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Original Article

Characteristics of Lung Cancer Patients with Brain Metastases based on Baseline Head Computerized Tomography (CT)-scan in Arifin Achmad Hospital October 2022 - June 2023

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Abstract

Background: The majority of lung cancer cases are often discovered at a late stage because it frequently develops without symptoms in the early stages. Many lung cancer deaths are caused by metastases to other organs. The purpose of this study was to examine the features of lung cancer patients with brain metastases using baseline CT-scan data.

Method: Between October 2022 and June 2023, a cross-sectional study was conducted at the Arifin Achmad General Hospital in Pekanbaru on all newly diagnosed lung cancer patients with brain metastases who also met the inclusion and exclusion criteria.

Results: Eight subjects of lung cancer with brain metastasis were found from 49 patients. All subjects were male with age mostly in between 40 and 60 years. Three subjects (37.5%) were Squamous Cell Carcinoma (SCC), four subjects (50%) were adenocarcinoma and 1 (12.5%) were SCLC.

Conclusion: This study discovered that 16.3% of subjects who met the inclusion criteria had lung cancer with brain metastases. Further research should be done on a cohort study and a preventive strategy for lung cancer with brain metastases.

Keywords: adenocarcinoma, brain metastases, CT-scan, lung cancer, SCC

INTRODUCTION

Lung cancer typically develops without symptoms in early stages and is frequently detected at a late stage. Many lung cancer deaths are caused by metastases to other organs. Lung cancer often metastasizes to the brain, liver, bones, and adrenal glands. Cancer spreading to brain is often lung cancer, which accounts for 30% to 60% of all brain metastases and has a 10:1 ratio to initial brain tumours. Delay in diagnosis risks causing brain herniation, resulting in disability and death.[1,2] Research conducted by Yosephine et al at Cipto Mangunkusumo Hospital and Dharmais Cancer Hospital found metastases in the brain 93.8% and 8.3% in the leptomeningeal.[3]

With improvements in systemic medication that can prolong survival, the prevalence of brain metastatic lung cancer is rising. Patients with untreated brain metastatic lung cancer had a survival time of one to three months. The combination of Whole Brain Radiotherapy (WBRT) and corticosteroids can increase the survival rate.

When Non-Small Cell Lung Carcinoma (NSCLC) patients with brain metastases were evaluated, Ali et al discovered an average survival rate of 7.8 months. Both metastases were detected both at the time of the initial diagnosis and as the disease advanced. On that study, the highest incidence of adenocarcinoma type brain metastases was 52%.[4] Research on the characteristics of lung cancer patients with brain metastases based on the baseline head CT-scan is required because incidence of brain metastatic from lung cancer is high.[1]

Lung cancer is a malignancy originating from the bronchial epithelium. In a broad sense, lung cancer refers to all forms of lung cancer, including tumour metastases in the lung and cancers that develop both inside and outside of the lung tissue.[1] Metastasis is the process by which cells from the main tumour escape, travel through the bloodstream to the tissue, and develop additional cancers.[2]

Metastasis in lung cancer includes intrapulmonary, extrapulmonary intratoracal and extratoracal metastasis. The brain, bone, liver, and adrenal glands are among the organs that extratoracial lung cancer can spread to. The most frequent malignancy to spread to the brain is lung cancer.[2] Brain metastasis is one of the neurological complications in systemic malignancies.[3]

Most metastases hematogenously (via blood vessels) enter the brain. After passing through the heart and venous circulation, tumour cells will settle in the first capillary they come into contact with, which is the lung. The left heart and later other organs are reached by the circulation of tumour cells. Since 20% of cardiac output goes to the brain, lung cancer, both primary and secondary, is frequently the cause of brain metastases.[5,6]

The grey-white matter border, where blood channels narrow to retain tumour emboli, is where brain metastases are most frequently discovered. The brain hemispheres receive 80% of the cerebral blood flow, followed by the cerebellum and brainstem. Because of this, the cerebrum accounts for 85% of brain metastases, the cerebellum for 10-15%, and the brainstem for 3%. However, the cerebellum is the site of around 50% of isolated metastases from these malignancies.[5,6]

Incidence of new cases of lung cancer in the world ranks highest compared to new cases of other cancers at around 1.8 million and caused 1.31 million deaths in 2012. The World Health Organization (WHO) in 2012 stated that lung cancer is included in five types of cancer with a high incidence rate. Lung cancer is a case that is mostly found in men. Research at the Jakarta Friendship Hospital on 167 lung cancer patients in the period 2004 - 2007 found a distribution of

106 men (63.5%) and 61 women (35.5%).[7–9]

Around 50% to 60% of cases of lung cancer spread to the brain, followed by 15% to 20% of breast cancer cases and 5% to 10% of melanoma cases. Brain metastases from kidney and digestive tract cancer are less prevalent.[10] Although the exact incidence is unknown, metastatic brain tumours are the most prevalent intracerebral tumours.

According to a study by Percy et al, there are 11.1 brain metastases for every 100,000 people. A study by Fogelholm et al in Finlandia found an incidence of brain metastases of 3.4 per 100,000 cancer patients. 20–40% of cancer patients have brain metastases, which are 10:1 more common than the original brain tumour.[6]

Patients with metastatic brain tumours are estimated to be 98,000 to 170,000 annually in the United States.[11] In anatomical pathology, the frequency of metastasis to the brain from lung cancer with a ratio of NSCLC is 36% and SCLC is 56%. In patients with NSCLC, half the population is diagnosed with brain metastases at initial diagnosis, and half the population will suffer from brain metastases at a later stage.[4,10] A study by Bonneta et al found a higher prevalence of adenocarcinoma types with brain metastases by 71% (74 of 103 samples) compared to SCC and large cell carcinoma types.[10]

Tumours that have spread, such as to the lymph nodes in the neck, will be found to be enlarged.[1] Tumours that spread to the brain usually show signs of focal neurological deficits such as hemiparesis, focal seizures, and ataxia. The most common location of lung tumour metastasis is in the frontal lobe of the cerebrum, while the cerebellum is rarely found. Lung tumours can also metastasize to the spinal cord, if they compress the anterior spinal artery causing transverse myelitis. Epidural metastases cause back pain, impaired autonomic function, sensory loss and ataxia.[2,12]

Radiology examination is one of the supporting examinations to determine the image and structure in the human body. Radiologic examination in lung cancer is needed before and after therapy for treatment evaluation. Lung radiology examinations, namely thoracic photographs, thoracic CT-scans, bone scans, bone surveys, abdominal ultrasonography (USG), head CT-scans, Positron Emission Tomography (PET) scans and Magnetic Resonance Imaging (MRI) are needed to determine the location of abnormalities, tumour size and metastases. Thoracic photography is the initial examination to assess suspect of lung cancer, if abnormalities are found, further radiological examinations will be performed. Contrast-enhanced chest CT-scans can more accurately detect cancers smaller than one cm and provide superior images of malignancy.[1]

Contrast thoracic CT-scans are needed for disease staging but are unable to detect metastases outside the thoracic cavity (distant metastases). A contrast-enhanced CT-scan of the head assesses the possibility of metastases to the skull

and brain. Even if there are no complaints or symptoms at the time of first diagnosis, head CT-scans should be performed in operable instances (stage I and II), but in advanced stage cases, they should be performed at the beginning or before two months of therapy. It is done for all cases because the results of the study show that 1/3 of cases with brain metastases do not show symptoms and signs.[1]

MRI is another imaging method to detect abnormalities in the brain and abnormalities in the nervous system or spine but is done at the request of a neurologist.[1,13] MRI is more recommended than CT-scans, especially in providing an anatomical picture of the posterior fossa of the brain adjacent to the base of the skull.[2]

Based on Rahman's research in 2019 on 182,977 NSCLC patients, the results of low specificity in finding brain metastases using head CT-scans were obtained so that additional imaging is needed, namely MRI. Additionally, this is consistent with National Comprehensive Cancer Network (NCCN) recommendations for NSCLC patients who have received a stage 2 or later diagnosis.[14]

The primary method for identifying lung cancer is bronchoscopy. It can be used to pinpoint the original lesion's site, monitor intraluminal tumour progression, and collect samples to confirm the presence or absence of cancerous cells. If abnormal appearance is found, bronchial biopsy, bronchial lavage, bronchial scraping or bronchial scraping should be followed. If the tumour is on the right, TBNA in the lower 1/1 carina or trachea (2 rings above the carina) at the 1 o'clock position will offer double information, including acquiring samples for cytology and details on metastasis to the subcarinal or paratracheal lymph nodes. TBLB if the lesion is small and peripherally located and fluoroscopic facilities are available, a lung biopsy via the bronchus should be performed.[1]

The histological classification of lung cancer according to WHO for clinical needs is NSCLC and SCLC. NSCLC consists of adenocarcinoma, SCC, Large Cell Carcinoma (LCC), and others. NSCLC accounts for 80%–85% of cases, making it the most prevalent form. Adenocarcinoma is the most common type with 40% of all lung cancer cases. It comes from type II alveolar cells, which also release substances like mucus. Adenocarcinoma grows more slowly and is easier to detect before it spreads to other organs compared to other types.[1,13]

There are only two subtypes of SCLC recognized by the current subclassification: pure SCLC and mixed SCLC. Mixed SCLC is a combination of small and large cell carcinoma. According to Nicholson et al, mixed SCLC was identified in 28% of cases, along with 16% LCC, 9% adenocarcinoma, and 3% SCC.[15]

Management of brain metastases from lung cancer generally consists of surgery, Stereotactic Radiosurgery (SRS) and WBRT. Patients with neurological symptoms caused by the tumour are given steroids. If the diagnosis is unclear or the lesion is substantial and creates a herniation, hydrocephalus, or mass effect, surgery is advised to acquire a histological

diagnosis. Though the prognosis for SCLC patients is often bad, brain metastases are thought to be radiosensitive. Therefore, if the patient presents with a single large lesion, steroid therapy may be given. If symptoms improve, WBRT or SRS is given in the hope of avoiding surgery even for large lesions (e.g. 3 to 4.5 cm).[5,16]

Patients with NSCLC such as adenocarcinoma or SCC are a little more complicated in decision making. Surgery is not an option for management in NSCLC patients with small brain lesions. If there is a single lesion less than 2 or 3 mm, therapy is often postponed for 6 to 8 weeks, and imaging is done again. This delay allows the lesion to increase in size and facilitates more accurate SRS. Data also suggest that SRS is a useful method in the management of NSCLC metastasizing to the brain, especially in patients with advanced systemic disease, small lesions (3 cm or smaller), or up to 5 lesions where craniotomy is not medically feasible.[5]

The purpose of this study was to examine the features of lung cancer patients with brain metastases using baseline CT-scan data.

METHOD

The study was conducted at Pulmonary ward of Arifin Achmad Hospital October 2022-June 2023. Based on baseline head CT-scans, characteristics of lung cancer patients with brain metastases are identified. Conceptual framework of the research is shown in Figure 1.

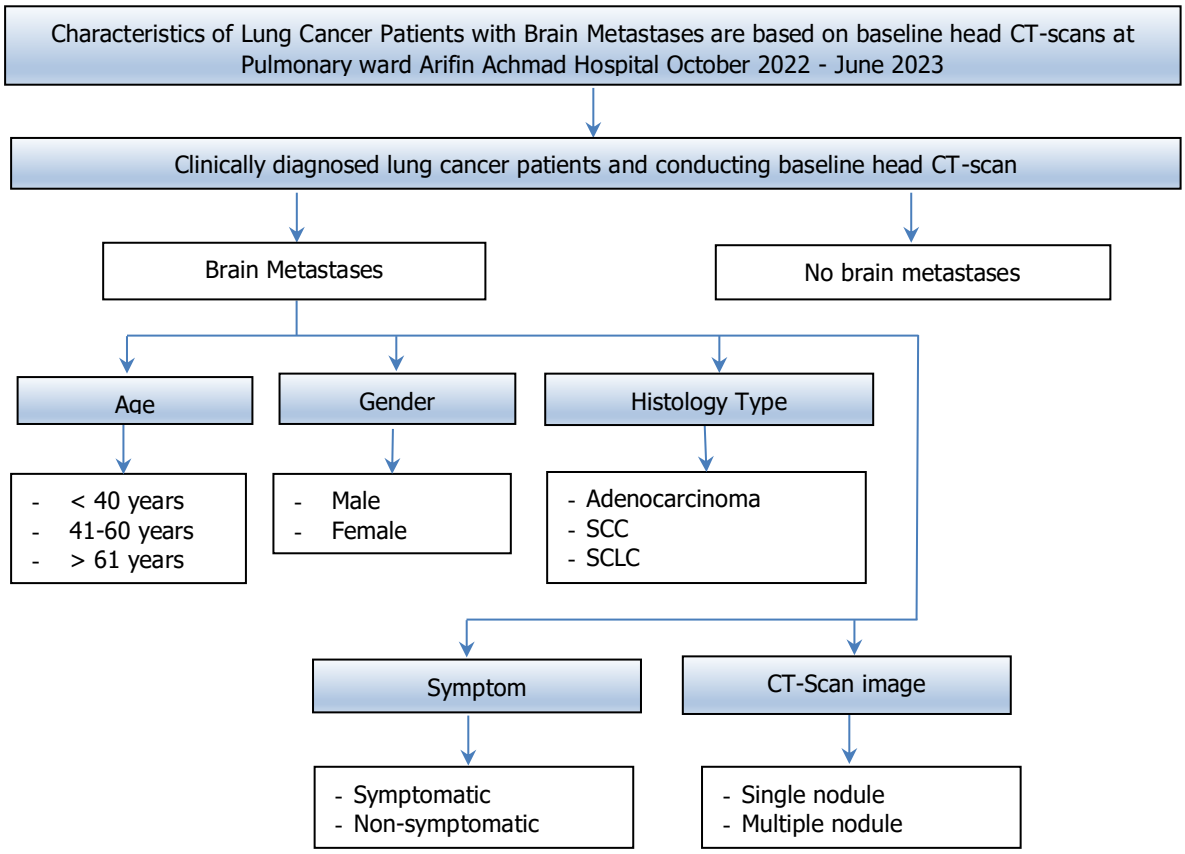

Figure 1. Research Conceptual Framework

The study population was all lung cancer patients who had an upright type based on the results of anatomic pathology and had performed a baseline head CT-scan with contrast. The research sample was lung cancer patients who were histologically upright and had met the inclusion and exclusion criteria by using total sampling technique.

Inclusion criteria were lung cancer patients whose type had been established and had a head CT-scan with contrast before undergoing second cycle first-line chemotherapy. Exclusion criteria were lung cancer patients during the diagnostic procedure, but the type was not established yet, lung cancer patients whose type was decided but had not had a head CT-scan with contrast. Other exclusion criteria were those who had an upright type and had a head CT-scan with contrast but after second cycle of first-line chemotherapy.

This research is an observational descriptive study, which analyses the results of head CT-scans with contrast from radiological data of lung cancer patients. Data was collected through radiological data and medical records of patients being treated.

The data is processed manually and then presented in the form of a frequency distribution table which is calculated as a percentage. The variables in this study were age, gender, symptom, and histological type of lung cancer based on head CT-scan with contrast in the pulmonary ward of Arifin Achmad General Hospital.

RESULTS

The inclusion criteria were met by 49 patients. From 49 patients that meet inclusion criteria, 41 people (88.2%) were no brain metastases and 8 (11.8%) were brain metastases.

In category no brain metastases patients, 12 subjects (29.2%) were SCC, 27 people (65.9%) were adenocarcinoma and 2 patients (4.9%) were SCLC. From metastases patients, 3 subjects (37.5%) were SCC, 4 people (50%) were adenocarcinoma and 1 patient (12.5%) were SCLC (Table 1).

Table 1. Characteristics of Research Results.

Variables	N (%)
Baseline head CT-Scan	
No brain metastases	41 (88.2%)
Brain metastasis	8 (11.8%)
Histology Type of no brain metastases	
SCC	12 (29.2%)
Adenocarcinoma	27 (65.9%)
SCLC	2 (4.9%)
Histology Type of brain metastases	
SCC	3 (37.5%)
Adenocarcinoma	4 (50%)
SCLC	1 (12.5%)
Age	
<40 years	0 (0,0%)
40 - 60 years	7 (87.5%)
>60 years	1 (12.5%)
Gender	
Male	8 (100%)
Female	0 (0,0%)
Nodule	
Multiple	5 (62.5%)
Single	3 (37.5%)
Symptom	
With Symptom	2 (25%)
Without Symptom	6 (75%)

Note: SCC=Squamous Cell Carcinoma; SCLC=Small Cell Lung Carcinoma

DISCUSSION

This study result is consistent with other studies by Waqar et al, who discovered that 10.4% of 457,482 NSCLC patients had brain metastases and 89.6% were not brain metastases.[17] Another study by Li et al in SCLC patients, found 15.5% had brain metastases and 84.5% without brain metastases from 11,093 SCLC patients.[18]

The percentage of lung cancer with brain metastases with adenocarcinoma was higher compared to SCC and SCLC. This study result is same to the study conducted by Ramadhaniah et al, the distribution of morphological types of brain metastatic lung cancer patients was dominated by adenocarcinoma 67.9%.[10] Another study by Yulianti et al found that adenocarcinoma was the most common type, around 77.1% (27 out of 35 patients).[19] In this study, no conclusions could be drawn on the comparison of the proportion of brain metastases between the types of NSCLC (adenocarcinoma and SCC) and representative SCLC because of the small number of samples for this type of SCLC.

All lung cancer patients who experienced brain metastases from the results of baseline head CT-scans during the period October 2022 - June 2023, were all male with most of the age range in between 40 and 60 years. The study's findings agreed with those of Waqar et al, whose investigation found that males had a 59.8% incidence rate for brain metastases.[20] This is consistent with the higher incidence of lung cancer in men, which is linked to smoking risk factors in Indonesia, where men are more likely than women to smoke.[21] An et al's study found that women were more likely than men to get lung cancer brain metastases.[22]

Based on nodule, 5 patients (62.5%) were multiple, and 3 (37.5%) subjects were single. 6 people (75%) were without symptom and 2 subjects (25%) were with symptom. The most common symptom are headache and dizziness.

CONCLUSION

Based on the findings of the baseline CT-Scan with contrast from 49 lung cancer patients, this study identified 8 lung cancer patients with brain metastases. To identify the data profile of lung cancer patients at Arifin Achmad Hospital with brain metastases from baseline and contrast head CT-scan images after 6 cycles of chemotherapy and link them with other preexisting risk factors, a further investigation with a bigger sample size is required.

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Original Article

Lung Cancer In Former Tuberculosis Patients at Arifin Achmad General Hospital, Riau Province

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Abstract

Background: There is ongoing discussion over the connection between lung cancer and pulmonary tuberculosis (TB). Future lung cancer cases in Indonesia, which has the second-highest TB case burden, are a cause for concern. The purpose of this study is to ascertain the connection between TB and LC at Arifin Achmad General Hospital in the province of Riau.

Method: From 2015 to 2018, we looked back on lung cancer patients at Arifin Achmad General Hospital in Riau Province who had received pulmonary tuberculosis and anti-tuberculosis treatment (ATT).

Results: From 203 patients, 24 patients (11.8%) had histories of TB. The patients' ages were from 41 years to 60 years. The most prevalent pathological findings were adenocarcinoma in 13 patients (54.0%). The most common cancer stage was advanced stage IIIB in 7 patients (29.2%).

Conclusion: The cases of TB infections were apparent in lung cancer patients, approximately around 11% of lung cancer cases. Therefore, it is necessary to assess the history of TB in lung cancer patients.

Keywords: anti-tuberculosis treatment, lung cancer, pulmonary tuberculosis

INTRODUCTION

Indonesia is the 2nd country with the highest burden of tuberculosis (TB) all around the world.[1] From 2020 to 2021, there an 18% increase in the incidence of TB, from 819 000 to 969 000. [1,2] By increased case of TB there is also a problem that estimated also increased case of lung cancer (LC).[3,4] This is due to the fact that several studies have shown an increase in the risk of LC among former TB patients. Polymorphic microbiomes may cause tumor-promoting inflammation and contribute to cancer, according to a new cancer signature discovered in 2022.[5]

Due to a paucity of evidence, the risk of TB to LC in Indonesia is currently debatable. In 2022, there are 13.007 new cases of TB in Riau based on Riau

Goverment data. This large number of cases is certainly a concern because the risk of LC after TB infection is linked to this data, so there is the potential for lung cancer cases in Riau to increase due to TB infection.

This study aims to outline the patient TB with a higher risk of LC in patients seen at the Arifin Achmad General Hospital as referral goverment hospital in Riau Province for LC in the Riau Province.

METHOD

A cross-sectional research methodology was used in this retrospective study. From 2015 to 2018, we gathered information from the medical records kept at Arifin Achmad General Hospital. This study population were all patients with lung cancer at Arifin Achmad General Hospital.

The following conditions had to be met for a patient to be included in the study: (1) TB history; (2) anti-TB treatment received prior to lung cancer diagnosis; (3) LC diagnosis based on anatomical pathology findings; and (4) positive and negative Ziehl-Neelsen staining for acid-fast bacillus in sputum smear. Patients who matched two out of four criteria were included in the study. There is a chance that LC was mistakenly diagnosed as TB, so in order to rule this out, we check the patient diagnoses using histological examination of the relevant medical records.

The following patients are excluded from this study: (1) those who have TB and LC co-infections and (2) extra pulmonary TB. The research received ethical clearance from Ethical Review Board for Faculty of Medicine, Riau University No. B/214a/UN19.5.1.1.8/UEPKK/2019.

RESULTS

Table 1 demonstrate characteristics of patients that included in this study. Male are dominant in this study by 91% compared to female (9%). The patients were dominated by elderly patients, 40–60 years old in 79.16% and >60 years old in 16.67%.

Table 1. Patients Characteristics (n=24)

Characteristics	n (%)
Sex	
Male	22 (91.00%)
Female	2 (9.00%)
Age (years old)	
<40	1 (4.17%)
40–60	19 (79.16%)
>60	4 (16.67%)
Sputum Smear	
Positive	12 (50.00%)
Negative	12 (50.00%)
Anti Tuberculosis Drug	
Category 1	13 (54.17%)
Category 2	11 (45.83%)
Type of LC	
Adenocarcinoma	13 (54.00%)
SCC	9 (37.50%)
SCLC	2 (8.33%)
Stage of LC	
I	1 (4.17%)
III a	5 (20.83%)
III b	9 (37.50%)
IV a	2 (8.33%)
IV b	7 (29.17%)
Time of diagnosis with TB before LC	
<5 years	20 (83.33)
5–10 years	3 (12.5)
>10 years	1 (4.17)

Note: SCC=Squamous Cell Carcinoma; SCLC=Small Cell Lung Carcinoma

Both AFB Sputum smear are equal positive (microbiologically TB) and negative (clinically TB). Most patients receive Category 1 of Anti Tuberculosis Drug (ATD) by 54.17% followed by Category 2 by 45.83%. For the pathological type of lung cancer, it was dominated by dominated by adenocarcinoma (54%), SCC (37.5%) and SCLC (8.33%).

For the stage of LC dominated by Stage IIB (37.5%) followed by IVb (29.17%), IIIa (20.83%), IVa (8.33%), and I (4.17%). Most of the LC patients had history of TB less than 5 years (83.33%), followed by 5 – 10 years after TB infection (12.5%) and more than 10 years (4.17%).

DISCUSSION

Studies looked into TB as an LC risk factor associated with aging. Younger individuals had a greater incidence of LC and TB. The Indonesian Society of Respirology (ISR) states that male patients who are over 40, have smoked in the past, are exposed to industrial hazard compounds, and have symptoms are at high risk for lung cancer (LC).[6] However, younger individuals were shown to have a higher likelihood of coexisting TB and LC.[7]

Regardless of smoking history or other factors, a meta-analysis revealed that TB at a younger age is a risk factor for developing LC. Additionally, the risk was higher in nations with high TB prevalence, upper-middle class economies, especially in the East Asian and Pacific region.[3] Due to common radiologic findings and symptoms such coughing, expectoration, fever, hemoptysis, and weight loss, TB and LC may be misdiagnosed.[8,9]

In this study, the incidence of cancer after TB infection was higher in the productive age group of 40-60 years (79%) and males (96.67%). So that this evidence supports the ISR statement that age >40 years, especially those with exposure are at risk of lung cancer, in this study also supports that patients with a history of TB also need more attention because it has the potential to increase the risk of lung cancer in the future. Therefore, it is expected that a history of TB needs to be a concern and become the basis for lung cancer screening.

Compared to other studies in Surabaya, similar incidences were dominated by men with an age range between 40-60 years. The type of lung cancer was also similarly dominated by adenocarcinoma at 90.8% in the Surabaya study and 54% in this study. For the staging itself, the study in Surabaya was dominated by NSCLC stage IV at 77.6% and in this study, it was dominated by stage IIb at 37.5%.[10]

In this study, only 1 person was found to have a long history of TB of more than 10 years, and other case reports have also found cases of post-TB squamous cell carcinoma after 30 years of treatment. This opens up the possibility that the effects of TB infection, which can lead to lung cancer, can also last for a long period of time.[11]

In our study, we found that duration <5 years post-TB dominated the incidence. In a meta-analysis, the incidence of lung cancer increased after 2 years of TB

diagnosis (HR=5.01; 95% CI=3.64-6.89) but decreased thereafter. However, this does not rule out the possibility that after >2 years we still find the incidence of lung cancer after infection from TB.[12]

Cancer formation is complex; however, it has been demonstrated that persistent inflammation can promote the growth and spread of tumors.[13] Tuberculosis induced chronic inflammation may lead to genetic changes in lung parenchyma cells. Through infected macrophages, TB can cause cell dysplasia and squamous cell aggregation. This held true for latent TB as well, which causes persistent inflammation and infection, increasing the risk of LC. [10,11]

Mycobacterium tuberculosis causes inflammation in the lung tissues by elevating inflammatory cytokines such INF-y, IL-1, IL-2, IL-12, and TNF.12,13 Patients with latent TB had an increased chance of developing LC (HR=2.69; P=0.17). No one who had isoniazid prophylaxis among 135 TB contacts got cancer. Because of this, reducing chronic inflammation requires treating TB, especially latent TB.[4]

Tuberculosis may raise the risk of cancer since it also has an immunosuppressive effect in the body through naturally existing regulatory T cells. By exposing cells to reactive oxygen and reactive nitrogen intermediates when it enters macrophages, TB may potentially cause cellular DNA damage. DNA damage, cytokinesis defects, and an increased frequency of apoptotic and necrotic cells were all seen in TB patients. Repeated tissue injury results in the creation of fibrotic scar tissue, which can induce fibrosis and increase the risk for tumor growth.[14–17] Tuberculosis induces a cytokine storm and lung epithelial cell proliferation through the production of cytokines by macrophages, dendritic cells, and alveolar type II pneumocytes.[18–20]

Potentially, bacterial toxin or other compounds produced by the mutagenesis of epithelium, which might disrupt the mechanisms that preserve genomic integrity or damage DNA, or stress cells in other ways that indirectly reduce the fidelity of DNA replication, could cause tumors.[5]

The limitation in this study was only conducted in one hospital. Arifin Achmad General Hospital is a referral health facility in Riau province. Interpretation data in this study needs further evaluation and examination to be implemented in minor policies.

CONCLUSION

This descriptive study showed LC for former TB patients in Arifin Achmad General Hospital dominated by male, age between 40–60 years old, received 1st category of ATD, adenocarcinoma, stage IIIb of LC, and had history of TB less than 5 years.

Suggestion for next study is multi-center study to analyze risk of LC in former TB patients in Indonesia, due to Indonesia is 2nd highest burden TB case in the world. We need to determine so macro-policy could implement to help post TB infection to have screening for risk of LC.

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Original Article

The Relationship Between SpO_2/FiO_2 Ratio to Community Acquired Pneumonia Patient Outcomes at Kolonel Abunjani Bangko General Hospital

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Abstract

Background: Acute lower respiratory tract infection causes high morbidity and mortality, which can be found in the form of pneumonia. Community acquired pneumonia (CAP) severe pneumonia can lead to acute respiratory distress. To diagnose acute respiratory disorders, namely Acute Lung Injury (ALI) and Acute Respiratory Stress Syndrome (ARDS), the ratio PaO_2/FiO_2 is used. This requires invasive action by taking an arterial blood sample, which is expensive and not available in all health facilities. An alternative is pulse oximetry, which measures the SpO_2/FiO_2 ratio and is available in health facilities. It is inexpensive and non-invasive. This study aims to determine the relationship between SpO2 and FiO2 with the outcome of community pneumonia patients at Kolonel Abunjani Bangko Hospital.

Method: The study design was a retrospective descriptive cross-sectional design. The research subjects were a total sampling of medical record data from inpatients with community acquired pneumonia for the period January-December 2022. The study variables included gender, age, SpO_2/FiO_2 ratio, and outcomes of pneumonia patients. Univariate and bivariate statistical tests were used to analyze the data.

Results: In this study, there were 43 subjects who met the inclusion criteria. The distribution of inpatient community acquired pneumonia patients, especially in the gender was mostly male (67.4%), the highest age was 56–65 years and >65 years (both 37.2%), the median SpO_2 was 94% (36-99%), the median SpO_2/FiO_2 ratio was 447 (171-471%), the highest outcomes were alive patients (36 patients). The ratio of SpO_2/FiO_2 >316 was the majority (33 patients). Based on the relationship between the SpO_2/FiO_2 ratio and the outcome of CAP with alive outcome was a SpO_2/FiO_2 ratio >236 was more numerous than SpO_2/FiO_2 ratio <236 with value of P=0.0005.

Conclusion: There is a significant relationship between the SpO_2/FiO_2 ratio and the outcome of community acquired pneumonia patients at Kolonel Abundjani Hospital Bangko.

Keywords: community-acquired pneumonia (CAP), SpO_2/FiO_2 ratio, outcome of community acquired pneumonia

INTRODUCTION

Oxygen is one of the vital elements in the process of metabolism that maintains the viability of all body cells. Normally, oxygen is obtained during the inhalation process. The delivery of oxygen to body tissues is determined by the interaction of the respiratory system. Lack of oxygen is characterized by hypoxia, which, in advanced processes, causes tissue death and can even be life-threatening.[1]

Hypoxemia is a condition in which there is a decrease in the concentration of oxygen in the arteries. The way to find out if there is hypoxemia is to monitor oxygen saturation levels ($SpO_{2)}$, which can measure how much oxygen concentration (O_2) can be carried by hemoglobin. The normal value of oxygen saturation is 95–100%. Oxygen saturation is important to monitor because it can indicate the adequacy of oxygenation or tissue perfusion in the patient, which will cause failure in oxygen transport because oxygen in the body is bound by hemoglobin and dissolved in blood plasma in small amounts.[1]

Acute lower respiratory tract infections cause high morbidity and mortality, which can be found in the form of pneumonia. Pneumonia can be divided into community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-acquired pneumonia (VAP).[2] Community-acquired pneumonia (CAP) is one of the most common infectious diseases and an important cause of mortality and morbidity worldwide. Typical bacterial pathogens that cause CAP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarhalis*.[3]

The incidence of CAP varies greatly from country to country. In the United States, CAP is estimated to occur in 248 out of 10,000 adults annually, whereas a Veterans Health Administration study recorded 472.2 cases per 100,000 people in 2017.[4] Influenza and pneumonia combined remain in the top 10 causes of death in the United States. This combination is responsible for 1.6% (53,495) of deaths in 2020.[5]

The incidence of CAP in Malaysia, the Philippines, and Indonesia is the most frequent cause of hospitalization for ages <5 years and >50 years. There are 988 cases of pneumonia per 100,000 people in Indonesia in 2015.[6] Based on data from the Jambi provincial health office's strategic plan for 2015, there was an increase in pneumonia cases, namely 50.6%.[7]

Severe pneumonia can progress to the occurrence of disturbances in the occurrence of acute respiratory distress. Acute respiratory distress is divided into two categories, Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). This is associated with high mortality and morbidity.[8]

Based on *the* American-European Consensus Conference (AECC) in 1994, the diagnostic criteria for ALI and ARDS are acute onset of disease, chest X-ray showing bilateral pulmonary infiltrates, less significant left ventricular dysfunction, and PaO_2/FiO_2 (PF) ratio <300 ALI and <200 ARDS. The first three components can be

found in the history, physical examination, and support such as an ECG and X-rays. However, the PF ratio criterion requires arterial blood sampling (blood gas analysis).[8]

Taking blood samples for blood gas analysis (BGA) is an invasive procedure. Meanwhile, pulse oximetry, which measures blood oxygen saturation (SpO_2), is the most common technique that can be used to monitor oxygenation in an effective and safe way without any invasive procedures. The SpO_2/FiO_2 ratio is expected to be one of the options for diagnosing ALI and ARDS as a substitute for the invasive PF ratio.[8]

In a study conducted by Emir Festic et al in 2015, it was shown that SpO_2 and FiO_2 are markers of impaired oxygenation at the time of admission to the hospital and a significant predictor of the development of early Acute Respiratory Distress Syndrome and mortality in hospitals. Patients who have a low SpO_2/FiO_2 ratio on admission have a tendency to die earlier than patients with a high SpO_2/FiO_2 ratio upon admission. In addition, it has been shown that SpO_2 and FiO_2 are useful for calculating organ failure scores in the absence of invasive arterial blood gas sampling.[9]

Kolonel Abundjani Bangko Hospital is a Regional General Hospital in Merangin Regency, Jambi Province, and is one of the referral hospitals. Due to limited reagents, an BGA examination could not be performed to diagnose ALI and ARDS at this hospital. One thing that can be done is to use oxygen saturation. Research on the relationship between SpO_2 and FiO_2 and community acquired pneumonia patient outcomes has never been studied. Therefore, the authors are interested in conducting research on the relationship between SpO_2 and FiO_2 and the outcomes of community acquired pneumonia patients at Kolonel Abunjani Hospital in Bangko.

METHOD

This research is a cross-sectional study with a retrospective design using secondary hospital data, namely medical records of patients treated in integrated rooms for the period January 2022 to December 2022.

The research subjects were all community acquired pneumonia patients who had been treated in the integrated room of the Kolonel Abundjani Hospital in Bangko. The inclusion criteria in this study were all patients diagnosed with CAP based on diagnostic criteria, namely: on the chest X-ray, there was an air bronchogram infiltrate coupled with several symptoms such as cough, body temperature >38ºC, history of fever, changes in the characteristics of purulent sputum, chest pain, and tightness; on physical examination, consolidation was found; bronchial breath sounds and crackles; leukocytes >10,000 or <4,500; treated in the integrated room of Colonel Abundjani Hospital Bangko.

Exclusion criteria for this study were patients not diagnosed with CAP and/or accompanied by other diseases that also affected oxygenation (asthma, Chronic

Obstructive Pulmonary Disease [COPD], bronchiectasis, Congestive Heart Failure [CHF], Chronic Kidney Disease [CKD]) and incomplete study data. The sample collection technique is total sampling.

Preliminary data such as age, sex, oxygen saturation data without being given O_2 while in the emergency room, and patient outcomes (alive or dead) were recorded in the data collection sheet. The research data were analyzed statistically with the help of the Windows SPSS (Statistical Product and Science Service) computer program version 25.0.

Analysis and presentation of data using univariate analysis to analyze the characteristics of one variable by conducting descriptive analysis. Distribution of data used frequency and percentage for categorical data, for numeric data used mean±SD if the data is normal or median (min-max) if the data is not normal. Bivariate analysis was used to analyze the relationship between the SpO_2/FiO_2 ratio and community pneumonia patient outcomes using the Chi-square test. If no two cells have an expected value of less than five, use the Kruskall-Willis test.

RESULTS

Of the 375 patients treated in the integrated room of Colonel Abundjani Bangko General Hospital for the period January 2022–December 2022, 62 were diagnosed with CAP. Of the 62 patients with CAP, 43 met the inclusion criteria and 19 met the exclusion criteria (Table 1).

Table 1. Demographic characteristics of community acquired pneumonia patients (N=43)

Characteristics	N (%)
Gender	
Man	29 (67.4%)
Woman	14 (32.6%)
Output	
Alive	36 (83.7%)
Died	7 (16.3%)
Age	
12-16	1 (2.3%)
17-25	1 (2.3%)
26-35	1 (2.3%)
36-45	2 (4.7%)
46-55	6 (14.0%)
56-65	16 (37.2%)
>65	16 (37.2%)
SpO_2% [median (min-max)]	94 (36-99)
SpO_2/FiO_2 [median (min-max)]	447 (171-471)

Table 1 shows the demographic characteristics of community acquired pneumonia patients who are treated in the integrated room of Kolonel Abunjani Bangko Hospital. Based on gender characteristics, there were 29 men (67.4%) and 14 women (32.6%). Based on the outcomes of community acquired pneumonia patients, it was found that 36 people (83.7%) lived and 7 people died (16.3%). Most of the community acquired pneumonia patients were aged 56–65 years and >65 years, with 16 patients (37.2%). The median SpO_2 of patients was 94%; the lowest was 36%, and the highest was 99%. The median SpO_2/FiO_2 ratio was 447, the lowest was 171, and the highest was 471.

Table 2 shows the analysis of the SpO2/FiO_2 ratio. Classified into 3 groups, namely <235, 236-315, and >316. SpO_2/FiO_2 ratio value <235 by 7 people

(16.3%), SpO_2/FiO_2 ratio value 236-315 by 3 people (7.0%), and SpO_2/FiO_2 ratio value >316 by 33 people (76.6%).

Table 2. Analysis of the SpO_2/FiO_2 ratio

Categories	N	%
<235	7	16.3
236-315	3	7.0
>316	33	76.7

Table 3 shows the relationship between the ratio of SpO_2/FiO_2 and the outcome of community acquired pneumonia. The value of the ratio SpO_2/FiO_2 was 235, and 7 patients died. The SpO_2/FiO_2 ratio value is 236-315, namely 3 people with lived outcomes. SpO2/FiO2 ratio >316 in 33 patients with survival outcomes This study found a significant relationship between the SpO_2/FiO_2 ratio and community acquired pneumonia patient outcomes, with value of P=0.0005. This means that the smaller the value of the SpO_2/FiO_2 ratio, the worse the outcome for community acquired pneumonia patients.

Table 3. Relationship between SpO_2/FiO_2 ratio and community pneumonia outcomes

Categories	Outcome				P
	Lived		Died		
<235	0	0.0%	7	100.0%	
236-315	3	100.0%	0	0.0%	0.0005
>316	33	100.0%	0	0.0%	
Total	36	83.7%	7	16.3%	

DISCUSSION

The diagnosis of ARDS should use the value of the ratio between the partial pressure of oxygen and the fraction of oxygen (PaO_2/FiO_2) using arterial blood (AGD). Blood Gas Analysis (AGD) is an invasive procedure, expensive, and not available in all places. In contrast, pulse oximetry is readily available, accurate, inexpensive, and non-invasive. The ratio of oxygen saturation to fraction of oxygen (SpO_2/FiO_2) has been validated in clinical studies for the diagnosis and as an alternative option for assessing the degree of hypoxaemia in ARDS.[10] The use of pulse oximetry as an alternative to assessing the degree of hypoxemia in the diagnosis of ARDS was first introduced in 2007.[11]

Based on the results of this study, it was found that the characteristics of gender were male, with the largest number being 29 people (67.4%) and women being 14 people (32.6%). Based on the outcomes of community acquired pneumonia patients, it was found that 36 people (83.7%) lived and 7 people died (16.3%). Most of the community acquired pneumonia patients were aged 56–65 years and >65 years, with 16 patients (37.2%). The median SpO_2 of patients was 94%; the lowest was 36%, and the highest was 99%. The median SpO_2/FiO_2 ratio was 447, the lowest value was 171, and the highest was 471, while the highest outcome was life, namely 36 patients, and 7 patients died.

This is the same as a study conducted by Fransisko et al, the sample size was 3,606 people. Based on gender, the majority were men (2,122 people) and women (1,484 people). The age 61–75 is the most, which is 992 people. Based on the outcome, 733 people died, 317 people were treated in the ICU, and 2050 people were treated normally.[12] In contrast to the study conducted by Bilan et al, of the 70

children enrolled in this study, 38 were female (54.3%) and 32 were male (45.7%). The mean age of the study population was 32 years and 5 months.[8]

Based on the analysis of the SpO_2/FiO_2 ratio Classified into 3 groups, namely <235, 236-315, and >316. The value of the SpO_2/FiO_2 ratio <235 is 7 people (16.3%); The value of the SpO_2/FiO_2 ratio 236-315 is 3 people (7.0%); and the value of the SpO_2/FiO_2 ratio > 316 is 33 people (16.3%).

This is the same as according to the Kigali modification, which defines the degree of hypoxic ARDS using the SpO_2/FiO_2 ratio with an intersection point less than or equal to 315.[13] Rice et al found that PaO_2/FiO_2 200 for ARDS and SpO_2/FiO_2 315 correlated with the ratio of PaO_2/FiO_2 300 for ALI.[11] Slightly different from the study by Bilan et al, they identified 181 cut points for ARDS and 235 for ALI. This cut-off point has a sensitivity of 71% and a specificity of 82% for diagnosing ARDS, and a specificity of 100% and a sensitivity of 57% for diagnosing ALI.[8]

This study obtains a relationship between ratios SpO_2/FiO_2 and community acquired pneumonia outcome, SpO_2/FiO_2 value <235. Seven patients died. SpO_2/FiO_2 ratio values ranged from 236-315 in three patients with survival outcomes. The SpO_2/FiO_2 ratio value >316 was needed to get 33 patients with survival outcomes. Based on the results of the Kruskal-Wallis test, the value P=0.0005, it means that there is a significant relationship between the SpO_2/FiO_2 ratio and the outcome of community acquired pneumonia patients at Kolonel Abundjani Bangko Hospital. This is similar to a study conducted by Lu et al, regarding the SpO_2/FiO_2 ratio as a non-invasive prognostic marker for intensive care patients with COVID-19. Shows that the SpO_2/FiO_2 ratio can serve as a marker of 1.82 times the risk of death.[14]

CONCLUSION

From this research it was found that significant relationship between the SpO_2/FiO_2 ratio and the outcomes of CAP at Kolonel Abundjani Bangko Hospital.

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Original Article

Relationship Between D-Dimer, Albumin Levels, and Outcome of COVID-19 Patients at Dr. M. Djamil General Hospital, Padang

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Abstract

Background: Several studies have found an increase in D-dimer levels in patients who died from a severe clinical condition. COVID-19 exhibits multi-organ dysfunction through several markers, including decreased albumin levels. There were some studies that were interested in understanding how D-dimer and albumin levels relate to the outcomes of COVID-19 patients. The aim of this study was to investigate the relationship between D-dimer, albumin levels, and patient outcomes.

Method: This was a cross-sectional study of all COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang, from January 1st, 2021 to December 31st, 2021.

Results: The majority of patients (40.71%) were in the group of 18 and 49 years old; more than half of the subjects (56.16%) were female; and obesity was the most common comorbidity (40.9%). The majority of the subjects (42.79%) had moderate clinical COVID-19. Higher D-dimer levels had a statistically significant independent relationship with unfavorable outcomes (P=0.0001). Lower albumin levels had a statistically significant independent relationship with unfavorable outcomes (P=0.0001). Higher D-dimer and lower albumin each contributed 12.6% to patient outcome. Increasing D-dimer levels per 1 ng/mL would increase the probability of an unfavorable outcome by 0.120 times, and on the other hand, increasing albumin levels per 1 g/dL would increase the probability of survival by 2.143 times.

Conclusion: Higher D-dimer levels independently had a relationship with an unfavorable outcome. Higher albumin levels were independently related to a favorable outcome.

Keywords: albumin, D-dimer, COVID-19, outcome, relationship

INTRODUCTION

The clinical presentation of COVID-19 varies from asymptomatic to critical for each individual.[1] Most patients have mild symptoms and a good prognosis, but it is estimated that 5-20% of symptoms worsen and require intensive care, particularly in elderly patients with comorbidities. Severe to critical symptoms have been reported in 20-26% of COVID-19 cases, necessitating adequate oxygenation and mechanical ventilation, with a poor prognosis and varying mortality rates. Clinicians must

identify clinical severity early to prevent disease progression, a poor prognosis, and death.[1]

Cytokine Release Syndrome (CRS) or cytokine storm contributes to the pathogenesis of acute respiratory distress syndrome (ARDS), coagulation dysfunction, and multi-organ dysfunction in COVID-19, increasing morbidity and mortality.[2] Hypercoagulopathy has been reported in the early stages of COVID-19; it is critical to detect it in patients, particularly those with risk factors for this increase.[3] Tang et al reported that the most common complications in COVID-19 patients who died were coagulopathy and thrombosis.[4]

Tang et al also observed a consistent relationship between D-dimer and prothrombin time at 28 days of death in COVID-19 patients in another study. Oxygen delivery barriers are caused by disseminated intravascular coagulation (DIC) events and multi-organ dysfunction caused by excessive thrombus deposition in the microvascular. Tang et al found that DIC occurred in 71.4% of patients who died.[5]

Early detection to assess the risk of disease progression is important because it affects therapy strategy and death prevention. Several studies found that D-dimer levels were higher in patients with severe clinical disease who died compared to non-survivors and survivors. The assessment of coagulopathy markers is a priority for COVID-19 patients at the start of treatment.[1,3] Increased D-dimer as a coagulopathy marker reflects hypercoagulopathy and thrombosis and can help clinicians decide whether to use anticoagulants in COVID-19 patients.[1,2,5]

Varikasuvu et al reported an association between D-dimer levels and COVID-19 progressivity in their study. High D-dimer levels are linked to an increased risk of coagulopathy and thrombosis in patients. Clinically significant Plasminogen Activator Inhibitor-1 (PAI-1) levels are elevated in COVID-19 patients, which can disrupt the fibrinolytic system and lead to thrombus formation. It can cause vasoconstriction due to hypoxemia via reduced blood flow and vascular occlusion, endothelial dysfunction, and inflammation, particularly in patients with co-morbidities such as hypertension, diabetes, and the elderly.[1,4]

Khodeir et al observed multi-organ dysfunction in COVID-19 through several markers that reflect this condition, including increased aspartate aminotransferase (AST), creatinine, and decreased albumin levels. Decreased albumin levels, with a mean of 3.0 g/dL, were strongly associated with disease progression in severe and critical cases.[3]

According to Violi et al, there was a strong correlation between hypoalbuminemia and hypercoagulopathy, as evidenced by an increase in serum D-dimer levels.[6] According to Aloisio et al, a serum albumin level of ≤3.5 g/dL was highly significant for a fourfold increase in D-dimer levels (upper value of 500 ng/mL) compared to a serum albumin level of >3.5 g/dL. As a causal relationship, this represents the harmonization of decreased albumin levels and increased D-dimer.[7]

Albumin has the ability to downregulate Angiotensine Converting Enzyme-2 (ACE2), which is important for modulating COVID-19 infection. According to Hariyanto et al, when albumin levels were low, ACE2 receptors were activated, and COVID-19 infectivity increased.[8]

Mahardhika et al also found increased D-dimer levels as coagulopathy markers and the inflammatory marker C-reactive protein (CRP) in patients with clinically asymptomatic conditions, which was unusual.[9] The challenge is determining how to detect worsening conditions early in the management of COVID-19 patients. Effective markers can assist in the screening, treatment, and prevention of serious complications.[8]

The authors were interested in examining how D-dimer and albumin levels were related to the outcomes of COVID-19 patients treated at Dr.M. Djamil General Hospital, Padang, based on the background and the limited research on the relationship between D-dimer, albumin levels, and patient outcomes.

METHOD

This was a cross-sectional retrospective study. The study was conducted from January to November 2022 at Dr. M. Djamil General Hospital, Padang. All COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang were tested for D-dimer and albumin levels between January 1, 2021, and December 31, 2021.

The COVID-19 patients treated in the isolation room who were examined for D-dimer and albumin levels; had complete medical record data; and were 18 years old and over, were eligible for the study. COVID-19 patients are divided based on their clinical level of severity, including mild, moderate, severe, and critical.

The COVID-19 patients who had previously received albumin therapy both orally and intravenously, confirmed COVID-19 patients >72 hours, patients with comorbid autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus (SLE), rheumatic heart disease, primary Sjogren's, fibrous bone dysplasia, juvenile idiopathic arthritis (JIA), and uveitis in JIA), chronic inflammation (Erdheim-chester disease, Behcet's syndrome, systemic sclerosis, large cell arteritis), hormonal disorders, thyroid disease, post-organ transplantation, kwarshiorkor malnutrition and nephrotic syndrome were all excluded from the study.

RESULTS

This study included all COVID-19 patients who were treated in the COVID-19 isolation room from January 1, 2021, to December 31, 2021, and met the inclusion and exclusion criteria. A total of 479 COVID-19 patients were selected to be analyzed from the 543 COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang. Table 1 shows the characteristics of COVID-19 patients treated at Dr. M. Djamil General Hospital, Padang.

Tabel 1. The COVID-19 Patients Characteristics Treated at RSUP Dr. M. Djamil, Padang (N=479)

The Characteristics of Patients	N	%
Age (year)		
18–49 year	195	40.71
50–59 year	120	25.05
60–69 year	101	21.09
≥70 year	63	13.15
Gender		
Male	210	43.84
Female	269	56.16
Comorbid		
Obesity	196	40.90
Hypertension	54	11.27
Diabetes melitus	47	9.81
Cardiovascular Disease	23	4.80
Chronic Kidney Disease	16	3.34
Malignancy	15	3.10
Chronic Pulmonary Disease	11	2.29
Cerebrovascular Disease	19	3.97
Chronic Liver Disease	13	2.71
Clinical Severity		
Mild	24	5.01
Moderate	205	42.79
Severe	106	22.13
Critical	144	30.06

Table 1 shows that majority of patients (40.71%) with COVID-19 were aged 18-49 years, and most of them (56.16%) were female. Obesity was the most common comorbid condition for 196 (40.9%) patients, followed by 54 (11.27%) patients with hypertension, 47 (9.81%) patients with diabetes, and 11 (2.29%) patients with chronic pulmonary disease. The majority of the subjects, 205 (42.79%) patients, had moderate clinical severity of COVID-19, and a small proportion had mild clinical severity (5.01%).

Table 2 shows that the following COVID-19 patient characteristics have a statistically significant relationship with the outcome of COVID-19 patients: age group 18-49 years, age group 60-69 years, age ≥70 years, comorbid of cerebrovascular disease, chronic liver disease, mild clinical severity, moderate clinical severity, and critical clinical severity.

Table 2. The characteristicss of COVID-19 patients in each outcome group treated at Dr. M. Djamil General Hospital, Padang

The Characteristics of Patients	The Outcome		P
	Alive (n=350)	Died (n=129)	
Age (year)			
18–49 year	168	27	0.0001*[a]
50–59 year	85	35	1.000
60–69 year	63	38	0.006*[a]
≥70 year	34	29	0.0001*[a]
Gender			
Male	146	64	1.000
Female	204	65	1.000
Comorbid			
Obesity	147	96	0.428
Hypertension	39	15	0.882
DM	34	13	0.906
CVD	16	7	0.698
CKD	12	4	0.859
Malignancy	10	5	0.570
COPD	7	4	0.476
CVA	9	10	0.010*[a]
CLD	7	6	0.113
Clinical Severity			
Mild	24	0	0.002*[a]
Moderate	187	18	0.0001*[a]
Severe	85	21	1.000
Critical	54	90	0.0001*[a]

Note: DM=Diabetes melitus; CVD=Cardiovascular Disease; CKD=Chronic Kidney Disease; COPD=Chronic Obstructive Pulmonary Disease; CVA=Cerebrovascular Disease; CLA=Chronic Liver Disease; *P<0.05 significant; [a]Pearson Chi-Square Test

Table 3 shows that D-dimer levels have a significant relationship with patient outcomes, with value of P=0.0001.

Table 3. The association between D-dimer levels and clinical outcomes in COVID-19 patients at Dr. M. Djamil General Hospital, Padang

D-dimer level (ng/mL)	Clinical Outcomes		R^2	OR	P	P adjusted
	Alive (n=350)	Died (n=129)				
≤500	71 (20.28%)	3 (2.32%)	0.126*[b]	0.120	0.0001*[c]	0.044*
>500	279 (79.71%)	126 (97.67%)				

Note: *P<0.05 significant; [b]Negerkerkle R Square; [c]Wald Test

Table 4. The association between albumin levels and clinical outcomes in COVID-19 patients at Dr. M. Djamil General Hospital, Padang

Abumin level (g/dL)	Clinical Outcomes		R^2	OR	P	P adjusted
	Alive (n=350)	Died (n=129)				
≤3.5	131 (37.42%)	79 (61.24%)	0.126*[b]	2.143	0.0001*[c]	0.0001*
>3.5	219 (62.57%)	50 (38.70%)				

Note: *P<0.05 significant; [b]Negerkerkle R Square; [c]Wald Test

D-dimer levels >500 ng/mL were statistically correlated with mortality outcomes and D-dimer levels ≤500 ng/mL had a statistically significant correlation with survival outcomes in COVID-19 patients at Dr. M. Djamil General Hospital, Padang.

D-dimer levels, statistically, contributed 12.6% to the outcome of COVID-19 patients. There was a negative effect, with each 1 ng/mL increase in D-dimer levels decreasing the patient's outcome probability by 0.120 times.

Albumin levels had a significant relationship with patient outcomes, as shown in Table 4, with value of P=0.0001. Albumin levels >3.5 g/dL had a statistically significant correlation with survival outcomes in COVID-19 patients at Dr. M. Djamil General Hospital, Padang and albumin levels ≤3.5 g/dL were statistically correlated with mortality.

Albumin levels contributed 12.6% to the outcome of COVID-19 patients, according to statistics. There was a positive effect, with each 1 g/dL increase in albumin levels escalating the patient's chances of survival by 2.143 times.

DISCUSSION

This study found that the most common age range was 18-49 years (40.71%)and this finding is consistent with the study by Klaiber et al in England, who found that the age range of 18-39 years (42.5%) had the highest incidence of COVID-19.[10] According to a report published in South Korea by Yu et al, the age group 20-39 years also had the highest incidence of COVID-19 (37%).[11] Nabilah also reported in an epidemiological study that the age range of 46 years had the highest incidence of COVID-19 in Semarang.[12]

The incidence of COVID-19 is closely related to age under 50 years; this is based on low adherence to poor preventive behavior and low adherence to social distancing, the habit of washing hands, wearing masks, and social interaction, all of which cause high transmission in young adults.[12,13]

These findings contradict the findings of Novelli et al in Italy, who reported that the majority of COVID-19 patients were over the age of 70. Age 70 is associated with high comorbidities and old

age, namely immunosuppression, which can reduce the immune system, resulting in high virulence and worsening the patient's clinical condition.[14]

The majority of COVID-19 patients were females according to this study. This is consistent with the findings of Fortunato et al, who reported that the incidence of COVID-19 is higher in women than in men.[15] The female gender of the East Asian race is said to have higher ACE2 receptor expression, increasing the likelihood of COVID-19 infection. Surendra et al in Jakarta reported different findings, saying that most COVID-19 patients were male.[16]

Novelli et al also reported the same result. Men (72.4%) were the most common COVID-19 patients in Italy. In contrast, men are more susceptible to COVID-19 infection due to innate immunity, steroid hormones, and sex hormone-related factors. Compared to men, the X chromosome in women reduces viral load thereby reducing inflammation.[14] Men are also associated with a poor lifestyle compared to women.[14,15]

This study obtained that obesity was the most common comorbidity in COVID-19 patients, followed by hypertension (11.27%), diabetes mellitus (9.81%), and a small proportion of chronic lung disease (2.29%). Tsang et al reported similar finding that obesity, diabetes mellitus, and hypertension were the most common comorbidities in COVID-19 patients. Comorbidities will increase morbidity and mortality in COVID-19 patients, particularly those over 60. Obesity, in combination with diabetes and hypertension, will worsen the outcome in COVID-19 patients.[17]

Novelli et al in Italy found that hypertension (53.3%) was the most common comorbidity, followed by obesity (21.2%), and diabetes (19.0%) among COVID-19 patients.[14] According to a reported study from China, the most common comorbidities were hypertension and diabetes mellitus, associated with older age.[16] Obesity can indirectly increase the expression of ACE2, which is produced by ACE2-expressing adipose cells. The abnormal cytokines and complement production cause an acute decrease in inflammation. This raises the likelihood of coagulopathy and contributes to COVID-19 mortality.[18]

The severity of COVID-19 is related to hypertension. The immune system is dysregulated in COVID-19 due to hypertension. Monocytes and other immune cells will produce more IL-6 and increase CD8+ T cells, which will produce tumor necrosis factor (TNF). This causes an increase in cytokine production.[14,17] Diabetes mellitus is said to be more vulnerable due to hyperglycemia, which decreases viral clearance, impairs T cell function, and increases inflammation.[14]

According to this study, the majority of patients had moderate clinical severity (42.79%). This is consistent with the findings of Varikasuvu et al, who discovered that the clinical severity in the majority of COVID-19 patients was mild to moderate; however, 20-26% of cases will be severe or critical.[1]

We found that the agerange of 18-49 years was significantly related to survival outcomes, with value of P=0.0001. This is consistent with a study by Gold et al in Georgia, which found that the age range of 18-49 years had a high survival rate (95.5%).[19] Tsang et al discovered that age played a significant role in increasing the case fatality rate (CFR) among COVID-19 patients by 3.4% as they got older.[17] This study found that the age ranges of 60-69 and ≥70 years were significantly related to the outcome of COVID-19 patients, with patients who died accounting for more than half of the survivors.

This report is consistent with a research conducted by Gold et al in Georgia in 2020, which stated that the mortality rate of COVID-19 patients in this age group was higher (35.6%).[19] This is consistentwith the findings of Tsang et al who discovered that the age range of 20-29 years had a CFR of 0-0.2%, the age range of 30-39 years had a CFR of 0.2-0.3%, and then continued to increase until age ≥80 years that had a CFR of 14.8-20.2%. In these COVID-19 patients, the risk of death is related to age and comorbidities.[17]

The Italian Institute of Health report also found that ages 60 and 80 were strongly related to the outcome of patients who died.[20] A high number of comorbidities are associated with old age, and in elderly patients, it is associated with immunosuppressive conditions that can weaken the immune system, resulting in high virulence and aggravating the patient's clinical condition. Aging is also linked to an inflammatory response.[14]

Except for cerebrovascular disease, which had a significant value of P<0.05, and chronic liver disease after adjustment, the results of this study revealed no significant relationship between comorbidities and the outcome of COVID-19 patients at Dr. M. Djamil General Hospital, Padang. This is consistent with the findings of Shang et al, who found that while comorbidities were not significantly related to the outcome of COVID-19 patients, age did play a significant role.[21]

Cerebrovascular disease is linked to an increased riskof severe COVID-19 and death, with odds ratios of 2.24 and 12.27, respectively. This results in disability, and SARS-CoV-2 can cause direct nerve damage or vascular problems such as stroke, as well as increased proinflammatory cytokines, which damage the vascular endothelium and increase blood coagulability.[22] The underlying mechanism is thrombus formation, cell damage, the endothelial barrier, the inflammatory response, or directly SARS-CoV-2 can damage endothelial cells via ACE2 receptors, resulting in vascular endothelial barrier damage and vascular rupture, particularly in the brain.[23]

According to Alwafi et al, chronic liver diseaseincreased the odds ratio for death in COVID-19 patientsby 1.92 times.[24] Chronic liver disease, according to Zhou et al, had no significant relationship with COVID-19 outcome.[25] Novelli et al in Italy reported that comorbidities such as hypertension, chronic kidney disease, malignancy, and

cardiovascular disease were strongly associated with the outcome of COVID-19 patients. Chronic kidney disease is associated with ongoing inflammation, which can aggravate COVID-19. Cancer is linked to immunocompromised states.[14]

Tsang et al also stated that age and comorbidities play a significant role in the outcome of COVID-19 patients, with cardiovascular disease being the leading cause of death. According to the Institute of Health in Italy, co-morbidities such as diabetes mellitus, hypertension, and cardiovascular disease played an important role in the clinical severity of COVID-19 patients, which had an impact on increasing COVID-19 patient mortality.[17]

In a study of 32,583 COVID-19 patients in Mexico, Marin et al discovered that obesity, followed by diabetes mellitus and hypertension, had a tendency for progression and mortality.[26] Obesity increases ACE2 expression via adipose cells. The abnormal cytokines and complement production cause an acute decrease in inflammation. This raises the likelihood of coagulopathy and contributes to COVID-19 mortality.[18]

According to the findings of this study, mild, moderate, and critical clinical severity have a significant relationship with the outcome of COVID-19 patients who do not have severe clinical severity. Clinical severity, from mild to moderate, is significantly associated with survival outcomes. The majority of those in this study were between the ages of 18 and 49. According to several studies, there were not many comorbidities that would have an impact on the severity of the clinical degree of COVID-19 patients at that age. The outcome of death due to old age is significantly related to critical clinical severity.

These findings are consistent with the findings of Varikasuvu et al, who found that the majority of COVID-19 patients with mild symptoms had a favorable prognosis; however, patients with severe and critical COVID-19 symptoms had a high mortality rate ($P<0.05$).[1] Comorbidities are also associated with old age, which will increase morbidity and mortality in COVID-19 patients, particularly those over 60 years old. Obesity, in combination with diabetes and hypertension, will worsen the outcome in COVID-19 patients.[14,17]

We found that our study is consistent with the findings of Marin et al in America, who found that D-dimer levels of 31,000 ng/mL at admission had a significant relationship with the high mortality rate of COVID-19 patients in hospitals.[26] Guadiana-Romualdo et al reported on 2,663 subjects in Spain that a D-dimer levels of 3,945 ng/mL at admission had a significant association with high mortality in COVID-19 patients ($P=0.001$).[27]

Caricchio et al reported that COVID-19 patients who experienced a cytokine storm had a mean D-dimer level of >500 ng/mL, while COVID-19 patients who did not experience a cytokine storm had a D-dimer level of >4,930 ng/ml.[28] In severe and critical COVID-19 patients, high serum levels of pro-inflammatory cytokines cause a cytokine storm. This will damage the vascular endothelium and activate the

coagulation cascade, but with SARS-CoV-2 immunity, it will result in coagulopathy. A rise in D-dimer levels in COVID-19 indicates coagulopathy. This is extremely complicated.[5,29]

There are at least two mechanisms: coagulation activation caused by SARS-CoV-2 infection and endothelial cell damage. By binding to ACE2, SARS-CoV-2 infects macrophages and endothelial cells. Tissue factor (TF) is then expressed by immune cells, causing cytokine overproduction and stimulating coagulation and endothelial cell damage.[29] Blood clots and fibrin deposition in blood vessels contribute to the obstruction of oxygen delivery to organs, resulting in multi-organ dysfunction and death complications in COVID-19 patients.[30]

According to Varikasuvu et al, the initial D-dimer level can predict the clinical severity of COVID-19 with a sensitivity of 55% and a specificity of 56%, and it can predict death with a sensitivity of 64% and a specificity of 66%.[1] In contrast to Mahardhika et al, who reported an increase in D-dimer and CRP levels in patients with clinically asymptomatic conditions, which was an unusual condition, this was due to age and comorbid factors in patients, which could also increase D-dimer levels.[9]

The most common complications in deceased COVID-19 patients are coagulopathy and thrombosis.[4] Tang et al found that DIC and multi-organ dysfunction occurred in 71.4% of patients who died.[4,5] Varikasuvu et al reported that there was a relationship between D-dimer and COVID-19 progressivity.[1]

High D-dimer levels are linked to an increased risk of coagulopathy and thrombosis in patients. Plasminogen Activator Inhibitor-1 (PAI-1) levels are elevated in COVID-19 patients, which can disrupt the fibrinolytic system and lead to thrombus formation. This can cause vasoconstriction due to hypoxemia via reduced blood flow and vascular occlusion, endothelial dysfunction, and inflammation, particularly in patients with co-morbidities such as hypertension, diabetes, and advanced age.[1,4]

We found that our study is consistent with the findings of Aloisio et al, who found that serum albumin levels of ≤3.5 g/dL were significantly higher for increasing D-dimer levels four times the upper limit value (upper value ≤500 ng/ml) than serum albumin levels of ≥3.5 g/dL. According to this study, there was a causal relationship between decreased albumin levels and increased D-dimer that affected patients in the severe and critical clinical group.[7] Caricchio et al studied albumin level in COVID-19 patients who experienced cytokine storms. COVID-19 patients with cytokine storms had albumin level of 2.7 g/dL, while the predicted value that caused a cytokine storm was 2.8 g/dL.[28]

An inflammatory mechanism can explain the decrease in the rate of albumin synthesis in COVID-19 patients. Inflammation inhibits albumin synthesis, particularly albumin mRNA, which is reduced by up to 90% during inflammation. Because albumin is a negative acute-phase protein, its synthetic potential is drastically reduced. Cytokines

are proteins that are produced during inflammation that degrade amino acids to increase the synthesis of acute-phase proteins that are required for the inflammatory process. Because albumin is not required for inflammation, these cytokines release amino acids from albumin synthesis.[31,32] Hariyanto et al also discovered that albumin could downregulate ACE2, which was critical for modulating COVID-19 infection. When albumin levels are low, ACE2 receptors are activated, and COVID-19 infectivity increases.[8]

Inflammation can impair hepatic albumin synthesis.[31,32] Hypoalbuminemia, or low albumin level, is thought to play an important role in the poor outcome of COVID-19 patients because it can cause pulmonary capillary leakage.[33] According to Khodeir et al, decreased albumin levels were strongly associated with disease progression in severe and critical cases, with a mean value of 3.0 g/dL, affecting the liver in both the survivor and non-survivor groups.[3]

According to Zerbato et al, the threshold for predicting a high risk of death within 90 days for COVID-19 patients is 3.23 g/dL in 15% of COVID-19 patients. The patient's need for mechanical ventilation was also linked to hypoalbumin at 3.17 g/dL.[34]

This study had limitations, including the use of a retrospective study with a cross-sectional design and data from patient medical records, as well as an uneven distribution of patients.

CONCLUSION

Higher D-dimer levels independently had a relationship with unfavorable outcome and higher albumin levels were independently related to a favorable outcome.

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Original Article

Evaluation of Mortality Risk Factors of COVID-19 in Jakarta Tertiary Hospital During Peak of Second Wave and Predictive Utility of Community RT-PCR Low CT Values

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Abstract

Background: The Delta variant of SARS-CoV-2 led to a surge in COVID-19 cases in Indonesia. This study aimed to assess the demographic profile and mortality rates of hospitalized COVID-19 patients in YARSI referral hospital, Jakarta, comparing pre-Delta and Delta wave periods. The study also investigated whether low CT values in RT-PCR tests indicated heightened viral transmission before the Delta wave surge.

Method: A retrospective analysis was conducted on 1,457 COVID-19 patients hospitalized at YARSI (January-August 2021) and 25,279 RT-PCR test results from walk-in patients (April-August 17, 2021). Differences were evaluated using Chi-square or Fisher's Exact Tests while binary logistic regression was used to assess mortality risk factors.

Results: There were increased proportions of pregnant women, patients aged 20-29 and those with coronary artery disease during the Delta wave. This period also showed a significant increase in mortality rates, with the highest seen in patients >60 years old or those with multiple comorbidities. Notably, most of the deceased patients (131 of 139) were unvaccinated. Analysis of RT-PCR data showed rising percentages of positive results with low CT values (below 21 or 15) from April to June.

Conclusion: The Delta wave saw a higher risk of hospitalization among young individuals and pregnant women, despite their low mortality risk. The unvaccinated and those with multiple comorbidities faced higher mortality risks. Increases in RT-PCR positivity with low CT values preceded the July COVID-19 case surge.

Keywords: COVID-19, Delta variant, mortality risk factors, PCR CT values, vaccine status

INTRODUCTION

SARS-CoV-2 Delta variant is the fourth variant of concern (VOC) designated by WHO due to its effective transmission and short incubation period. Delta variant has quickly dominated circulating variants in Indonesia.[1] In Indonesia, genomic surveillance shows that Delta has become a major variant since the beginning of May 2021. This upsurge of Delta variant is followed by spike of COVID-19 cases and mortality in reaching a peak in July 2021, including Jakarta.[2]

Genomic surveillance in Indonesia shows that Delta variant has contributed up to 85% of COVID-19 cases setting off second wave of COVID-19. In July 2021, 56,767 new cases were recorded with up to 26% positivity rate. Jakarta, the capital city of Indonesia, has also experienced peak of COVID-19 cases at that time, setting off unprecedented crisis of health care facilities including shortage of trained staffs and oxygen supplies.[2]

Previous reports from Singapore and United Kingdom suggest that Delta infection increases risk of hospitalization and mortality.[3,4] However, the impact of Delta surge on mortality of hospitalized COVID-19 patients in Indonesia was largely unknown. Moreover, Indonesia has begun the COVID-19 vaccination drive using inactivated virus vaccine technology since January 2021, primarily targeting elderly (60 years and older) and healthcare workers.[5] In May 2021, two-dose vaccine coverage among elderly in Jakarta was 55% and increased to 80% in July.[6] The vaccine using inactivated COVID-19 virus manufactured by Sinovac is the most common COVID-19 vaccine used in Indonesia.[7]

There were three objectives in this study. First, to identify clinical profiles of COVID-19 patients which were disproportionately higher during Delta (June to August 2021) than previous (January to May) waves. Second, to describe and identify clinical predictors associated with mortality of COVID-19 patients during Delta wave. Lastly, explored the utility of RT-PCR CT values to predict viral transmission preceding the Delta wave. Clinical profile and vaccination status of deceased patients would be interesting to explore and may help in shaping future policy while facing future emergence of COVID-19 variants.

METHOD

This retrospective study was conducted following the approval of the Ethical Clearance Committee of YARSI Hospital, ensuring adherence to the ethical standards of research. Laboratory and clinical data from YARSI Hospital electronic medical record systems were collected for all patients treated with positive SARS-CoV-2 RNA test between January and August 17th 2021 (N=1,457 patients).

Parameters to be compared included demographics (age and gender), comorbidity, length of hospitalization, laboratory parameters (blood glucose, D-dimer, neutrophil-lymphocytes ratio/NLR and c-reactive protein/CRP) and mortality.

Case-fatality risk was calculated among patients with in-hospital mortality (ie, COVID-19 deceased patients divided by COVID-19 deaths plus survivors of COVID-19).

In addition, records of RT-PCR test results were also accessed from 25,279 individuals referred to YARSI Hospital from surrounding community such as clinics and drive-thru sites from the period of April to August 2021. Parameters to be evaluated were positivity rates, median CT values and percentages of low CT values set arbitrarily at <15 and <21.

Descriptive data were presented as percentage comparing clinical parameters of all COVID-19 patients admitted to YARSI Hospital between January to May 2021 (pre-Delta variant) and June to August 2021 (Delta variant). No statistical sample size calculation was made and sample size was equal to the number of laboratory confirmed COVID-19 patients admitted at YARSI hospital during the study period to evaluate risk factors of hospitalization and mortality.

Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as medians (interquartile ranges/IQR). Differences between groups were assessed using chi-square or Fisher's exact tests for categorical variables. Differences were considered significant when p values were <0.05 for a two-tailed test. A binary logistic regression was used to evaluate risk factors associated with mortality including the variable of interest (wave) to assess differences in mortality between study waves. Factors included in the model were those with statistical significance in the univariable analysis. The results of the multivariable analysis were reported as odds ratios (OR) with the 95% confidence intervals (CI). StatPlus (AnalystSoft Inc) was used to perform statistical calculation.

RESULTS

Overall, there were 1,457 COVID-19 patients confirmed by laboratory tests between January to August 2021. As shown in Table 1, during the first five months of 2021 (January to May), there were 736 COVID-19 patients, with 721 patients added in just three months (June to August) which coincided with rising prevalence of COVID-19 Delta variant of concern (VOC). Comparative study revealed significant demographic differences between pre-Delta wav e (January to May) and Delta wave (June to August).

During Delta wave, there were more cases of pregnant women (0.5% vs 1.8%; OR=3.36; 95% CI=1.09-10.35; P=0.019), patients belonging to age group 20-29 years old (7% vs 13%; OR=1.99; 95% CI=1.39-2.86; P=0.0002) and patients with coronary artery disease comorbidities (5.3% vs 8.5%; OR=1.85; 95% CI=1.19-2.87; P=0.02) using univariate analysis. However, after adjusted to age and comorbidities, pregnancy variable reached borderline significant (aOR=2.99; 95% CI=0.96-9.32; P=0.05).

Table 1. Univariate and multivariate analysis of factors associated with admission to YARSI hospital in the pre-Delta (January to May 2021) and Delta (June to August 2021) waves

Parameters	Pre-Delta wave (N=736)	Delta wave (N=721)	OR (95% CI)	P	aOR (95% CI)	P
Gender						
Male	387 (53%)	378 (52%)	0.99 (0.81-1.22)	0.95	---	---
Female	349 (47%)	343 (48%)				
Age groups						
0-4	13 (1.8%)	7 (1.0%)	0.55 (0.22-1.37)	0.18	---	---
5-9	7 (1.0%)	6 (0.8%)	0.87 (0.29-2.61)	0.81	---	---
10-19	22 (3.0%)	25 (3.5%)	1.17 (0.65-2.09)	0.61	---	---
20-29	52 (7.1%)	94 (13.0%)	1.97 (1.38-2.81)	0.0001*	1.99 (1.39-2.86)	0.002*
30-39	113 (15.4%)	102 (14.1%)	0.91 (0.68-1.21)	0.52	---	---
40-49	137 (18.6%)	137 (19.0%)	1.03 (0.79-1.33)	0.85	---	---
50-59	192 (26.1%)	180 (25.0%)	0.94 (0.74-1.19)	0.62	---	---
60-69	127 (17.3%)	105 (14.6%)	0.82 (0.62-1.08)	0.16	---	---
70 and older	73 (9.9%)	65 (9.0%)	0.90 (0.63-1.28)	0.56	---	---
Comorbidities						
None	322 (43.8%)	307 (42.6%)	0.95 (0.77-1.17)	0.65	---	---
Single	236 (32.1%)	261 (36.2%)	1.2 (0.97-1.49)	0.10	---	---
Multiple	178 (24.2%)	153 (21.2%)	0.66 (1.08-0.18)	0.18	---	---
Type of comorbidities						
Diabetes	179 (24.3%)	152 (21.1%)	0.83 (0.65-1.06)	0.14	---	---
Hypertension	270 (36.7%)	231 (32.0%)	1.0 (0.66-1.01)	0.06	---	---
Obesity	33 (4.5%)	35 (4.9%)	1.09 (0.67-1.77)	0.74	---	---
CAD	39 (5.3%)	61 (8.5%)	1.65 (1.09-2.5)	0.02*	1.85 (1.19-2.87)	0.01*
CKD	14 (1.9%)	19 (2.6%)	1.4 (0.69-2.81)	0.35	---	---
Malignancy	8 (1.1%)	7 (1.0%)	0.89 (0.32-2.47)	0.83	---	---
TB	11 (1.5%)	12 (1.7%)	1.12 (0.49-2.54)	0.79	---	---
Alzheimer	2 (0.3%)	2 (0.3%)	1.02 (0.14-7.27)	0.98	---	---
Geriatric	9 (1.2%)	5 (0.7%)	0.56 (0.19-1.69)	0.30	---	---
Pregnancy	4 (0.5%)	13 (1.8%)	3.36 (1.09-10.35)	0.02*	2.99 (0.96-9.32)	0.05*
HIV	1 (0.1%)	3 (0.4%)	3.07 (0.32-29.6)	0.30	---	---
Asthma	25 (3.4%)	22 (3.1%)	0.9 (0.5-1.6)	0.71	---	---
Others	37 (5.0%)	44 (6.1%)	1.23 (0.78-1.93)	0.37	---	---

Note: *significant (P<0.05); CAD=Coronary Artery Disease; CKD=Chronic Kidney Disease; TB=Tuberculosis; HIV=*Human Immunodeficiency Viruses*

Mortality rates during pre-Delta and Delta waves were 7.2% and 11.9% respectively (Table 2). Mortality risks were higher in Delta wave for individuals with advanced age (>60 years, OR=1.81; 95% CI=1.19-2.76; P<0.05) or having multiple comorbidities (OR=2.3; 95% CI 1.57-3.35; P=0,0001). The most common comorbidities associated with higher risk of mortality in Delta wave were hypertension, diabetes, obesity, chronic kidney disease and geriatry. Interestingly, young age (20-29 years old) and individuals with coronary artery disease were not associated with mortality risk during Delta wave despite having significantly higher cases.

Table 2. Univariate and multivariate analysis of factors associated with in-hospital mortality in YARSI Hospital between pre-Delta wave versus Delta wave

Parameters	Pre-Delta wave	Delta wave	OR (95% CI)	P	aOR (95% CI)	P
Total	53 (7.2%)	86 (11.9%)	1.75 (1.22-2.5)	0.0001*	1.95 (1.35-2.83)	0.0001*
Gender						
Males	24 (45.3%)	45 (52.3%)	0.88 (0.62-1.25)	0.4787	---	---
Females	29 (54.7%)	41 (47.7%)	1.1352	0.4787	---	---
Age groups (years)						
0-4	0 (0.0%)	0 (0.0%)	---	---	---	---
5-9	0 (0.0%)	0 (0.0%)	---	---	---	---
10-19	0 (0.0%)	0 (0.0%)	---	---	---	---
20-29	1 (1.9%)	2 (2.3%)	0.16 (0.05-0.52)	0.0001*	0.22 (0.07-0.70)	0.0001*
30-39	4 (7.5%)	5 (5.8%)	0.38 (0.19-0.75)	0.01*	0.56 (0.27-1.14)	0.01*
40-49	8 (15.1%)	15 (17.4%)	0.84 (0.52-1.34)	0.46	---	---
50-59	12 (22.6%)	29 (33.7%)	1.26 (0.86-1.85)	0.24	---	---
60-69	17 (32.1%)	21 (24.4%)	2.26 (1.51-3.39)	0.0001*	1.81 (1.19-2.76)	0.0001*
70 and older	11 (20.8%)	14 (16.3%)	2.39	0.0001*	1.81 (1.11-2.96)	0.002*
Comorbidities						
None	7 (13.2%)	10 (11.6%)	0.16 (0.095-0.269)	5E-12*	0.24 (0.14-0.41)	2.2E-7*
Single	18 (34.0%)	42 (48.8%)	1.50 (1.05-2.14)	0.026	1.21 (0.84-1.74)	0.31*
Multiple	28 (52.8%)	34 (39.5%)	3.26 (2.27-4.69)	0.0001*	2.3 (1.57-3.35)	0.0001*
Types of comorbid						
Diabetes	26 (49.1%)	31 (36.0%)	2.75 (1.91-3.96)	0.0001*	2.01 (1.38-2.93)	0.0001*
Hypertension	33 (62.3%)	45 (52.3%)	2.82 (1.97-4.03)	0.0001*	1.76 (1.20-2.59)	0.0001*
Obesities	6 (11.3%)	11 (12.8%)	3.46 (1.93-6.21)	0.0001*	4.80 (2.58-8.91)	0.0001*
CAD	4 (7.5%)	11 (12.8%)	1.65 (0.92-2.96)	0.09	---	---
CKD	2 (3.8%)	7 (8.1%)	3.62 (1.64-7.99)	0.0001*	3.0 (1.33-6.80)	0.01*
Malignancy	0 (0.0%)	2 (2.3%)	1.49 (0.33-6.73)	---	---	---
TB	2 (3.8%)	1 (1.2%)	1.41 (0.41-4.84)	0.58	---	---
Alzheimer	1 (1.9%)	1 (1.2%)	---	---	---	---
Geriatric	2 (3.8%)	2 (2.3%)	4.27 (1.31-13.96)	0.02*	2.01 (0.6-6.72)	0.26
Pregnancy	0 (0.0%)	2 (2.3%)	1.10 (0.25-4.90)	0.90	---	---
HIV	1 (1.9%)	1 (1.2%)	---	---	---	---
Asthma	3 (5.7%)	1 (1.2%)	0.89 (0.31-2.53)	0.83	---	---
Others	1 (1.9%)	2 (2.3%)	0.34 (0.11-1.09)	0.07	---	---

Note: *significant (P<0.05); CAD=Coronary Artery Disease; CKD=Chronic Kidney Disease; TB=Tuberculosis; HIV=*Human Immunodeficiency Viruses*

The age of deceased patients in Delta wave (57 years old) was younger than previous wave (60 years old) but did not reach statistical significance (Table 3). Furthermore, there were no significant differences in terms of measured blood glucose, CRP, D-dimers and NLR. The number of deaths from each causes such as acute respiratory distress syndrome (ARDS), cardiac arrest and thromboembolism/coagulopathy were also similar to each other, except there was less incidence of sepsis during Delta wave (P=0.0413). Most deceased patients were not vaccinated as shown in both pre-Delta wave (98%) and Delta wave (90.6%).

Table 3. Clinical and laboratory parameters in deceased patients

Parameters	Pre Delta wave	Delta wave	P
Age [media (min-max)]	60 (51-68)	57 (49-66)	0.231
Blood glucose (mg/dL) [media (min-max)]	158 (118-283)	131 (108-192)	0.099
CRP (mg/dL) [media (min-max)]	8.7 (1.45-17.4)	9.32 (3.52-15.4)	0.574
D-Dimer (ug/mL) [media (min-max)]	1.5 (0.5-5.8)	0.9 (0.43-2.7)	0.15
NLR [media (min-max)]	6.43 (3.74-13.1)	7.2 (4.12-13.1)	0.76
Vaccine status			
None	52 (98%)	78 (90.6%)	0.022*
Completion	1 (1.9%)	8 (9.3%)	--
Length of stay	7 (4-13)	7 (3-12)	0.488
Cause of death			
ARDS	36 (68%)	64 (75%)	0.407
Cardiac arrest	43 (81%)	69 (80%)	0.896
Thromboembolism/Coagulopathy	20 (37%)	40 (46%)	0.31
Sepsis shock	31 (59%)	35 (41%)	0.0413*
WHO Clinical Progression scales			
Mild	21 (39.6%)	44 (51.1%)	0.185
Moderate	25 (47.1%)	40 (46.5%)	0.939
Severe	5 (9.4%)	2 (2.32%)	0.0627

Note: CRP=C-Reactive Protein; NLR=Neutrophil Lymphocyte Ratio; ARDS=Acute Respiratory Distress Syndrome

Table 4 CT values of population RTPCR test results performed by YARSI Hospital serving surrounding community

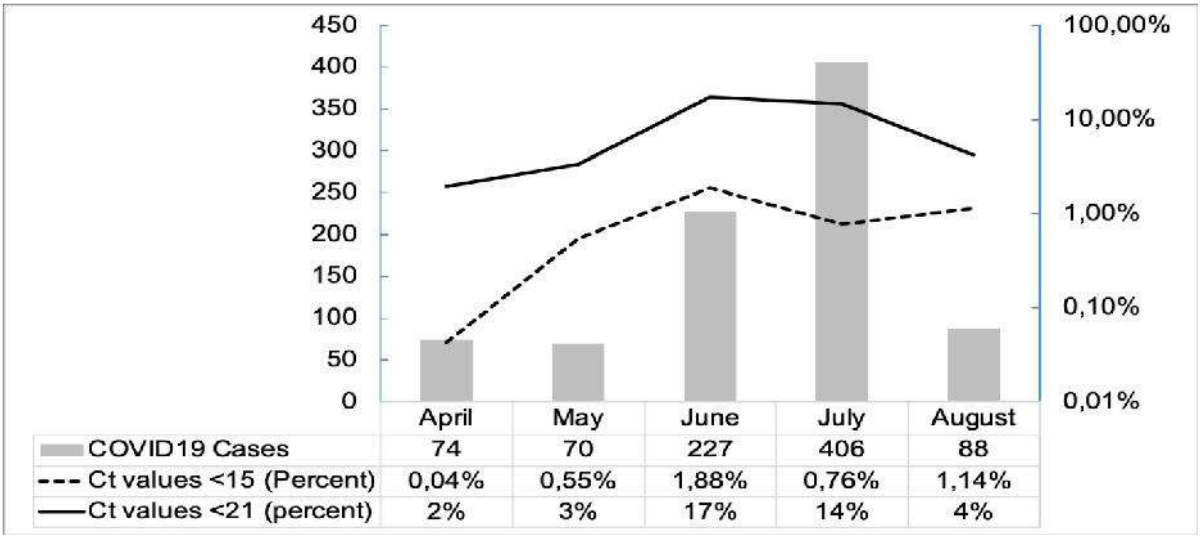
Months	COVID-19 cases in YARSI Hospital (N=865)	RT-PCR tests surrounding community (N=25,279)	Median of RT-PCR CT values in the community	Positivity Rate of RT-PCR testing in the community	Percent of CT Values <21	Percent of CT values <15
April	74	2339	29	16,7%	1,9%	0,04%
May	70	2183	32	18,3%	3,3%	0,55%
June	227	7379	23	46,0%	17,4%	1,88%
July	406	10748	26	57,3%	14,5%	0,76%
August	88	2630	32	25,9%	4,2%	1,14%

Note: RT-PCR=Real Time Polymerase Chain Reaction

The proportion of mortality in vaccinated patients was significantly higher in Delta wave (P=0.0413). Lastly, length of hospital stay (median 7 days) was similar between two waves (P=0.488).

To explore possible circumstances preceding second wave, obtained RT-PCR test results since April 2021 from the surrounding community. As shown in Table 4, the positivity rate of COVID-19 RT-PCR testing in the community mirrored the number of COVID-19 cases admitted to YARSI hospital each month. The positivity rate reached its peak in the month of July (57%) and went down to 25% in August. Furthermore, there was a trend of decreasing median of CT values in positive test results. The lowest median occurred in the month of June (CT value 23) which suggested low CT values could be more common in this month.

Low CT values had been thought to correlate with high viral load and may predict high level of infectiousness and epidemic trajectory.



	April	May	June	July	August
COVID19 Cases	74	70	227	406	88
Ct values <15 (Percent)	0,04%	0,55%	1,88%	0,76%	1,14%
Ct values <21 (percent)	2%	3%	17%	14%	4%

Figure 1. Relationship between monthly cases of COVID-19 patients and low RTPCR Ct values. Solid gray bars indicate the number of patients admitted to YARSI hospital. Solid line represents trend of low Ct values (under 21) and dashed line low Ct values (under 15). Left y-axis represents the number of COVID-19 cases. Right y-axis is percentage of low Ct values with respected cut-off 21 or 15. Low Ct values of RTPCR may be associated with relatively high viral load

The tracking the percentage of low CT values using two arbitrary cut-off CT values (15 and 21). As shown in Figure 1, low CT values (less than 21) were found in April and May 2021 (2% and 3% respectively). The percentage increased to 17% in June 2021 which preceded the doubling of COVID-19 cases in July.

On the other hand, while using 15 as the cut-off for CT values, the percentage increased from 0,04% in April to 0,55% in May. This tenfold rise of the percentage of low CT values in May was followed by significant surge of COVID-19 cases in June. Moreover, the percentage of low CT values dropped to 0.76% in June, followed by declining numbers of COVID-19 cases in August.

Pre-Delta wave was defined as January to May 2021, while Delta wave was June to August 2021. Categorical variables were presented as frequency and percentages. Chi-square or Fisher's exact test was applied to frequency distribution accordingly. Those with significant p values are indicated in bold ($P<0.05$ indicated that the difference was statistically significant). aOR means adjusted Odds Ratio.

DISCUSSION

Several countries including Indonesia have been impacted by the surge of new COVID-19 cases associated with Delta variant of SARS-CoV-2. This observations in a single tertiary hospital not only showed several key results regarding affected population and mortality rates, but also offered insights regarding vaccination status and potential utility of low CT values to predict active transmission in the community. First, during second wave there was a significant rise of hospitalization among young patients and those without known comorbidities. A study from the UK demonstrates that Delta variant mostly infected younger patients, which is consistent with this finding.[4]

Moreover, unvaccinated population was more susceptible to Delta infection. Another recent study in Singapore comparing three VOCs (Alpha, Beta and Delta) found that the median age of Delta infected patients in Singapore was around 48 which is highly similar to this cohort.[3] Furthermore, Delta might cause more severe cases compared to other variants.

However, it could not evaluate the virulence impact of Delta variant in this cohort because it did not genotype patients for VOCs. Interestingly, a hospital study in Yogyakarta, Indonesia suggests that the mortality risk between Delta and non-Delta variants were not significantly different.[8] Nevertheless, old age and comorbidity continue to be consistent predictors of poor outcome regardless of variants.

There were more pregnant female patients during the second wave in this cohort compared to the first. In the United States, during the surge of Delta variant between May to July 2021, the numbers of pregnant women with COVID-19 had been increasing with up to 25% requiring hospitalization due to severe or critical symptoms.[9] In addition to the rising number of pregnant COVID-19 patients during Delta wave, this cohort also showed mortality rate of 22%. While the pathophysiology was not clear, the deceased patients had pregnancy related comorbidity especially hypertension which might exacerbate the symptoms.[10]

COVID-19 cases generally affect older population with high prevalence of comorbidities, but it observed an increasing proportion of young patients without comorbidities during Delta wave. This shift in COVID-19 proportion has been previously described in Brazil during the wave associated with Gamma variant in February 2021 and was attributed to young population doing more rigorous daily activities due to economic necessity while having relatively smaller coverage of vaccination, which mainly prioritized the elderly population.[11] Although there was no fatalities in children (age 0-18 years old) in this cohort, they remained susceptible to Delta variants. Recent outbreak in California elementary school showed that an unmasked, symptomatic teacher reading a book out loud caused up to 50% infection among 22 students.[12]

Comparison of mortality rates revealed that males and hypertension remained consistent as risk factors for poor outcome in COVID-19. This was also seen in the second wave. While there was increased number of hospitalization in young adults and children, no fatalities were found. However, the possibility of long term effect of COVID-19 among surviving children and young adults should be monitored closely. Recent reports showed that the frequency of persistent symptoms may affect between 15%-46% of children within 2-4 months post COVID-19 infection.[13,14]

In this cohort, pregnant women showed mortality rates of 20%. Although not statistically significant, some pregnancy may induce hypertension, a comorbid which also causes higher rates of mortality during the Delta wave. Many studies found that COVID-19 patients with hypertension

tend to have worse prognosis than normotensive patients. As many as 23.7% hypertensive patients suffered from severe COVID-19, compared to 13.4% of non-hypertensive patients.[15]

Another study showed that 35.8% of COVID-19 patients with hypertension needed to be admitted to ICU, received mechanical ventilation or resulted to death, compared to 13.7% in patients with normal blood pressure.[16] Another study that examined 138 patients who tested positive for COVID-19 in China described that 58.3% of patients with hypertension were admitted to ICU, higher than patients with normal blood pressure (21.6%).[15] In a large-scale cohort study with 1590 sample size from 575 hospitals, hypertension showed an independent association to severe covid with hazard ratio=1.575; 95% CI=1.07-2.32.[16]

Since there were high mortality rates in patients aged 60 years old and under, it examined laboratory parameters in deceased patients and compared the results between young (<60) and old patients. There were no significant differences in NLR, blood glucose and D-dimer among deceased patients during Delta wave. Previous literature review suggests that these laboratory parameters have been associated with poor outcomes in COVID-19 in Asian patients.[17]

The role of ethnicity has been investigated in a study from the United Kingdom where it's found that elevated (ALP × ALT)/albumin ratio is a reliable mortality predictor for Caucasian patients while NLR (>7.8) is poor prognostic marker for all ethnicity.[18]

Recent study has compared laboratory parameters among patients infected with alpha, beta and delta variants and found similar values of NLR across all variants, but the level of CRP (median 28 mg/L) in significantly higher in Delta infected patients.[3] This study could not corroborate the CRP value because it did not have access to variant genotyping within this cohort.[19]

The majority of deceased patients in this cohort was not vaccinated. As per July 2021, up to 80% of elderly citizens in Jakarta have been vaccinated. This implies protective effect of vaccination which had begun in January 2021.[6] A retrospective study from Canada showed that Delta variant imposed higher risk of mortality in unvaccinated population.[20]

Within this cohort, there was significantly higher proportion of deceased patients who had been vaccinated during Delta than pre-Delta wave. The increased proportion may reflect the increasing vaccination coverage during the Delta wave period in Jakarta. Alternatively, there is a possibility of lower vaccine effectiveness against Delta as suggested by in vitro neutralization study of Delta variant using serum of vaccinated individuals.[21]

The effectiveness of COVID-19 vaccine using inactivated virus platform against Delta variant has been studied in China.[22] In spite of the presence of many mutations in Spike protein in Delta and lower titre of neutralizing antibody induced by vaccine, this study indirectly suggests

that unvaccinated individuals remain at high risk of mortality regardless of the type of variant causing COVID-19 infection.[21] Therefore, vaccination program should remain a priority targeting high risk population especially the elderly and individuals with comorbidities.

This study also had observed increased proportion of low CT values within the surrounding community in the month of April and May, or at least two months before the surge occured in July. Hospital bed occupancy and RT-PCR testing positivity rates have been used to estimate epidemiologic trajectory. However there might be limitations due to delay in reporting and bias in sampling. Hay et al found that CT values found in population may offer better prediction of epidemiologic trajectory. High proportion of individuals with positive RT-PCR and low CT values at a given time suggests an increase in epidemic trajectory.[23]

The utility of low CT values to predict epidemiologic trajectory has been validated in Hong Kong, which is able to estimate real time viral transmission within the community. This CT value approach is useful even in areas with limited testing capacity or surveillance.[24] Another study from UK which encompassed period of high transmission of Alpha variant also shows that variation in CT values within confirmed cases may be useful as early warning indicator because the rising or declining proportion of low CT values in the community preceded the higher or lower incidences of COVID-19, respectively.[19] Similar to UK study, the inverse association of low CT values and increasing viral transmission in the population is also observed in Italy.[25]

In the month of August, the number of COVID-19 patients decreased significantly. Interestingly, there was a slight rise of low CT value percentage in the community, i.e. 0,76% in July to 1,14% in August. However, this rising percentage was not followed by another surge in the following month of September onwards.[26]

There were two possible explanations, namely massive vaccination drive and PPKM (restricted public activities) that had been enforced within Jakarta and other cities around Jakarta. Recent modelling study suggests that combination of vaccination drive and non-pharmaceutical intervention may mitigate impact of Delta variant in the community.[26] This data of CT values from the community may help in making decision to initiate, prolong or end PPKM based on continuous monitoring of proportion of low CT values.

CONCLUSION

The surge of variant of Delta in Indonesia also affects the city of Jakarta. Compared to profile of hospitalized patients in previous period, the Delta period (June to August 2021) yielded higher proportions of young population, pregnant women and individuals with heart problem. While COVID-19 vaccine coverage was between 55% (May 2021) and 80% (July 2021) among elderly, mortality during Delta

period was dominated by unvaccinated individuals.

Preceding the Delta period, surveillance data showed that the proportion of low CT values from surrounding community was increasing. Therefore, vaccination program and continuous monitoring of CT values may be helpful to mitigate risk of COVID-19 cases in developing countries.

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Case Report

Bronchoscopic Balloon Dilatation for Tuberculosis-related Bronchial Stenosis: A Rare Case

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Abstract

Background: Bronchial stenosis is known as a complication of endobronchial tuberculosis (EBTB). The incidence of stenosis affects quality of life. A minimally invasive therapeutic strategy, bronchoscopic balloon dilatation (BBD), can be chosen to manage the disease.

Case: A 29-year-old woman suffered from bronchial stenosis, which appeared after completing treatment for tuberculosis (TB). She was diagnosed with TB around the middle of her pregnancy. She received anti-tuberculosis treatment for six months. Two years later, she complained of a persistent cough for two weeks prior to hospitalization. A complete stenosis of the left main bronchus with atelectatic on the left lung was seen on a chest CT scan. The result was confirmed with a bronchoscopy procedure. There were no mycobacteria or other suspicious organisms found in bronchial washings. Bronchoscopic balloon dilatation action was successful.

Discussion: Endobronchial tuberculosis is a tuberculous infection that affects the tracheobronchial tree. It can be treated with minimally invasive procedures like bronchoscopy or surgical interventions. If the stenosis is mild or moderate, several procedures such as balloon dilatation, stents, laser photoresection, argon plasma coagulation, and cryotherapy are often performed. Bronchoscopy balloon dilatation nowadays has become a more preferred treatment option for tracheal and bronchial stenosis because it may be areliable and effective method.

Conclusion: The BDD procedure in this patient showed good results. This procedure is fast, easy, safe, minimally invasive, and the symptoms resolve quickly. It can be concluded that BBD is a safe and effective therapy for TB-related bronchial stenosis, but the long-term effects of the procedure remain to be monitored.

Keywords: bronchial stenosis, bronchoscopy, tuberculosis

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB). Transmission occurs through droplets between individuals and generally attacks the lungs, although it can occur in extrapulmonary cases. Pulmonary

TB is a common disease worldwide. In terms of prevalence, the South-East Asia Region contributes to 39% of sufferers worldwide. It is estimated that around 3.4 million new cases of TB are reported in this region each year.[1]

Indonesia has the second-highest number of TB cases worldwide, after India. Ten to forty percent of people with pulmonary TB also suffer from endobronchial tuberculosis (EBTB), which is a tracheobronchial infection.[2] It is difficult to determine the precise incidence of EBTB since many individuals with pulmonary TB do not undergo tests like a CT scan or bronchoscopy to help aid the diagnosis. The second decade of life is when EBTB most often occurs. Productive chronic cough is the most typical symptom.[3]

There are multiple theories about the etiology of EBTB, such as implantation from adjacent parenchyma, erosion through infected lymph nodes, and peri-bronchial seeding by hematogenous spread.[2] Histologically, edema of the mucosa with submucosal lymphocytes and obstruction constitute the first insult, followed by granuloma development and ulceration. Stenosis will eventually occur due to fibrous hyperplasia and contracture development.[4]

Bronchial stenosis is one of the complications of EBTB, but most patients will not experience severe bronchial stenosis or obstruction. The incidence of bronchial stenosis related to TB is about 68%, and it is thought to be the most common cause of tracheobronchial stenosis in Asian countries.[5]

This complication is irreversible despite adequate anti-tuberculosis drug administration. It is frequently encountered in women and affects the left bronchus.[6] The left main bronchus is anatomically closer to the aortic arch and mediastinal lymph nodes; infection of the lymph nodes will spread more quickly to the left bronchus than to the right bronchus. This stenosis will lead to specific symptoms like dyspnea or stridor, retention pneumonia, retention of secretions, and atelectasis.

This is a case of a patient who underwent interventional bronchoscopy with stenosis of the left main bronchus and a history of TB.

CASE

A 29-year-old woman was diagnosed with pulmonary TB about halfway through her pregnancy in 2020. She had an increasing cough and shortness of breath. Anti-tuberculosis drug treatment was initiated without a confirmed chest x-ray (CXR) due to her pregnancy. After six months of medication, the doctor stated that she was clinically cured without CXR evaluation because she was still pregnant.

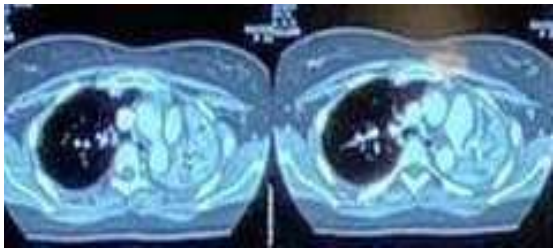

Figure 1. A chest CT scan shows left main bronchial stenosis and atelectasis of the left lung

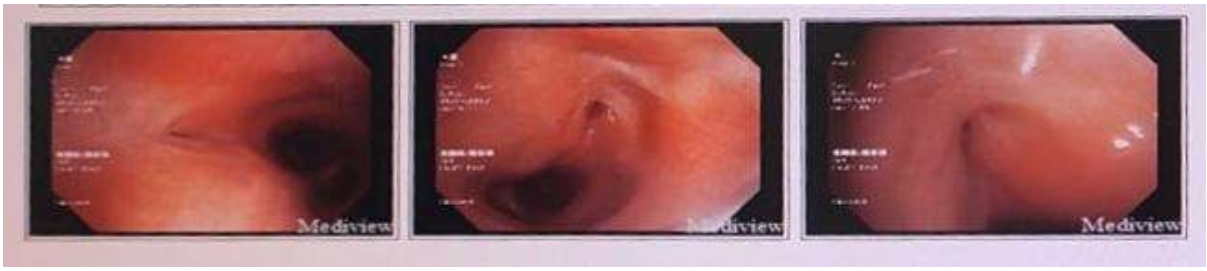

Figure 2. Bronchoscopic image demonstrating that there is stenosis of the left main bronchus

About two years later, she complained of a persistent cough for two weeks prior to hospitalization.

Chestauscultation found absent breath sounds in the left lung. Oxygen saturation was at 99% in room air. The laboratory results were normal. The patient underwent a CXR, which revealed left lung atelectasis, and a chest CT scan showed complete stenosis of the left side of the main bronchus (Figure 1).

The patient was advised by a pulmonologist for further bronchoscopic evaluation. A recent bronchoscopy procedure reported stenosis of the left main bronchus, preventing the scope from passing through (Figure 2). There was no sign of a mass lesion or mucus blockage. Mycobacteria or other suspicious organisms were negative in bronchial washings. GeneXpert MTB/RIF test result was also negative.

After bronchoscopy procedure, the patient was evaluated with a three-dimensional computed tomography reconstruction (Figure 3 A-C). The result was total stenosis on the left main bronchus. It was decided to attempt bronchoscopy balloon dilatation to treat the lung obstruction.

She was referred to Persahabatan Hospital, a National Respiratory Referral Center, for pulmonary intervention. The procedure was done under general anesthesia.

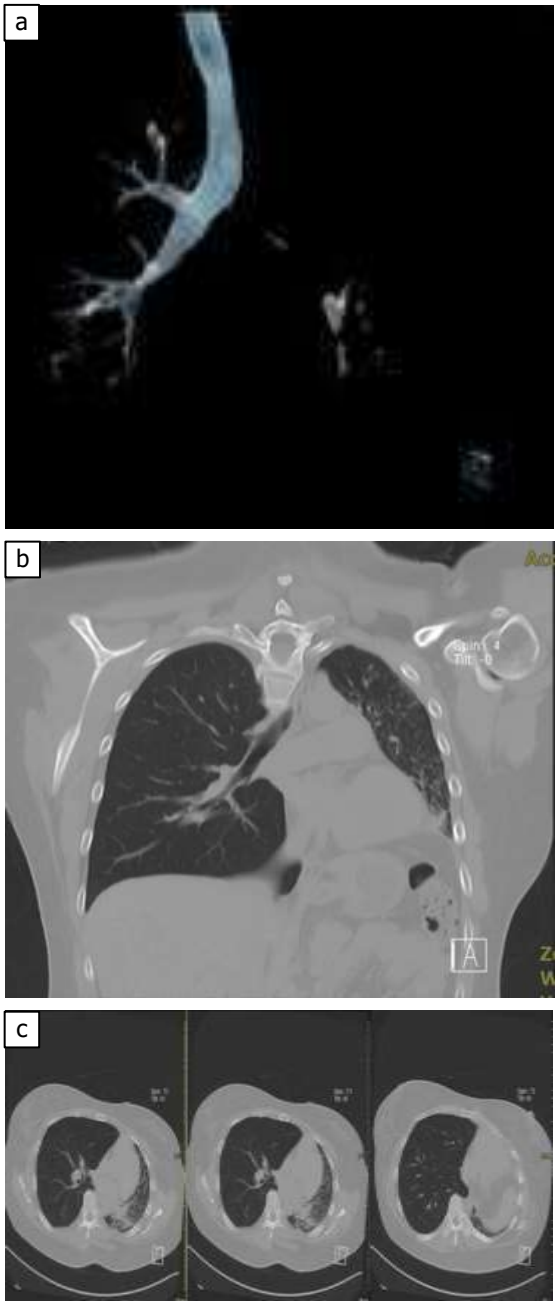

Figure 3. (a) A 3D-CT scan of the lung demonstrates stenosis of the left main bronchus; (b) Axial chest CT scan; (c) Coronal view

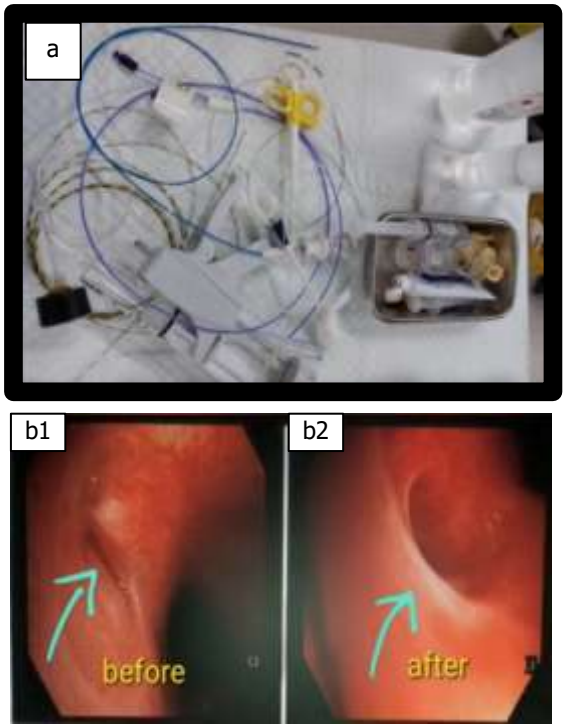

Figure 4. (a) Single-Use Pulmonary Balloon Dilatation Catheter (b1) Left main bronchus before procedure. (b2) After the procedure

By stretching and widening the bronchial wall, the balloon dilates the stenotic left main bronchus (Figure 4A-B2). The procedure was completed successfully without any complications. Her symptoms improved after the treatment. Immediate follow-up CXR showed no sign of atelectasis. She was discharged and scheduled for a chest CT scan evaluation in six months.

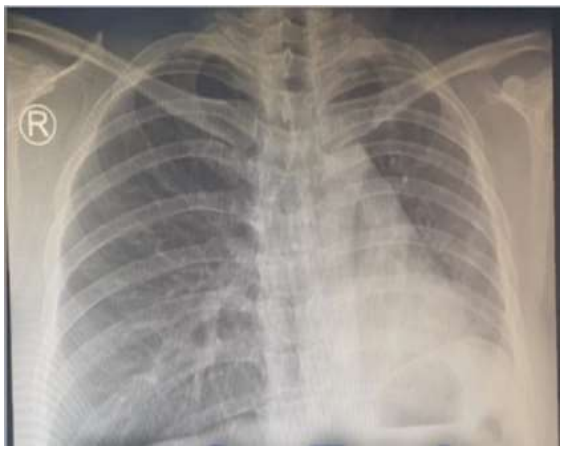

Figure 5. A post-procedural CXR revealed that the atelectasis on the left lung had resolved

DISCUSSION

Endobronchial tuberculosis (EBTB) is a tuberculous infection that affects the tracheobronchial tree. It can occur as a result of direct infiltration from the lungs, implantation of microorganisms through secretions or sputum, hematogenous dissemination, lymphatic dissemination, or erosion of lymph nodes within the trachea or bronchi.[7]

It is most common found in women in their second and third decades of life. Considering that bronchial lumen diameter is significantly smaller in women than in men, retained sputum can make the bronchi vulnerable to mycobacterial infection. It explains why the disease has a higher prevalence in women.[6] Severe bronchial stenosis frequently occurs early on, during, and after the treatment of EBTB.

There are several theories that explain the cause of airway stenosis in EBTB, such as destruction of bronchial cartilage by mural tuberculoma obstructing the bronchial lumen, intramural caseous material, cicatricial annular stricture caused by fibrosis, and destruction of bronchial cartilage by caseous necrosis.[8]

The first two etiologies are mostly seen in active EBTB. After completion of anti-TB treatment, intramural inflammation and caseous material will be replaced by fibrotic tissue, which will then result in stricture of the bronchial lumen. Furthermore, inflammation in the bronchial lymph nodes will worsen the condition of

fibrosis. Various techniques have been introduced to restore airway patency.[7]

It can be treated with minimally invasive procedures like bronchoscopy or surgical interventions. If the stenosis is mild or moderate, several procedures such as balloon dilatation, stents, laser photoresection, argon plasma coagulation, and cryotherapy are often performed.[8] The surgical treatment should be considered individually based on the severity of the stenosis and potential risks to the pulmonary parenchyma. It could vary from surgical bronchoplasty to lobectomy or pneumonectomy.

In recent years, advances in bronchology and the development of numerous invasive diagnostic and therapeutic approaches known as interventional pulmonology have opened up fresh opportunities in the field of lung diseases. Currently, minimal intervention therapy with bronchoscopy procedure has been widely used to treat this disease. It benefits a small percentage of people who are not eligible for surgery (i.e., multiple lesions, long segments, and inadequate pulmonary reserves).[9]

Bronchoscopy balloon dilatation (BBD) nowadays has become a more preferred treatment option for tracheal and bronchial stenosis. It may be a reliable and effective method to dilate the obstructed bronchus by expanding and stretching the fibrotic tissue in the bronchial wall.[10] This technique has a success rate ranging from 6.3% to 73%.[11]

If balloon dilation fails to resolve the stenosis, a stent should be placed as quickly as possible. BBD is associated with lower morbidity and mortality rates. There are various advantages to bronchoscopic balloon dilatation over other procedures. It is simple, fast, well-tolerated, less invasive, and can be done under general or local anesthesia. It also gives immediate relief and increases airway dimensions while improving lung function.[10] The most common side complication of this procedure is pneumothorax, mediastinal emphysema, laceration of the tracheal and bronchial walls, and hemoptysis.[12]

Based on our patient's case, although it was not detected until the stenosis became symptomatic, it is most likely that the stenosis was caused by EBTB, considering our patient's history of TB in 2020. Diagnosis using CT imaging and bronchoscopy remain useful techniques in patients with pulmonary TB to identify potentially sequelae such as bronchial stenosis.

CONCLUSION

Bronchoscopy balloon dilatation (BDD) is a first-line therapy in this case because of its advantages and effectiveness. This procedure was performed without a stent because using airway stents in TB sequelae carries several risks, such as migration, mucostasis, and the development of granulation tissue. This will cause a recurrence of bronchial stenosis and possible invasive surgical procedures in the future. Bronchoscopy balloon dilatation has become widely recognized as a successful treatment for

benign bronchus stenosis, although the procedure's long-term effects remain to be monitored.

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Case Report

A Rare Case of Completely Healed Pneumomediastinum Due to Asthma Exacerbation in A Young Male Patient

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Abstract

Background: The term pneumomediastinum (PNM) refers to the presence of air within the mediastinal cavity. This illness is uncommon but can arise in adolescents with severe asthma attacks. In children aged 5 to 34, the incidence of pneumomediastinum after an acute asthma attack is 1 in 25,000. Men made up the majority of patients (76 percent of all cases). Pneumomediastinum can be diagnosed with the assistance of a chest CT scan.

Case: A young man was diagnosed with pneumomediastinum due to an acute asthma attack in this case report. Symptoms of uncontrolled asthma include shortness of breath that worsens with wheezing, chest tightness, and a nonproductive cough. Since the age of 12, the patient in this instance has been receiving salbutamol inhalers. The physical examination revealed polyphonic lung respiration and subcutaneous crepitus in the neck, shoulders, and anterior chest. With adequate management of an asthma episode, pneumomediastinum recovers spontaneously, followed by recurrent symptomatic status, physical examination, and radiography examination.

Discussion: Acute asthma exacerbations are one of the factors that can lead to spontaneous pneumomediastinum, in which mediastinal air can permeate the tissue and generate a pneumothorax, and if there is air in the subcutaneous area, it can lead to subcutaneous emphysema.

Conclusion: Pneumomediastinum was a rare incidence, pulmonologists examining young adults with acute asthma exacerbations should evaluate for pneumomediastinum. In usual asthma therapy, a chest CT-scan is essential to screen for pneumomediastinum.

Keywords: asthma attack, chest CT-scan, secondary pneumomediastinum

INTRODUCTION

A morbidly obese young man was brought to the emergency room of Haji Adam Malik General Hospital due to asthma exacerbation and pneumomediastinum. This page describes the case, how to spot the symptoms, and how to decide the diagnosis and therapy.

Another word for the presence of air in the mediastinum is pneumomediastinum.[1,2] Pneumomediastinum is a rare disorder that occurs in 1/100,000 spontaneous births or 1/44,500 emergency department visits, with a higher incidence in children (1/800-1/15,500). Others predict a prevalence of 1 in 25.000 among individuals aged 5 to 34. The overwhelming majority of patients are male (76% of all cases). Multiple physicians have discovered that pneumomediastinum is more prevalent than previously believed as a result of underdiagnosis.

If a causal factor is identified, the mediastinal air is categorized as secondary pneumomediastinum. Pneumomediastinum can be induced by respiratory disorders, particularly asthma or upper respiratory infection exacerbations accompanied by a severe cough. Common risk factors include asthma, interstitial lung disease, COPD, bronchitis, lung cysts, lung cancer, frequent vomiting, and trauma (including iatrogenic diseases). Other drugs, including cocaine, marijuana, and methamphetamine, have been linked to pneumomediastinum in recent years.[2–5]

Spontaneous pneumomediastinum (SPM) (Figure 1) is the introduction of air into the mediastinum of otherwise healthy individuals in the absence of a definite reason, such as surgery, air following perforation, infection, or trauma.[1]

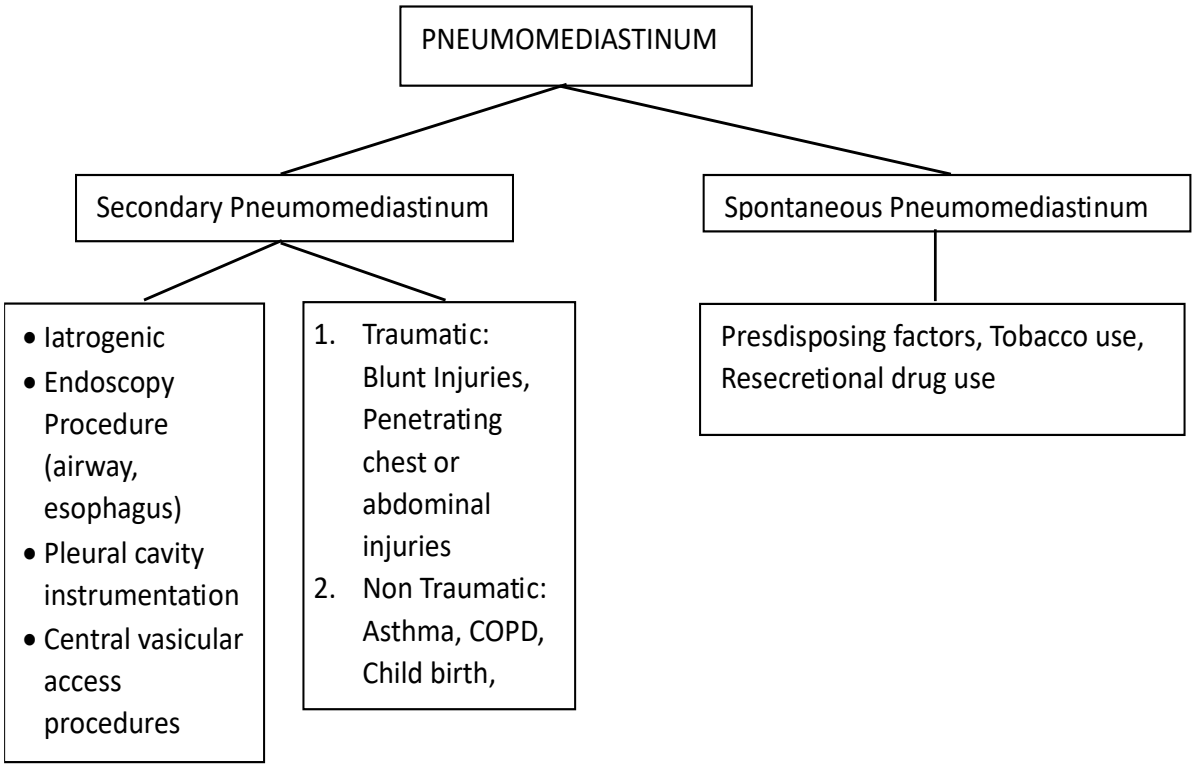

Figure 1. Classification of pneumomediastinum

Air in the mediastinum is also considered spontaneous if mechanical ventilation or the Valsalva maneuver are not employed. This phenomenon is observed in a significant proportion of persons for whom the source of pneumomediastinum cannot be determined.[6]

Pneumomediastinum is also induced by a difficult valsalva maneuver, delivery, rapid ascent during diving, foreign bodies entering the airway and lungs, anorexia, sporting activities, and inhaling toxic fumes. Despite the identification of a possible causative factor, multiple investigations have enabled the usage of the broader term SPM.[1,6] The lack of clarity has caused debate among authors, as it is obvious that secondary pneumomediastinum is more common than SPM.

The first Pneumomediastinum reports date back to 1819 by Laennec, who described this condition as secondary to trauma.[1–3] Hamman described a postpartum patient with subcutaneous emphysema and pneumomediastinum, a condition that is now known as the Hamman syndrome.[6–8]

A sudden increase in intrathoracic pressure results in an increased intra-alveolar pressure, leading to alveolar rupture, with leakage of air along mediastinal planes. Hamman further described the crepitus heard with the heartbeat on chest auscultation, the pathognomonic sign of spontaneous pneumomediastinum, known as Hamman's sign. Spontaneous pneumomediastinum is mostly seen in young male patients. Several cases of pneumomediastinum in asthma attack have been reported.[6–8]

An abnormal increase in pressure in the mediastinum, which, like the pleural cavity, is susceptible to low and negative pressure, causing air dissection between the mediastinal structures that support the mediastinum, is also a possible cause of pneumomediastinum. A sudden decrease in intravascular pressure can also result in a pressure gradient in the perivascular regions.[1]

By means of loose alveolar fatty tissue in the neck, upper abdomen, or skin, air can escape (subcutaneous emphysema). Air can also enter the pleura and peritoneum, leading to pneumothorax and pneumoperitoneum, respectively.[9]

Acute asthma exacerbations are one of the factors that can lead to spontaneous pneumomediastinum, in which mediastinal air can permeate the tissue and generate a pneumothorax, and if there is air in the subcutaneous area, it can lead to subcutaneous emphysema.[10] Severe asthma exacerbations are life-threatening medical crises, and aggravating conditions such as pneumomediastinum must be assessed during a physical exam.[11]

Management of asthma exacerbations and pneumomediastinum consequences consists of proper management of asthma exacerbations followed by re-evaluation of symptom status and physical inspection of any pneumomediastinum abnormalities. Upon resolution of an asthma exacerbation, the pneumomediastinum often vanishes.[4]

CASE

A 29-year-old male with an overweight BMI was referred to the emergency room of Haji Adam Malik General Hospital due to asthma exacerbation characterized by increased shortness of breath (SOB), wheezing, chest tightness, and a non-productive cough. His asthma was not under control.

This patient, who has suffered from asthma since the age of 12, regularly used a salbutamol inhaler. He asserted that he had never been reviewed by a physician because the problem was always use a salbutamol inhaler. Since childhood, he has occasionally experienced shortness of breath, which was triggered by household dust, cigarette smoke, car exhaust, and fatigue.

In the last two weeks, there have also been reports of coughing and drying up of mucus. No cases of fever were detected. No night sweats were found. There is an asthmatic grandmother in the family. He has been exposed to dust and cigarette smoke as a contractor (rental of musical instruments) for the previous five years. Patient frequently experiences shortness of breath, which hinders activities and sleep, and wakes up 1-2 times a week at night due to shortness of breath.

The patient was hemodynamically stable, conscious, had a blood pressure of 110/70 mmHg, heart rate of 112 bpm, respiratory rate of 32, normal temperature, room air oxygen saturation of 92%, and a nasal oxygen saturation of 97% at 4 lpm.

On examination, he was tall, obese, alert, oriented, and talked in coherent phrases. His BMI was greater than 25. The examination of the patient's respiratory system indicated polyphonic breathing in both lungs and crepitations in the neck, shoulder, and anterior chest.

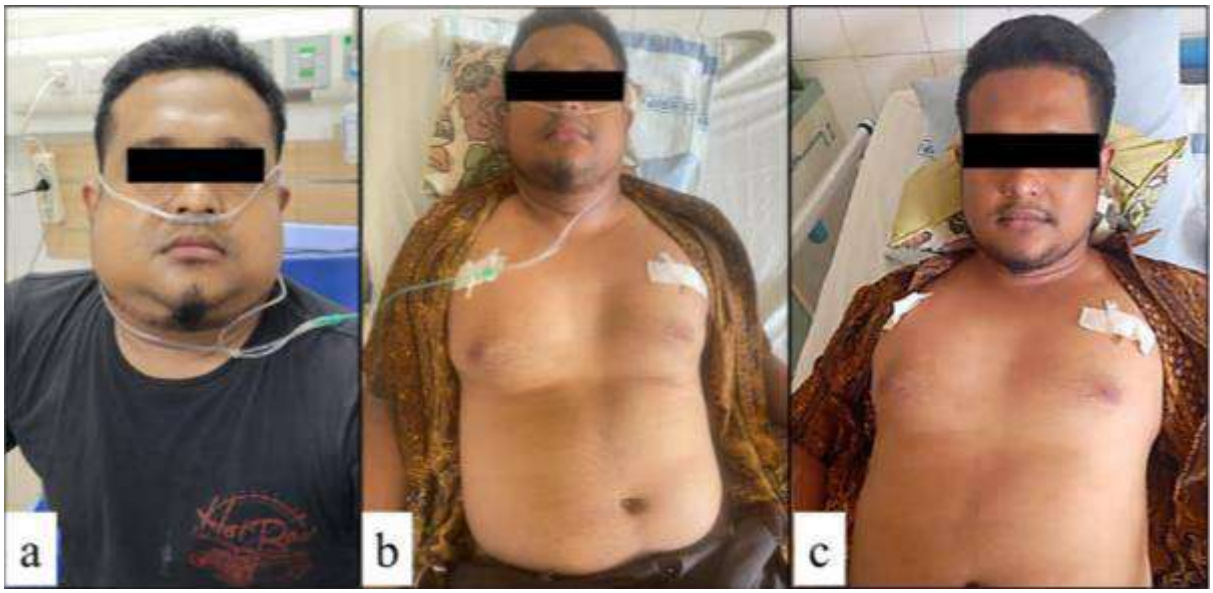

Figure 1. (a) Day 1 ER. b) Day 7 in the ward. c) Day 9 in the ward. Resolving the clinical appearance of facial and neck edema seen in clinical examination

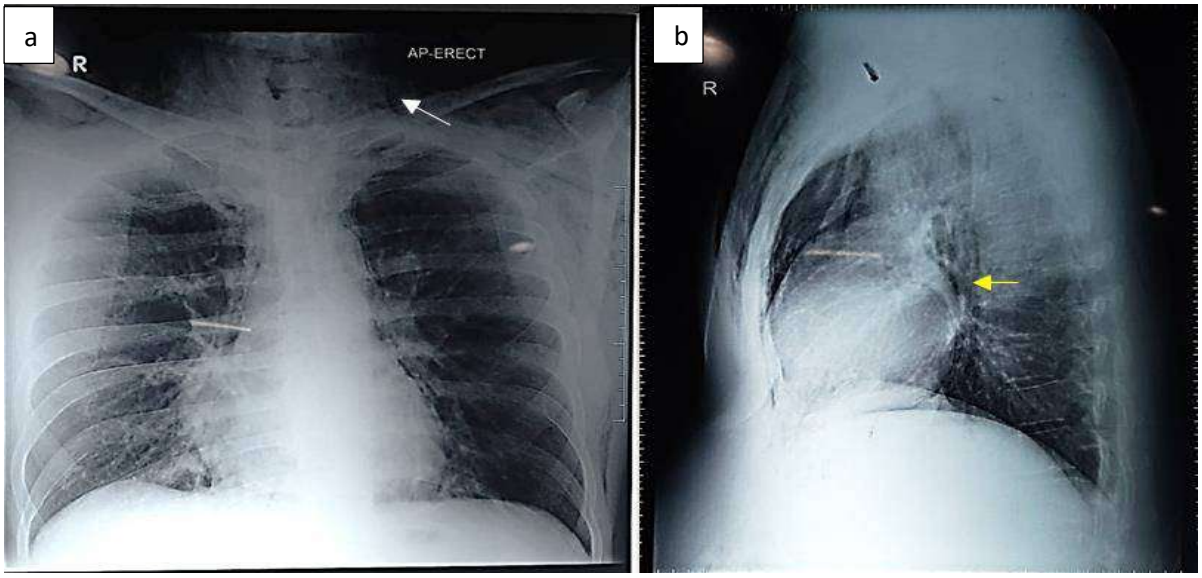

Figure 2a. Subcutaneous emphysema (white arrow) in the neck and supraclavicular region; and 2b. Free air in the mediastinum (yellow arrow)

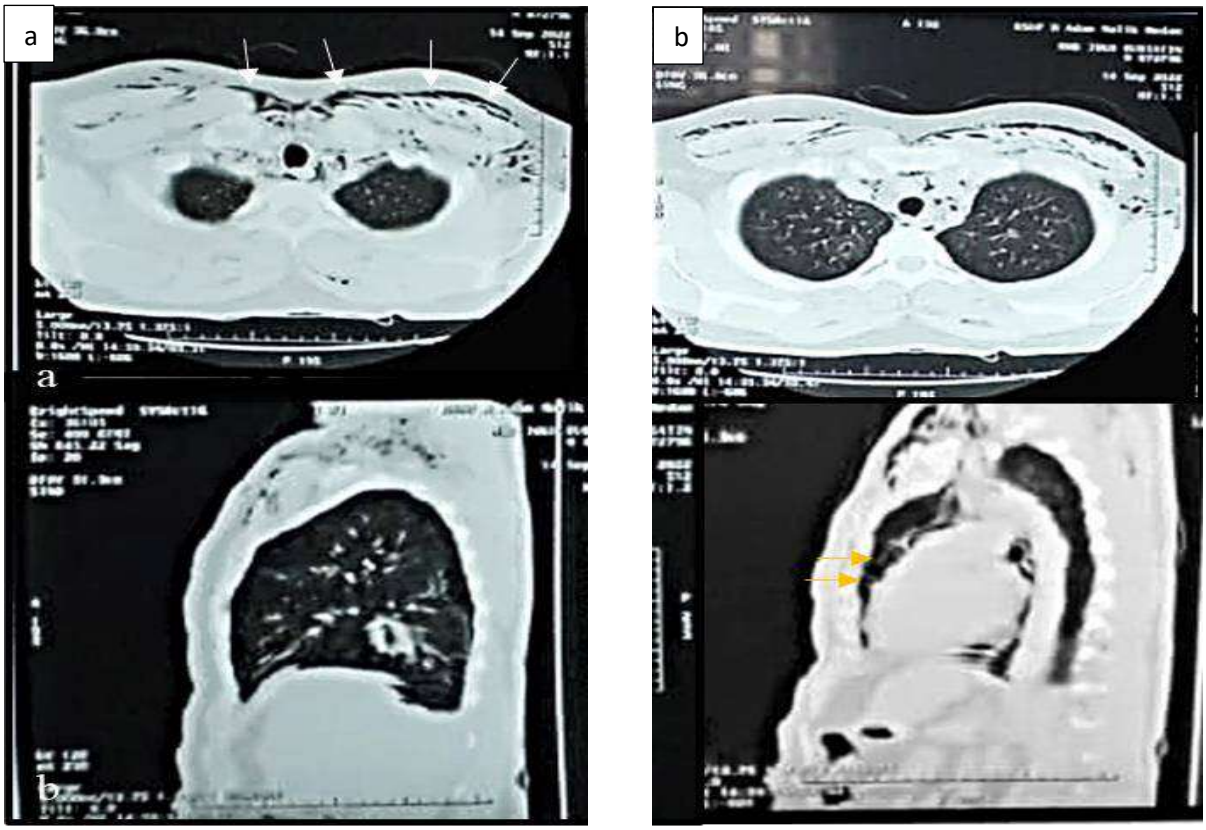

Figure 3. Thoracic computed tomography (CT) (a) axial view and (b) sagittal view.
Subcutaneous emphysema extending to the neck and chest wall (white arrow) and free air in the anterior part of the mediastinum (yellow arrow) where pneumomediastinum was confirmed and pneumothorax was excluded.

The patient was nebulized with salbutamol in the emergency department, and the blockage was treated with inhaled salbutamol 2.5 mg and budesonide 1 mg every 20 minutes for 1 hour. Salbutamol 2.5 mg for 8 hours and budesonide 0.5 mg for 12 hours were continued concurrently.

The blood count revealed a predominance of neutrophils, normal eosinophils, normal electrolytes, and high

IgE, with a total IgE level of 389.2 (the normal range was less than 100). The EKG revealed a sinus rhythm. The arterial blood gases in the chamber demonstrated uncompensated respiratory acidosis (pH=7.33; pCO_2=51.0; base excess=0.3; and HCO_3=26.9).

Chest radiography (Figure 2) revealed normal lungs with air in the mediastinum and no pleural lines, devoid of bilateral supraclavicular subcutaneous emphysema and pneumomediastinum. On a chest CT scan (Figure 3), the images of the mandible, colli, supraclavicular, and right and left anterior chest wall s were different. The description also showed the extent of the surrounding environment. No consolidations, nodules, or masses were observed in either lung; the mediastinum had a healthy appearance.

There are an improvement of CO_2 collection in the BGA series two days after treatment of respiratory acidosis. The IgE test revealed a total of 389.2.

This patient was subjected to a radiological examination, which pointed out pneumomediastinum and subcutaneous emphysema (Figures 2a and b). From there, PFT was also carried out with spirometry results: FEV_1/FVC=50.27; FEV_1=21.7 percent of prediction, FEF_{25-75}=10.3, and the conclusion was: airway obstruction due to asthma exacerbation was observed, characterized by severe obstruction with moderate restrictive disorders and small airway obstruction.

Serial CXR was performed after eight days of treatment. The patient was discharged home eight days after the subcutaneous emphysema appeared to improve. He received treatment for asthma exacerbation, hypoxia, and bronchodilator nebulization. In the emergency room, he underwent needle decompression of the front of his chest. Six days later, a CXR resulted in complete healing (Figure 3).

DISCUSSION

Pneumomediastinum is a rare clinical condition that affects emergency department staff in hospitals. It is also known as "Hamman's syndrome" because Louis Hamman was the first to describe a series of cases with this condition.[1] It is defined by a mediastinum that is intact. The incidence of this condition is less than 1:44000, or approximately 1/25,000 among those aged 5 to 34; the majority of patients (70%) are male.

However, the incidence may be higher due to the fact that many patients do not visit the emergency room or are misdiagnosed, so mild symptoms could be attributed to muscle discomfort or concerns. Pneumomediastinum is a rare consequence of asthma exacerbation, with an incidence between 0.2% and 0.3%. However, if this problem is not discovered and treated promptly, it can have fatal consequences. The potential consequences of tension pneumomediastinum require strict clinical surveillance in the critical care unit.[6,7]

About 25% of people with pneumomediastinum do not experience coughing episodes. The exact pathophysiology is unknown. Asthmatics,

on the other hand, may experience subsequent air freezing due to narrowing of the airways or mucus retention, especially after minimally repeated coughing.[12]

This creates an increase in alveolar pressure, which causes rupture of the alveoli and allows air to enter the interstitial spaces of the lungs. When the mediastinum is removed, the air leakage may persist along the perivascular sheath, resulting in mediastinal emphysema.[12]

Chest CT-scans are becoming increasingly important for diagnosing pneumomediastinum. Vianello from Italy examined 45 consecutive adult patients diagnosed with severe acute aggravation of asthma with probable pneumomediastinum. Pneumomediastinum was observed in five patients (11%); one instance was detected by CXR and four patients were detected solely by chest CT scan.[13]

If all significant causes have been ruled out, the treatment of pneumomediastinum is typically conservative and requires simple sedation, anti-anxiety medications, oxygen, and analgesics.[7,14] Usually, a 24-hour observation requires hospitalization, as in our case. Rarely, compression of large vessels or trachea may require a videothoracotomy or even a thoracotomy. Extensive subcutaneous emphysema necessitates modest surgical procedures, such as a skin incision, a small subcutaneous drain, or even a chest drain. In all circumstances, post-discharge follow-up is recommended.[15,16]

In this scenario, the long-term objective of treatment should be asthma control and prevention of exacerbation. In this example, there were both clinical and radiographic indications of subcutaneous emphysema, but solely radiographic indications of pneumomediastinum. When supportive care is provided and effective asthma control is achieved, this patient's symptoms and clinical presentation will improve within a few days.

A case described by Ojeda et al suggested that asthma and tracheal diverticulum might have a role in the etiology of pneumomediastinum. We recommend including latent pneumothorax in the differential diagnosis for patients with an acute asthma attack who did not respond to standard treatment.[15] Subcutaneous emphysema is a disorder characterized by the presence of air in the tissue beneath the skin.[9]

As a result of chest compressions, massive air collection can be life-threatening, resulting in progressive hypoxemia and hypercapnia. Other complications of pneumomediastinum include substantial subcutaneous emphysema or pneumothorax, which frequently necessitate minimal treatment, such as a skin incisions and chest tube drainage. Air can also be cut off in the rear of the pharynx and peritoneum, producing pain and difficulty breathing. Rarely, air can escape between the mediastinum and the upper spine, resulting in the formation of a bronchus (free air in the spinal canal).[9,16]

CONCLUSION

A young man was diagnosed with pneumomediastinum due to an asthma episode. Although this was a rare incidence, pulmonologists examining young adults with acute asthma exacerbations should evaluate for pneumomediastinum. In usual asthma therapy, a chest CT-scan is essential to screen for pneumomediastinum and rule out other probable causes of pneumomediastinum. Requirements include conservative treatment and treatment of the underlying condition, along with routine monitoring and follow-up. Early detection can prevent subsequent complications and result in a positive prognosis.

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Literature Review

Diagnosis and Management for Pulmonary Tuberculoma

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Abstract

Pulmonary tuberculoma, prevalent particularly in tuberculosis (TB)-endemic regions, often appears as a solitary nodule of less than 30 mm, or a tumor of more than 30 mm on radiological examinations. It may also present with a combination of abnormalities, such as multiple nodules with infiltration or pleuritis. Benign solitary pulmonary nodules represent up to 25% of all resected solitary pulmonary nodules, with approximately 5-24% of these identified as pulmonary tuberculoma post-surgery. This condition is prevalent particularly in TB-endemic regions, and must be considered while determining the diagnosis, especially for patients at high risk for lung cancer. Modalities for diagnosing pulmonary tuberculoma include chest radiography, USG, CT scan, PET scan and bronchoscopy with transbronchial biopsy. The treatments for pulmonary tuberculoma are anti-TB drugs and surgery. Pulmonary tuberculoma responds poorly to anti-TB drugs and requires long-term treatment. Surgery is performed when the diameter of tuberculoma still increases after adequate anti-TB treatment.

Keywords: diagnosis, management, pulmonary tuberculoma

INTRODUCTION

Pulmonary tuberculoma is a prevalent condition, although specific data on its prevalence in Indonesia is not currently available. Clinically, the symptoms and signs of pulmonary tuberculoma do not differ from those of lung cancer, making it challenging to differentiate between the two. The extent and characteristics of the abnormalities play a crucial role in the diagnosis. Pulmonary tuberculoma is often found as a solitary pulmonary nodule on radiological examination. A solitary pulmonary nodule is a single, round, or oval nodule with well-defined margins and a size of ≤ 30 mm. In tuberculosis (TB)-endemic countries, pulmonary tuberculoma is common and must be differentiated from other causes of solitary pulmonary nodules.[1–3]

In countries with low number of TB cases, a solitary pulmonary nodule is a risk of malignancy. Solitary pulmonary nodules can be benign (pulmonary hamartoma, hemangioma, inflammatory pseudotumor, lymph node hyperplasia and tuberculoma) or malignant (squamous cell carcinoma, adenocarcinoma and bronchoalveolar carcinoma). More than 25% of solitary

pulmonary nodules subjected to surgical resection turn out to be pulmonary tuberculomas. Invasive procedures such as transthoracic biopsies and surgery are often required to diagnose and treat pulmonary tuberculoma.[1–3]

Pulmonary tuberculoma is a rare manifestation of pulmonary TB. Approximately 6-9% of pulmonary TB infection develop into tuberculoma. Tuberculomas are commonly found in the form of cavities or calcifications, have well-defined margins and are usually located in the upper lobes of the lungs. Tuberculoma most often occurs between the ages of 17 to 35, with the youngest being 15 years and the oldest 51 years, and are more common in males than females. Most tuberculoma cases do not cause symptoms and are often found during radiological examinations for lung cancer screening in high-risk lung cancer groups. As many as 58% of pulmonary tuberculoma is suspected as primary lung cancer based on radiological examination results.[4–6]

Tuberculosis is included in the ten leading causes of death worldwide. Based on geographical area, the highest number of TB cases in the world are in Southeast Asia (44%), Africa (25%) and the West Pacific (18%). Eight countries with the highest number of TB cases, covering two-thirds of all TB cases in the world are India (26%), China (8.5%), Indonesia (8.4%), Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%). Tuberculosis is the main cause of death from infectious diseases, ranking above Human Immunodeficiency Virus (HIV). In 2019, it was estimated that there would be 845,000 new cases of TB in Indonesia, with 19,000 among them also yield positive HIV results. The death rate among TB patients is 92,000 for patients with negative HIV and 4,700 among the positives.[7,8]

The clinical signs and symptoms of TB may vary between patients. Radiological examination may shows either miliary TB, TB pleuritis, tracheobronchial TB or tuberculoma. Pulmonary tuberculoma is a homogeneous round-shaped opacity, well-defined and caused by Mycobacterium tuberculosis (MTb). Pulmonary tuberculoma is also known as Assmann's focus, solitary or round focus, coinage lesion, tuberculous nodule and caseous nodule. This nodule resembles a tumor and originates from enlarged caseous tubercles in the lung.[2,5,9]

Tuberculoma has a diameter ranging from 1 to more than 10 cm. Tuberculomas are most often found in the lungs and central nervous system. It can be found in primary or post-primary TB cases. The inoculation of MTb in bronchioles causes an immune reaction mediated mainly by alveolar macrophages and forms a granuloma. Granuloma can develop into a tuberculoma by growing in size and covered by connective tissue, with caseous necrosis in the middle.[2,5,9]

PATHOGENESIS OF PULMONARY TUBERCULOMA

The pathogenesis of TB is closely related to the host's immune response and

the number of inhaled droplet nuclei. Only some people exposed to MTb will develop TB disease. Droplet nuclei can reach the respiratory bronchioles and alveoli. The MTb bacteria that enter through the airways will latch onto the lung tissue and form pneumonia nests called primary foci. The primary focus can occur anywhere and causes inflammation of the lymph passages leading to the hilum (local lymphangitis) and then enlargement of the hilar lymph nodes (regional lymphadenitis). The primary focus and regional lymphangitis are known as the primary complex.[8]

Primary complexes will undergo one of several events, including healing without any defects, leaving little scars (such as Ghon nests, fibrous lines and calcification nests in the hilum) or spreading either through *percontinuitatum* spread to the surrounding tissue, bronchogenic spread either on one or both sides of the lung, lymphatic spread to the lymph nodes or hematogenous spread through bloodstream. The severity of hematogenous spread depends on the body's immune resistance and virulence of the bacteria themselves. This spread might cause extrapulmonary TB and result in either recovery with sequelae or death.[8]

Primary TB infection begins with inhalation of MTb into the lungs, then phagocytosis of MTb by alveolar macrophages occurs and infection can progress with or without lung damage. Among 90-95% of healthy individuals will experience a latent infection for several years and potential for reactivation. During the active infection phase, infected macrophages cause an inflammatory response and form granulomas. Activation of the adaptive immune system causes macrophages to become giant cells (Datia Langhans cells), foamy macrophages surrounded by T and B cells. Other macrophages phagocytose dead macrophages.[10]

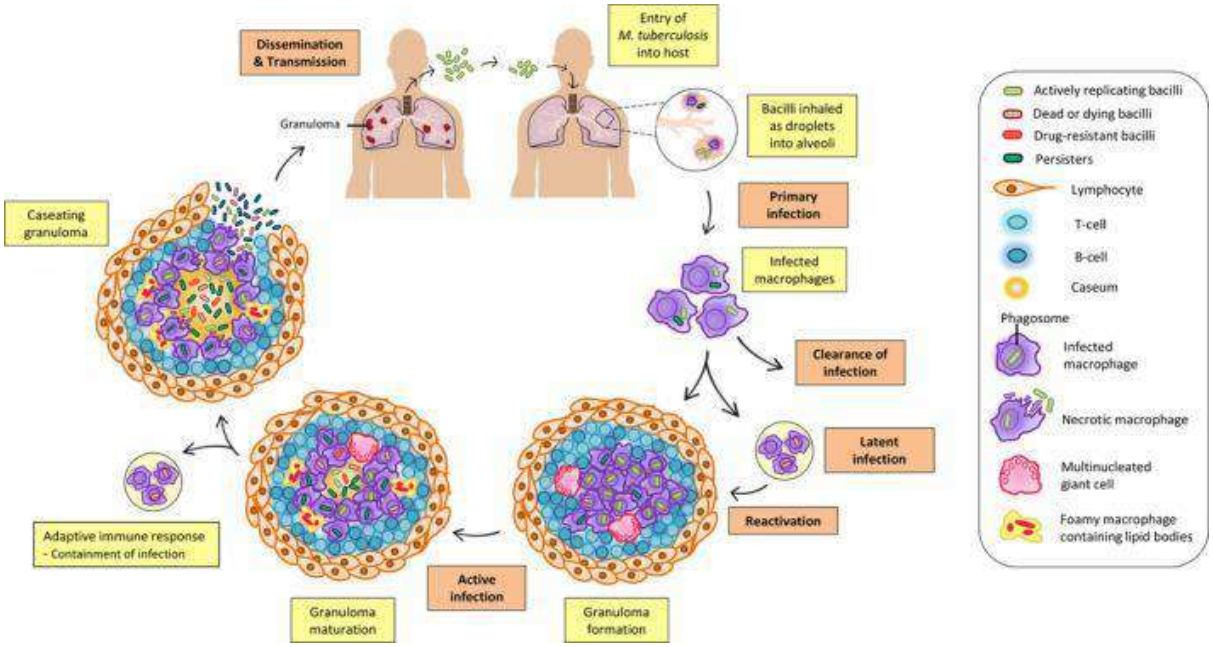

Figure 1. Pathogenesis of tuberculosis[10]

DIAGNOSIS OF PULMONARY TUBERCULOMA

Diagnosis of tuberculoma is challenging, not only because it requires invasive procedures such as needle aspiration or transthoracic biopsy and open thoracotomy, but also because it can be accompanied by cancer in some rare cases. In general, patients with tuberculoma can be asymptomatic. Some cases of tuberculoma can yield symptoms such as chest pain, cough with or without blood, body weakness, decreased appetite or symptoms of TB in general. There may be a history of TB treatment or previous TB contacts. Physical examinations might show no abnormalities.[4,8,9]

Microbiological diagnosis of pulmonary tuberculoma is determined through the findings of acid-fast bacteria (AFB) on microscopic examination or culture of the sputum, AFB from bronchoalveolar drainage samples or positive results in polymerase chain reaction (PCR) testing. Research conducted by Sochocky et al stated that 17 out of 30 tuberculoma cases showed positive results of AFB in sputum culture. The tuberculin test can be performed to rule out the differential diagnosis of lung cancer.[11]

Radiological examinations that can be carried out in the diagnosis of tuberculoma are chest radiography, ultrasonography (USG), thoracic computed tomography (CT) scan and positron emission tomography (PET) scan. Examination of the chest radiography in the posteroanterior position may show a radioopaque lesion, round or oval with flat and smooth edges with diameter around 1.5-8 cm. Tuberculoma nodules are more frequently found in the upper lobes of the lungs, can be solitary or multiple with central necrosis lesion. Other features in chest radiography that might be important in diagnosing and determining prognosis for tuberculoma are satellite nodules, calcifications and cavities. Calcifications are found in 20-30% of tuberculoma cases.[11,12]

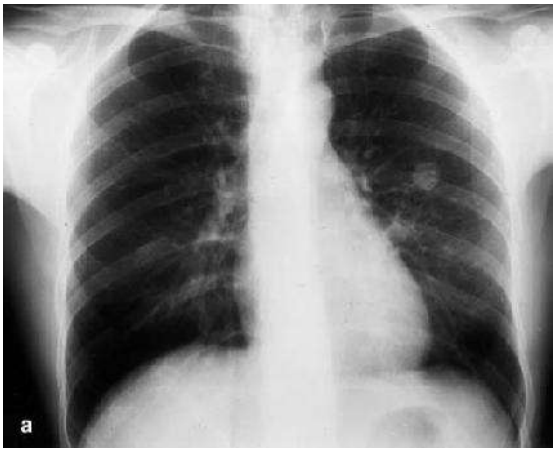

Figure 2. A tuberculoma chest radiograph showing a solitary pulmonary nodule in the left hemithorax[12]

Thoracic USG is carried out by administering contrast fluid (4.8 ml of sulfur hexafluoride added to 5 ml of normal saline) intravenously, followed by the examination itself to find patterns of contrast enhancement. A study conducted by Cao et al evaluated 21 tuberculoma patients and found three patterns of contrast enhancement on ultrasound results, namely rim enhancement (only the peripheral parts that enhance contrast but not the central), homogeneous enhancement (homogeneous echogenicity) and heterogeneous enhancement (multiple echoic and hypoechoic areas on ultrasound).[1]

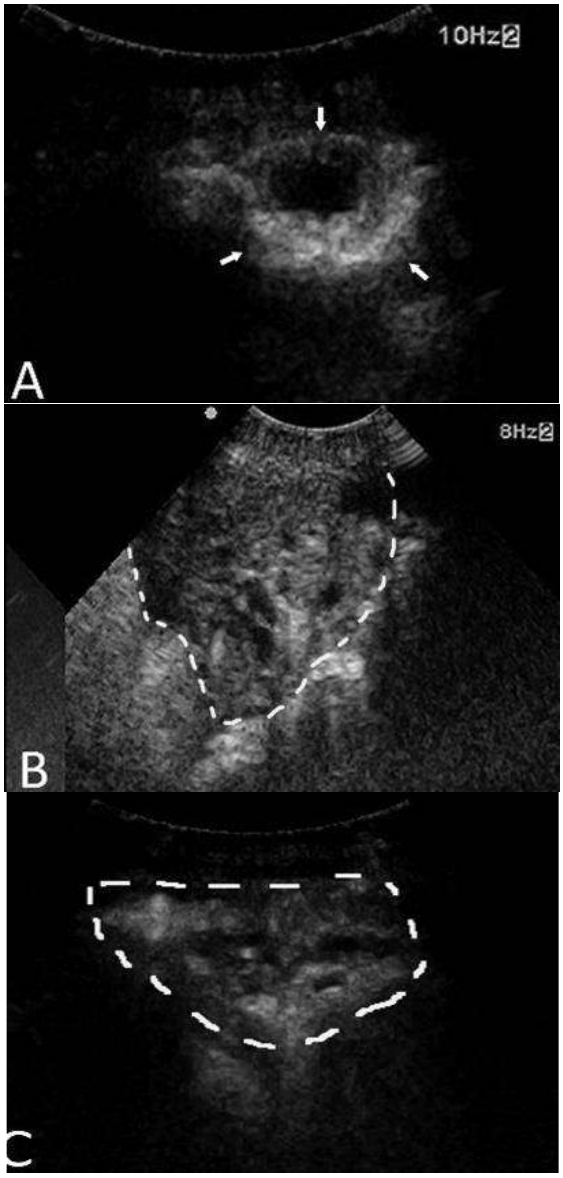

Figure 3. Tuberculoma ultrasound pattern after contrast administration. A) Rim enhancement; B) Homogeneous enhancement; C) Heterogeneous enhancement[1]

Thoracic CT scan with contrast in tuberculoma cases might generate an image similar to lung cancer or tumor metastases in the lung. A study by Totanarungroj et al described that tuberculoma lesions could be found anywhere but were more common in the upper lobes of both lungs. Compared to lung cancer, imaging of tuberculoma more commonly showed multiple lesions, smaller in size (<2 cm), round or polygonal in shape with flat and smooth edges, had satellite nodules, with less nodule enhancement and air bronchogram. Tuberculoma also possessed dense central calcifications and no internal cavities. Bronchovascular invasion also rarely happened.[13] Pulmonary tuberculoma is said to be inactive if the diameter size of the nodule on the CT scan persists for more than three months.[11]

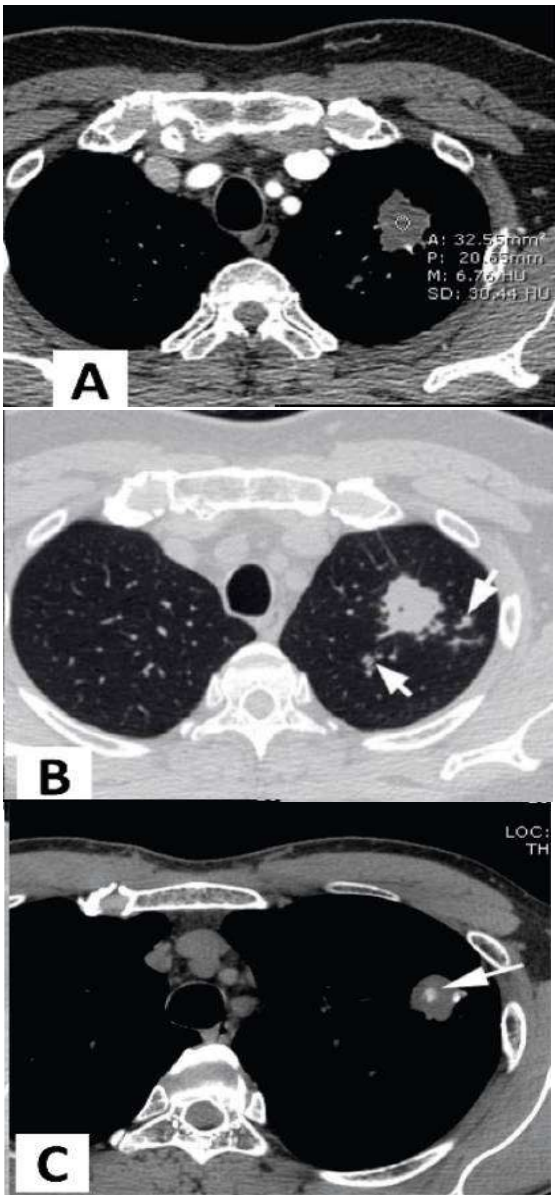

Figure 4. Thoracic CT scans with contrast in a patient with tuberculoma. A. Polygonal, non-enhancing nodule in the left upper lobe. B. Satellite nodule (arrow). C. Central calcification (arrow)[13]

Positron emission tomography is a non-invasive examination. In tuberculoma cases, PET scans are often interpreted as false positives for malignancy. Since active glucose metabolism happens during active granulomatous inflammation, this results in the accumulation of 18F-fluorodeoxyglucose (18F-FDG), similar to lung cancer. One way to differentiate tuberculoma and lung cancer is by using 11C-choline. Choline uptake in tuberculomas is lower than in cancer cells because cancer cells require choline to maintain phospholipid synthesis in cell membranes.[3,14]

Bronchoscopy is important for diagnosing solitary pulmonary nodules, both benign and malignant. The aim of bronchoscopy is to avoid thoracotomy in non-malignant cases and sampling for malignant nodules. Flexible fiber bronchoscopy and transbronchial biopsy are the most frequently performed procedures. The size of the nodule affects the success rate of the procedure.[15]

A study by Lai et al showed that the success rates for diagnosis of nodules sized <2 cm, 2–4 cm and >4 cm in diameter were 35.3%, 64.5%, and 68.8%, respectively. Flexible fiber bronchoscopy, transbronchial biopsy, bronchial brushing and bronchial washing yielded a diagnostic success rate of 40-80% for nodules >2 cm in size. Bronchoscopy findings in tuberculosis cases include granulomatous ulcers, solitary ulcers, hyperplastic lesions and fibrous stenosis.[15]

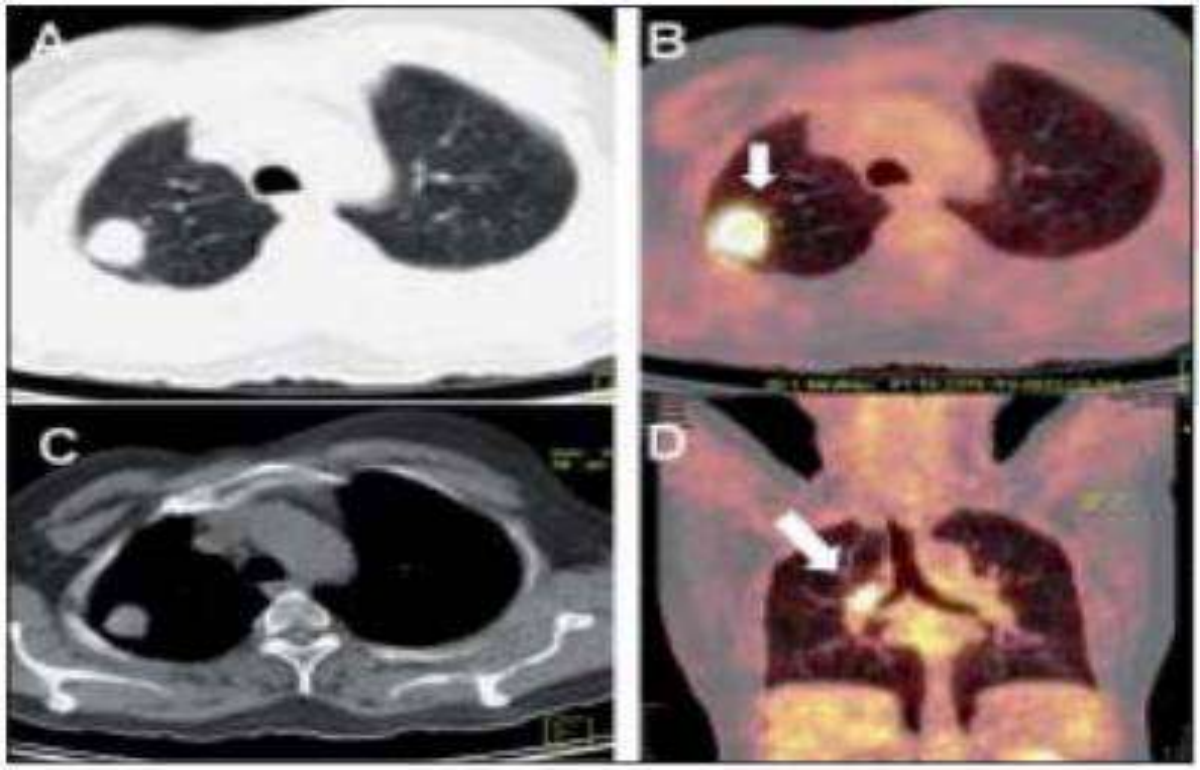

Figure 5. Pulmonary tuberculoma. Axial lung (A) and mediastinal window (C) CT images show a soft tissue density nodule in the right upper lobe of the lung. Axial (B) and coronal (D) PET/CT images reveal intense FDG uptake in the nodule (SUV_{max} of 19.0) and an enlarged right parabronchial node (arrows), suggesting a malignant neoplasm. Wedge resection and histopathologic examination of this solitary pulmonary nodule revealed TB. In TB endemic countries like India, FDG-avid lung lesions need to be interpreted cautiously[16]

MANAGEMENT OF PULMONARY TUBERCULOMA

Antituberculosis Drugs

Anti-TB drugs remains the mainstay of the management of pulmonary tuberculoma. Tuberculoma usually responds poorly to anti-TB drugs and requires long-term treatment. A clinician must be real careful in evaluating the effect of anti-TB drugs in tuberculoma cases because tuberculoma usually shrinks in size after the administration of anti-TB drugs for three months, as described in a study by Lee et al on 45 patients with tuberculoma.[2,4]

In this study, the smallest tuberculoma was found in the diameter of 23.2±10.8 mm, while the largest was 32.1±17.8 mm. Anti-TB drugs were given in the duration of 11.7±3.7 months. There were three kinds of anti-TB regiments given to the subjects, namely combination of rifampin, isoniazid, ethambutol, and pyrazinamide (38 patients), the combination of rifampin, isoniazid, and ethambutol (as many as six patients) and combination of ethambutol, streptomycin, cycloserine and levofloxacin (one patient due to poor liver function).[2,4]

After three months of anti-TB treatment, 18 patients (40%) showed a reduction (>25%) in tuberculoma diameter, while 25 patients (55.6%) experienced no change and two patients (4.4%) showed enlargement. This evaluation was repeated on the 6th, 9th and 12th month of anti-TB administration, which found a decrease in tuberculoma diameter in 24 patients (57.1%), 25 patients (59.5%) and 32 patients (76.2%), respectively. At the end of follow up period (27.0±10.2 months after initial anti-TB administration), there were 37 patients (82.2%) in the decreased group, seven (15.6%) in the no change group and one (2.2%) in the increased group. Continuous administration of anti-TB drugs for a long time wasn't found to be useful if the diameter does not decrease and might cause drug resistance instead. If the size of tuberculoma increases after receiving adequate treatment, lung resection is the treatment of choice.[4,9]

Surgery

Before performing surgery to manage tuberculoma, two things should be considered: the spread of MTb bacteria after surgery and the possibility of bronchopleural fistula. Surgery is performed as both diagnostic and therapeutic measures. Diagnostic surgery should be considered if other modalities have been performed without yielding any satisfactory results, while therapeutic surgery might be useful especially in cases of massive blood coughing.[2,9]

Indications for surgical management include prolonged sub-febrile fever, tuberculoma with the diameter of >3 cm, size of tuberculoma not decreasing after six months of anti-TB drugs administration, positive smear or culture, lung parenchymal damage, multiple tuberculomas in one lobe and suspected lung cancer or metastases.[2,9]

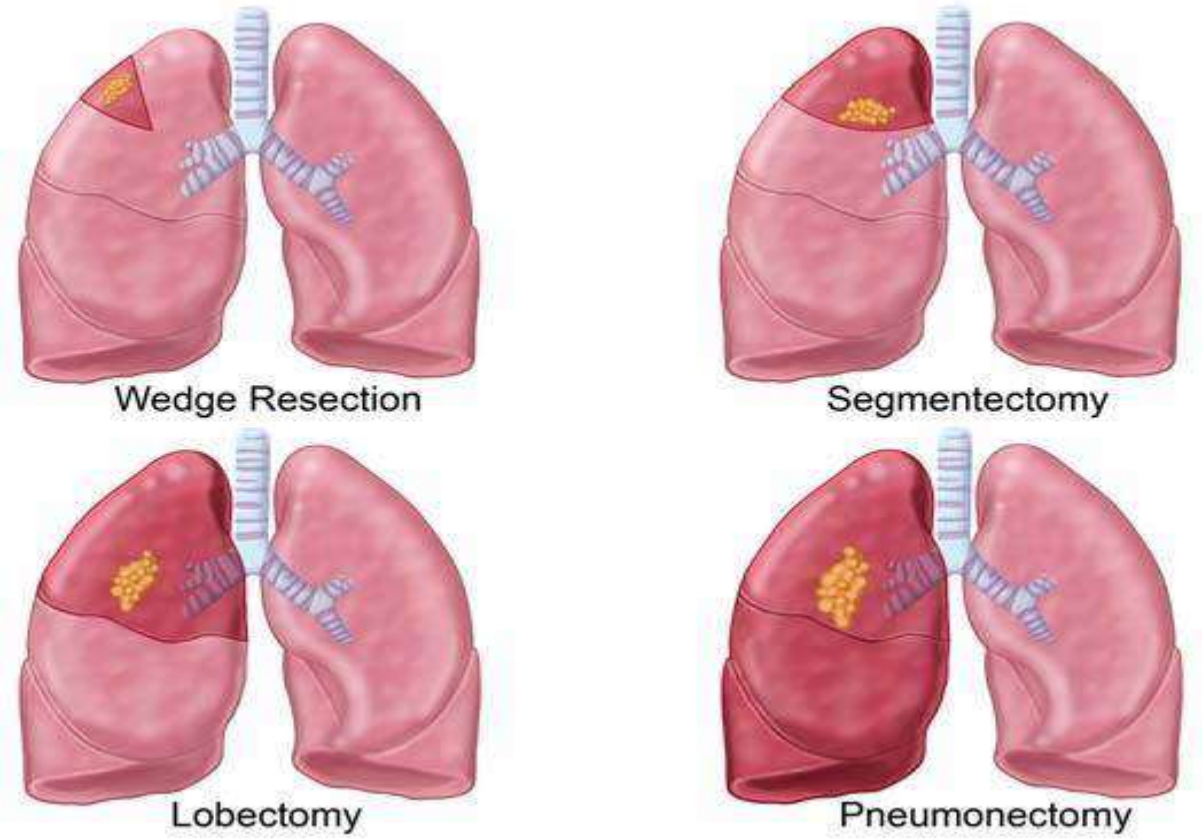

Figure 6. Lung Resection Technique[17]

Surgery might be performed through open lung resection or video assisted thoracoscopic surgery (VATS) with the condition in which no anti-TB drugs resistance is found and anti-TB drugs have been administered at least two months before the procedure.[2,9]

The choice of resection performed is based on the shape and location of the tuberculoma. If the lesion is peripheral, a wedge resection technique can be performed, while lobectomy is preferred if there are multiple lesions in one lobe. Nowadays, a less invasive surgical technique called tubeless VATS has been developed. This procedure was performed with no intubation nor general anesthesia, only using intercostal innervation block and sedation since only one hole incision was made. The advantages of this technique are short anesthetic time, minimal postoperative pain, faster postoperative healing and minimal incision. Anti-TB drugs administration is continued for 6-12 months postoperatively to prevent the progression or recurrence of tuberculosis.[2,9]

CONCLUSION

Pulmonary tuberculoma is often found as a solitary pulmonary nodule on radiological examination. The diagnosis of pulmonary tuberculoma is obtained from the history, physical examinations, laboratory and radiology examinations. Diagnosis modalities include chest

radiography, USG, CT scan, PET scan and bronchoscopy with transbronchial biopsy. The management of pulmonary tuberculoma is anti-TB drugs administration and surgery. Anti-TB drugs are recommended to be given for more than 6 months and surgery is indicated if the size of the tuberculoma does not decrease after administration of anti-TB drugs.

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