrobial peptides are critical components of innate immunity against pathogens and are primarily present in phagocytic cells. Several studies have shown that antimicrobial peptides with high antimycobacterial activity but low immunogenic properties are promising therapeutic agents. Among several peptides studied, it is known that cathelicidin LL-37 is one of the antimicrobial peptides that responds very well to *M.tb*. Gonzales-Curiel et al. showed a higher expression of cathelicidin in inactive TB compared to latent TB. Arliny concluded that the cathelicidin level obtained was higher in the active TB DM group than in the active TB without TB infection, the LL-37 cathelicidin level >30 ng/ml became one of the predictor factors in latent TB DM to active TB in addition to the HbA1c factor > 10 and a history of smoking.

Several studies conducted on TB patients with DM showed increased levels of Th1 (IFN-γ, IL-2), Th17 (IL-17A), IL-10, and decreased levels of T regulatory (CD4+, CD25+, CD127-). This suggests different regulation of immune responses in TB patients with DM and TB without DM. Several studies that tried to compare the immune response in the two groups turned out to get different results, so it is still unclear how this change in immune response occurs in the two groups. In latent TB, it is suspected that there are also changes in the natural and adaptive immune responses. However, very few studies explain this relationship, thus is difficult to obtain clear information.[13,14,21]

Cytokines types 1 and 17 and IL 1 are cytokines known to affect a person's susceptibility to TB. Nathella et al. stated that diabetes could alter the balance of these cytokine levels in latent TB infection.[21] In DM, latent TB inflammatory cytokines type 1 (IFN, TNF and IL 2), 17 and IL 1 and other pro-inflammatory cytokines were reduced compared to those without DM. Other systemic pro-inflammatory cytokines such as IL 1β, IL-18 and IL-10 also decreased, but not type 2 cytokines. The

poor glucose control will affect the progression of latent TB to active TB. CD8+ lymphocyte cells are known to have a minor role in *M.tb* infection, but it is known that in latent TB DM subjects, the expression of cytokines involving CD8+ lymphocyte cells is also reduced.[25] It can be concluded that DM will change the immune response by introducing CD4+ and CD8+ lymphocytes cells to be suboptimal and increasing the risk of developing active TB. In people with DM, progression to active TB results from impaired function of alveolar macrophages regardless of previous exposure to infection. Although this mechanism has not been thoroughly studied, there is evidence that 10–20% of latent TB have transcriptional signs of active TB from the peripheral blood; this supports the opinion that the latent TB subgroup may have clinically hidden but biologically active foci of infection and therefore have a high risk of developing infection progress to active TB.

Until now, there is no firm recommendation whether patients with DMT2 are given or not given latent TB prophylaxis; unlike in other populations, ITBL prophylactic therapy has not been fully evaluated, no specific studies are determining the efficacy of preventive therapy against the onset of active TB in DMT2 patients, as well as a more in-depth study of the antimicrobial effect of drugs used to treat diabetes (metformin) or other antidiabetic drugs.

The susceptibility of DM patients to TB infection originating from immunity is not yet fully understood. The increased risk of TB infection in DM patients is caused by several factors, including the direct effect of hyperglycemia and insulin resistance and indirectly through the function of macrophages and lymphocytes. Impaired immune response in DM patients facilitates primary TB infection or reactivation of latent TB.

Demographic Aspects of Latent TB in DM

Data on the prevalence of latent TB in DM in Indonesia is unknown because there is only a few research data that measures this. Arliny obtained data that there were 33.9% latent TB in DM patients without complications of decreased kidney function.[24] Koesomadinata obtained data on the prevalence of latent TB in DM patients of 38.9%. quoted from 24 Data on latent TB in DM patients from other countries varied, 50% in Mexico, 28.2% in Singapore, and 28.5% in Malaysia.[24] Almost all research obtained data that more male were diagnosed with latent TB than female, with the most age range being 53.4–59.5 years. From the research, it is known that the duration of DM is one of the risks of latent TB. Research conducted by Merza et al. found a significant relationship between the duration of diabetes 10 years with latent TB (OR 2.692; 95% CI 1.016–7.267).95(43) quoted from 24

Epidemiological studies conducted in the United States showed that patients with poor glycemic control had a 2.2 times risk of developing latent TB than patients without a history of diabetes. DM patients who have a fasting blood glucose >130 mg/dL have a 2.6 times risk of developing latent TB than patients without a history of diabetes.122(44) quoted from 24 Martinez et al., in their study, obtained a mean HbA1c in latent TB diabetic subjects of 7.5%. This value is lower than that obtained in Arliny's research, which is 8.4%.quoted from 24

Arliny obtained data that latent TB DM had a lower BMI than DM without TB infection and higher than active TB DM.[24] There is a significant difference in BMI between latent TB DM and active TB. One of the causes of the increased risk of latent TB in people with diabetes is the relationship between adipose tissue and *M.tb* replication. Adipose tissue constitutes 15–25% of the total body mass and is an active production site for hormones and mediators of inflammation. The increasing prevalence of obesity has led to a greater incidence of T2DM, and weight gain is usually (though not always) associated with T2DM. People with T2DM have a 2–3 times risk for infection and TB disease, so there may be a potential relationship between adipose tissue and disease pathogenesis. In addition to regulating energy homeostasis, adipose tissue is rich in macrophages and is involved in producing cytokines. Adipose tissue contains adipocytes, monocytes, and macrophages. It is

suspected that body fat tissue can provide a shelter for *M.tb* to hide and escape from the immune system. Research Ugarte-Gil et al. found that *M.tb* can reach into the fat cells and survive there. A large number of infections will cause *M.tb* to have large numbers in adipose tissue.

CONCLUSION

Diabetes can induce changes in the immune response to TB infection, both natural and adaptive immune responses. Disruption of the innate immune response followed by a hyperreactive adaptive immune response causes an increased risk of TB infection in diabetes. Although several pathophysiological and immunological pathways are known to play a role in diabetes, and ITBL as well as active TB, more in-depth research is still needed on screening and prophylactic therapy for latent TB in DM.

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Role of Interventional Radiology in the Management of Massive Hemoptysis

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Abstract
Massive hemoptysis is one of the emergencies in respiratory system, representing hemorrhage of the bronchial or pulmonary vascular system into the respiratory tract. Massive hemoptysis is a life-threatening condition due to high risk of asphyxia it may induce. Bronchial artery embolization (BAE) is an interventional radiology procedure dedicated in the emergency management of massive hemoptysis. BAE is known for its great success rate and low risk of complications. Proper catheterization technique, recognition of bronchial artery variant anatomy and appropriate selection of embolic material agent proves essential in determining the success of this procedure. As a minimally invasive procedure, BAE is highly recommended to be used in cases of massive hemoptysis. ***(J Respirol Indones 2021; 41(4): 300–7)***
Keywords: *hemoptysis; bronchial artery embolization; angiography; interventional radiology; emergency*

Peran Radiologi Intervensi pada Tata Laksana Hemoptisis Masif

Abstrak
Hemoptisis masif adalah salah satu kegawatdaruratan dalam sistem pernapasan yakni terjadinya perdarahan sistem vaskular bronkial atau pulmoner yang mengisi saluran pernapasan. Hemoptisis masif merupakan kondisi yang mengancam jiwa karena terdapat risiko tinggi untuk terjadinya asfiksia. Bronchial artery embolization *(BAE) atau embolisasi arteri bronkial merupakan sebuah prosedur radiologi intervensi yang ditujukan untuk menjadi tata laksana kegawatdaruratan pada kasus hemoptisis masif. BAE diketahui memiliki angka keberhasilan yang tinggi dan risiko komplikasi yang rendah. Teknik kateterisasi yang tepat, pengenalan varian anatomi arteri bronkial dan pemilihan agen bahan emboli yang tepat berperan penting dalam menentukan keberhasilan prosedur ini. Sebagai sebuah prosedur yang minimal invasif, BAE sangat direkomendasikan dalam kasus-kasus hemoptisis masif.* ***(J Respirol Indones 2021; 41(4): 300–7)***
Kata kunci: *hemoptisis; embolisasi arteri bronkial; angiografi; radiologi intervensi; gawat darurat*

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INTRODUCTION

Hemoptysis or coughing up blood is the expectoration of blood due to bleeding in the airways under the larynx or bleeding that comes out through the lower respiratory tract of the larynx.[1] Massive hemoptysis can be life-threatening, with a mortality rate of more than 50% without adequate bleeding control.[2–5] Ninety percent of the source of massive hemoptysis comes from the bronchial circulation and 5% from the pulmonary circulation. Another small proportion originates from the aorta (aortobronchial fistula, ruptured aortic aneurysm, or systemic arterial circulation to the lungs).[1–3]

Hemoptysis occurs in 30% of patients with lung carcinoma, with 10% of them experiencing massive bleeding.[2–7] The severity of hemoptysis depends on several factors, such as history of disease, coagulation, and hemorrhagic shock.[4]

Bronchial Artery Embolization (BAE) is a diagnostic and therapeutic procedure in interventional radiology that has an important role in cases of massive hemoptysis. Aortography and angiography of the bronchial arteries have good diagnostic value in identifying the source of bleeding. On the other hand, embolization as a minimally invasive therapeutic procedure has high effectiveness in terminating the bleeding.[2,3] The following description introduces and explores the roles of interventional radiology in the form of BAE on massive hemoptysis cases.

DISCUSSION

BAE was first reported as a treatment option for massive and life-threatening hemoptysis by Remy, et al. in 1973.[2,6] Compared to invasive surgery, BAE is a minimally invasive procedure that is relatively safer and has higher effectiveness plus lower risk of complications because BAE does not impair pulmonary function. Patients with massive hemoptysis generally have a poor pulmonary function. Therefore, they had a high risk for anesthesia and surgery with a mortality rate of about 7.1–18.2% and increasing to 40% in emergency surgery.[2]

Indication

BAE procedures can be performed in hemoptysis cases with various etiologies. Pathological processes that indicate BAE include:[1,5,6]

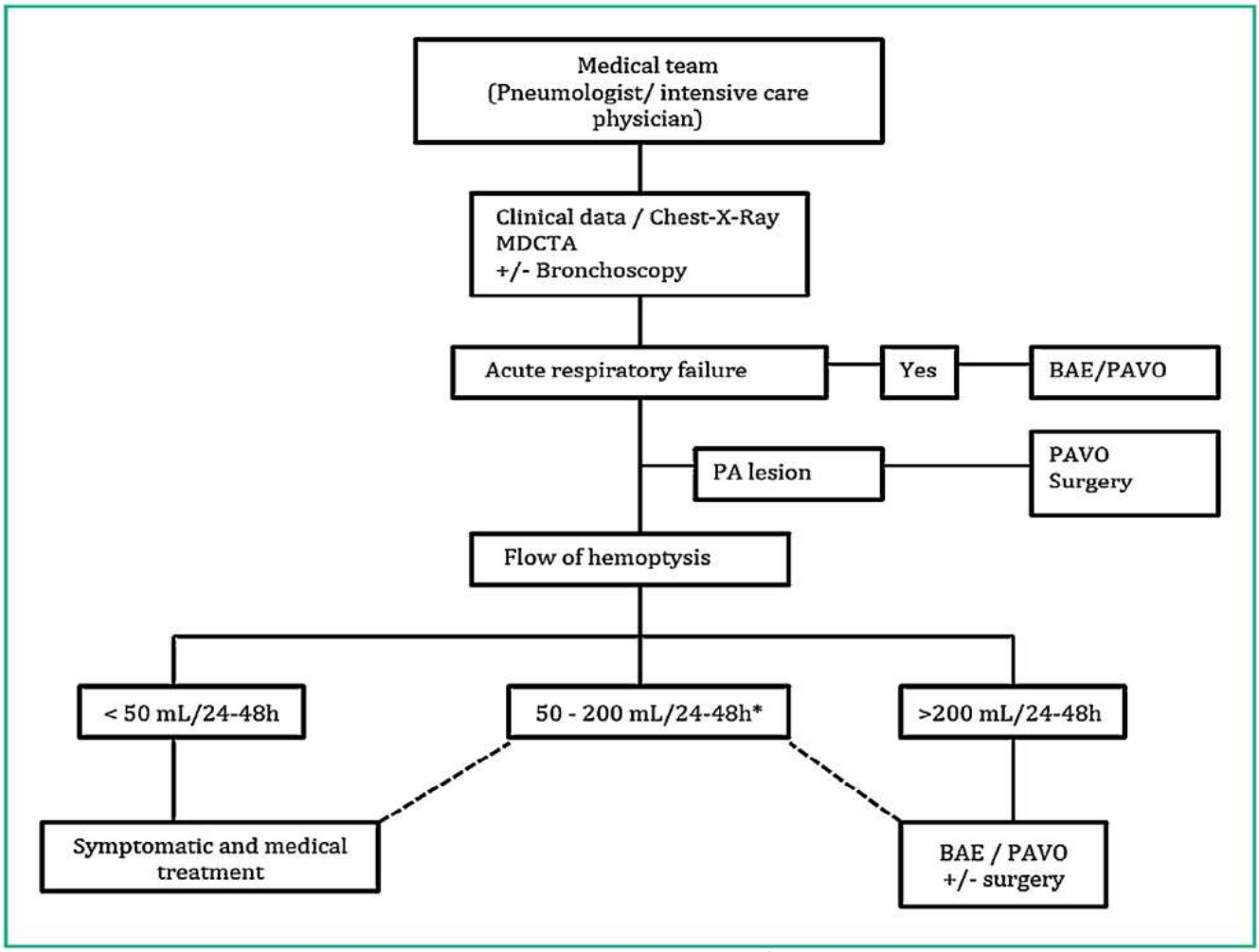
- Life-threatening hemoptysis, i.e., bleeding 300 mL in 24 hours, bleeding 100 mL per day for at least 3 days, or minor bleeding with hemodynamic instability.
- Diffuse interstitial lung disease and chronic granulomatous disease.
- Diseases that can trigger hemoptysis, i.e., cystic fibrosis, tuberculosis, bronchiectasis, interstitial pulmonary fibrosis, fungal infections (e.g., aspergillosis), ruptured bronchial artery aneurysm, arteriovenous fistula, neoplasm, Bechet disease, cryptogenic.

Contraindications

As a life-saving emergency procedure, BAE has no absolute contraindications. Relative contraindications to BAE include general angiographic contraindications, namely impaired coagulopathy, the presence of the major radiculo medullary artery of the target artery (e.g., the target artery also supplies the spinal cord), and congenital pulmonary artery stenosis (CPAS). In patients with CPAS, pulmonary parenchymal perfusion relies almost entirely on the bronchial artery system, so the BAE procedures carry a higher risk. All of these relative contraindications do not prevent BAE from being performed. Careful preparation and planning are required before BAE can be completed in patients with these contraindications.[2,5]

Pre-Procedure Preparation

The management of massive hemoptysis should focus on airway patency to prevent aspiration of blood, which could lead to asphyxia. The patient's respiratory and hemodynamic status are evaluated and optimized as possible. In emergency cases, transfusion of fresh-frozen plasma or platelets can be performed intra-procedurally to optimize blood coagulation function.[4–6]



Note: BAE= Bronchial Artery Embolization; PAVO= Pulmonary Artery Vaso-Occlusion.[1]

Figure 1. Algorithm for the management of life-threatening hemoptysis.

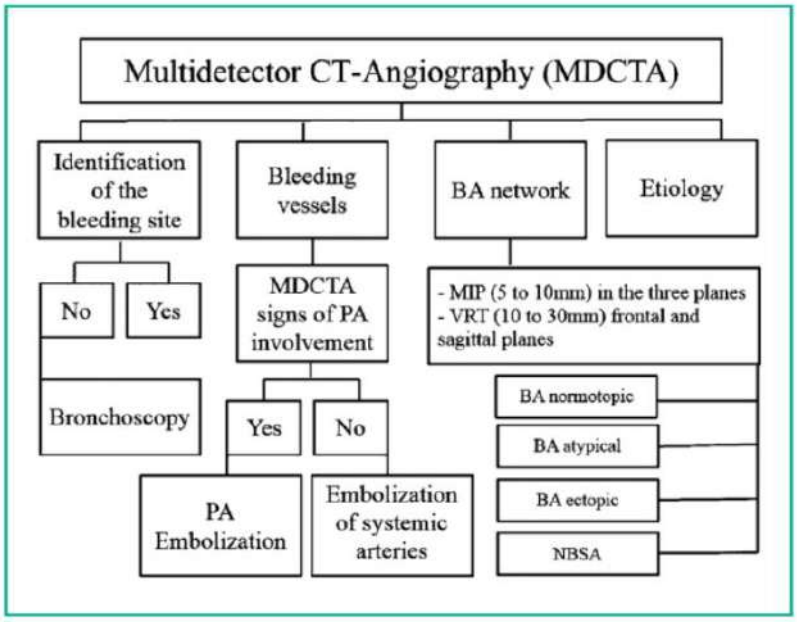
The considerations for endotracheal intubation are evaluated based on the patient's condition. Moderate sedation is generally adequate to stabilize the patient's condition and position during the procedure.[4–6]

Preprocedural diagnostic imaging includes chest radiography to identify the etiology of hemoptysis and to estimate the site of bleeding. Computed tomography (CT) or CT angiography (CTA) is performed when the patient's condition is permitted to evaluate the size and extent of the lung lesion, as well as to identify the source of bleeding (Figure 2 and 3). Bronchoscopy can help localize the site of bleeding. However, in the case of massive bleeding, blood in the bronchial tree can obscure the visual field and make it difficult to identify the source of bleeding.[5,6]

Catheterization Technique

Arterial access through the common femoral artery is carried out using a 5F femoral introducer sheath. In younger patients, the 4F size can be applied. As a first step, descending thoracic aortography is performed to evaluate the location and anatomic variant of the bronchial arteries that branch directly from the aorta. In addition, aortography can also assess structural abnormalities of the bronchial arteries and identify non-bronchial circulation.[2,5]

The commonly used angiographic catheter for selective bronchial artery catheterization is the cobra type catheter. Other types of angiographic catheters such as Simmons-1, headhunter, and Yashiro can also be utilized as alternatives to bronchial arteries catheterization.



Note: MDCTA= Multidetector CT-angiography; MIP= Maximum Intensity Projection; VRT= Volume Rendering Technique; PA= Pulmonary Artery; BA= Bronchial Artery; NBSA= Non-Bronchial Systemic Artery.[1]

Figure 2. Utilization of CTA in identifying the etiology and localizing the source of bleeding.

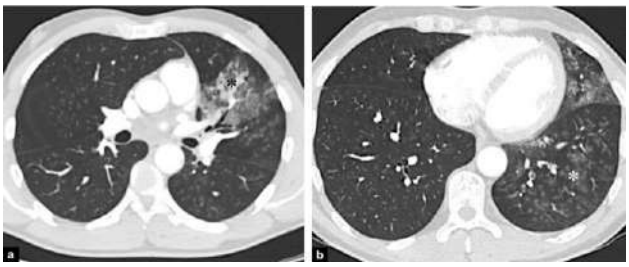


Figure 3. (a) Axial CT shows focal alveolar changes (stars) surrounded by a ground-glass opacity in the linguistic lobe suggesting hemorrhage in that region. (b) Axial CT at the level of the lung bases depicts a nodular ground-glass opacity (star) in the inferior lobe of the left lung, indicating an extension of hemoptysis to the inferior lobe.[1]

Furthermore, super-selective catheterization is carried out using a microcatheter on the branch of the bronchial arteries which are identified as the source of bleeding. The tip of the catheter is positioned as stable as possible at the mouth of the bronchial artery to prevent non-target arterial branch catheterization. Superselective angiography with manual contrast injection will be performed once more post-catheterization to confirm catheter position and to localize the bleeding source.[1,2]

Bronchial Artery Anatomy Variants

The bronchial circulation has four variants of the branching pattern of the bronchial arteries, (Figure 4):

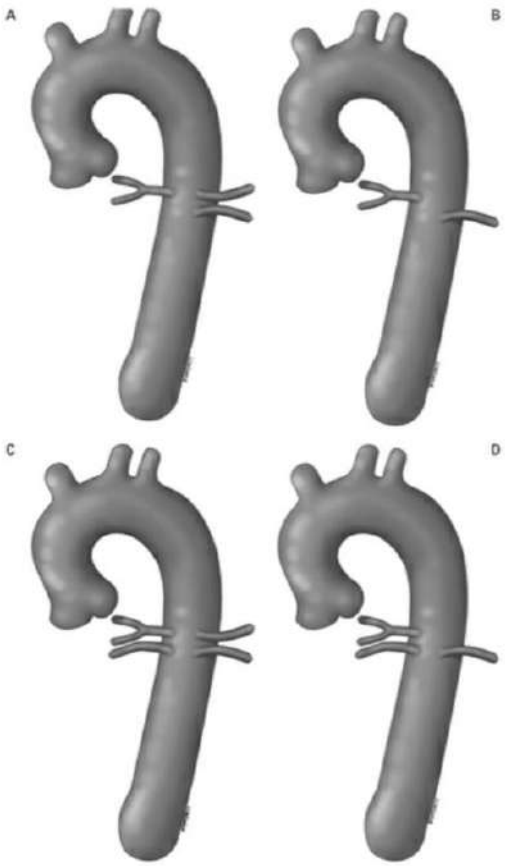


Figure 4. Illustration of four variants of the bronchial arterial supply. (a) Two bronchial arteries on the left and one on the right that manifests as an ICBT. (b) One on the left and one ICBT on the right. (c) Two on the left and two on the right (one ICBT and one bronchial artery). (d) One on the left and two on the right (one ICBT and one bronchial artery). ICBT: intercostobrachial trunk.[2]

- Two separate branches on the left and one on the right as the intercostobrachial trunk (ICBT) in 40% of individuals.
- One branch on the left and one ICBT on the right in 21% of individuals.
- Two separate branches on the left and two separate branches on the right (one ICBT and one bronchial artery) in 20% of individuals.
- One branch on the left and two separate branches on the right (one ICBT and one bronchial artery) in 9.7% of individuals.

Identification of the bronchial artery variant is an essential step in preparing for the BAE procedure. These anatomic variants can be identified on CTA or thoracic aortogram (Figure 5).[1,2]

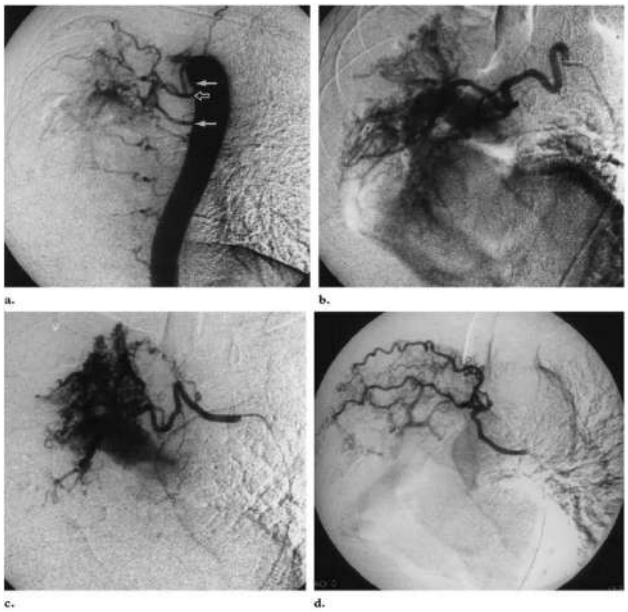


Figure 5. Thoracic aortographic features of massive hemoptysis. (a) Thoracic aortography shows hypertrophy of two bronchial arteries (solid arrows) and one intercostal artery (open arrows) supplying a hypervascular lesion in the superior lobe of the right lung. (b) Selective angiography of the superior bronchial artery. (c) Selective angiography of the inferior bronchial artery showing bronchopulmonary shunting. (d) Selective angiography of the intercostal arteries shows bronchopulmonary shunting.[2]

In general, there is one right bronchial artery originating from the intercostal arteries, the ICBT, located on the posterolateral aspect of thoracic aorta. The right and left bronchial arteries generally emerge from the anterolateral aspect of the aorta. The bronchial arteries supply the trachea and extrapulmonary as well as intrapulmonary respiratory tract, bronchovascular bundles, nervous system, regional lymph nodes, visceral pleura, esophagus, and aortic vasa vasorum. In one-third of cases, one bronchial artery may be located ectopically from the caudal aspect of aortic arch. Other variations of the bronchial arteries may originate from the costocervical trunk, thyrocervical trunk, and the internal mammary artery.[2–4,7]

Angiographic Findings

Angiographic findings in massive hemoptysis may include contrast extravasation, pseudoaneurysm/aneurysm, or abnormal vascularity, e.g., hypertrophy of tortuous bronchial arteries, neovascularization, or shunting of pulmonary arteries or veins. Contrast extravasation is a specific finding in bronchial hemorrhage but only visualized in 3.6–10.7% of cases.[2,4,6]

Normal diameter of the bronchial artery in adults is 1.5 mm at the proximal estuary and 0.5 mm in the distal segment near the bronchopulmonary insertion. The hypertrophied (>2.0 mm) bronchial arteries are visualized as contrast-enhanced nodular or tubular structures in the mediastinal region and around the central airways on chest CT or thoracic CTA with intravenous contrast. Bronchial artery hypertrophy has a predilection for the retro-esophageal, retrotracheal, retrobronchial, posterior walls of the main bronchi, and the aortopulmonary window.[2,4]

Non-bronchial circulation may originate from the intercostal, thoracic, inferior phrenic, thyrocervical, vertebral, axillary, subclavian, and internal mammary arteries. The coaxial microcatheter system (Renegade, Progreat) can reach the target bronchial arteries more easily, minimizing the risk of vasospasm, avoiding non-targeted embolization of the spinal cord arteries, and reducing the risk of reflux of embolic material into the spinal branches of the aorta. Non-bronchial systemic collateralization should be assessed and monitored. Hemoptysis that rapidly recurs post-BAE often indicates the contribution of the systemic vascular system to the source of bleeding.[2,6]

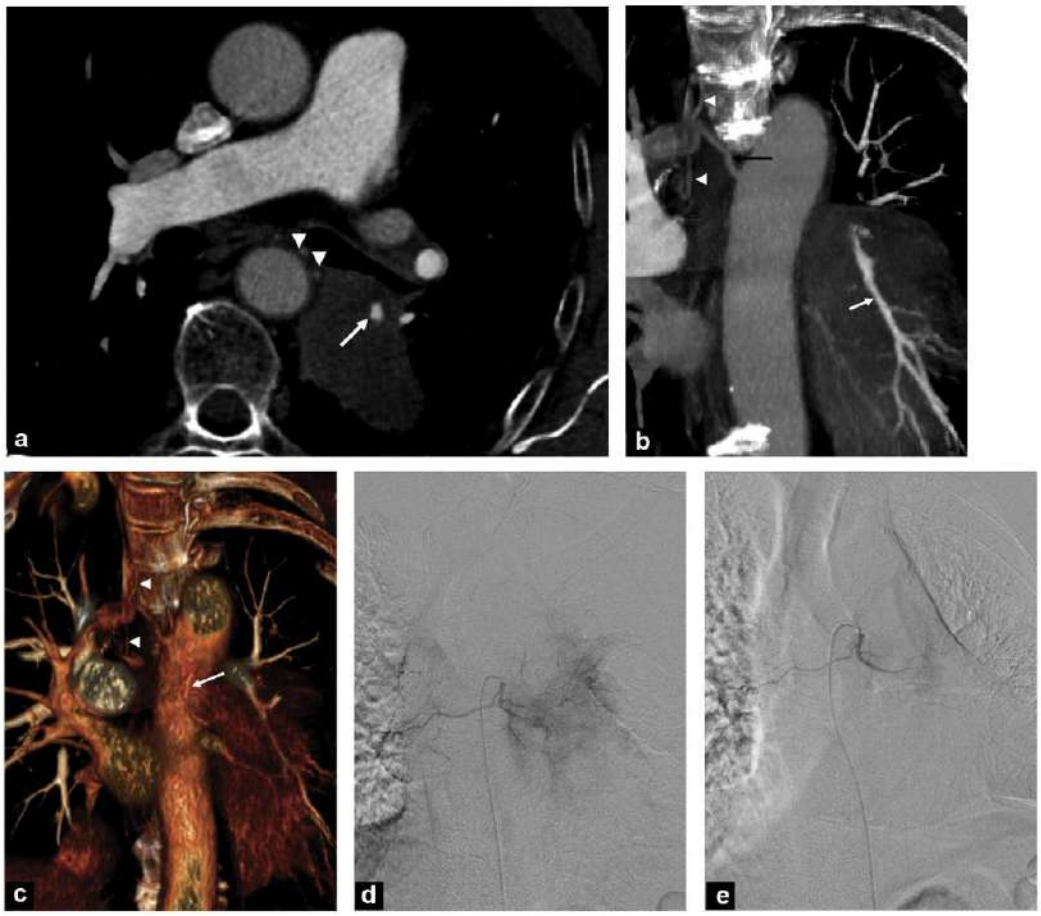


Figure 6. Non-small cell lung carcinoma in the lower lobe of the left lung with hemoptysis of 40 mL/day for several weeks, which is getting larger. (a) Axial CT shows stenosis of the left pulmonary artery (arrows) by tumor and left bronchial artery hypertrophy (arrowheads). (b) The coronal reconstruction shows a mass at the left hilum surrounding the pulmonary artery (white arrow) and hypertrophy of the IBCT (black arrow) providing collateral to the right bronchial artery (arrowhead). (c) VR reconstruction (volume rendering) showing IBCT branching into the right bronchial artery (arrowheads) and the proximal opening of the common right-left bronchial trunk (CRLBT; arrows), providing vascularization to the left lung and right inferior bronchial artery. (d) CRLBT angiography shows hypervascularization at the left hilum without systemic-pulmonary shunting. (e) Postembolization CRLBT angiography using non-resorbable particles with a diameter of 250 umm showed significantly reduced tumor vascularity.[1]

Selection of Embolic Agent

Several choices of embolic agents can be used in BAE. The use of embolic agents that can pass through the bronchopulmonary anastomoses should be avoided (minimum diameter 325 µm). Embolic agents that cause distal occlusion of peripheral branches supplying the bronchi, esophagus, or vasa vasorum of the pulmonary artery and aorta, should also be avoided to prevent complications such as necrosis of the vascular wall.[1,3,5]

An absorbable gelatin sponge is the most commonly used embolic agent because it is inexpensive, easy to use, and has a controlled particle size. The disadvantages are that it decomposes spontaneously, resulting in recanalization and repeated bleeding and also its non-radiopaque nature under X-rays. Polyvinyl alcohol particles, non-resorbable embolic agents with particle diameters of 350–500 µm, and microspheres are alternative embolic agents that can be used.[1,2,8]

Liquid embolic agents (isobutyl-2 cyanoacrylate, absolute ethanol) can not be used as they are able to cross the bronchopulmonary anastomoses, resulting in non-pulmonary embolization target, moreover, it has a serious risk of complications, such as non-target tissue necrosis. Platinum coils are not used in BAE because their relatively large size which means that these embolic agents can only occlude proximal blood vessels. If hemoptysis recurs, the presence of platinum coils

actually closes the bronchial artery access and prevents embolization.[2,5]

Postprocedure Treatment

Post-procedure, treatment in an intensive care unit for patients with life-threatening hemoptysis is carried out with the length of treatment depends on the patient's hemodynamic status and complications rate. Routine post-angiography care includes regular monitoring of vital signs, inspection of access sites, pain control, antiemetic therapy if needed, and neurological consultation if the patient shows signs and symptoms of anxiety.[1,5]

Success Indicator

BAE success is defined as successful catheterization of the target artery as the source of bleeding and the successful delivery of embolic agents until extravasation of contrast is no longer visualized. BAE success can be achieved in 90% of cases. The clinical success of BAE can be judged on the basis of:[1,2,6,8]

- Massive hemoptysis can be controlled post-BAE;
- The recurrence rate varies depending on the etiology and chronicity of the disease;
- Rapid re-occurrence of hemoptysis post-BAE indicates the involvement of non-bronchial systemic arterial supply;
- Long-term relapse is generally due to vessel collateralization, recanalization of embolized vessels and disease progression.

Complications

Common complications of angiography include complications at the site of arterial access, such as hematoma, pseudoaneurysm, occlusion, and contrast-related complications. Postembolization syndrome, namely fever, leukocytosis and pleuritic chest pain should be treated with supportive management.[1,2,5,8] Specific post-BAE complications are:[2,5]

- Spinal cord ischemia as a serious complication which occurs in 1.4–6.5% of cases due to non-target embolization of the anterior spinal artery.
- Dysphagia which occurs in 0.7–18.2% of cases due to esophageal necrosis by embolization of the esophageal branches, usually resolves spontaneously.
- Other rare complications include pulmonary infarction, transient cortical blindness, aortic and bronchial necrosis, bronchoesophageal fistula and non-target organ embolization (e.g., mesenteric artery embolization resulting in ischemic colitis).

CONCLUSIONS

Massive hemoptysis is an emergency in respiratory system with high mortality rate. Both bronchial and non-bronchial arterial system embolization is a safe and effective non-surgical treatment in patients with massive hemoptysis. Knowledge of the anatomical variations of the bronchial arteries and an understanding of the pathophysiology of massive hemoptysis are required before doing BAE. The choice of the embolic agent also plays an essential role in determining the success of BAE. Indicators of success can be assessed clinically and radiologically. Patients undergoing BAE procedures are at risk for several complications, but pre-procedure preparation and vigilance, as well as selective arterial catheterization techniques, can reduce the risk of these complications.

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