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Original Article

Differences in IL-6 Levels Based on Clinical Severity and Outcome of COVID-19 Patients at Dr. M. Djamil Hospital

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Abstract

Background: A cytokine storm is defined by elevated levels of proinflammatory cytokines such as interleukin-6 (IL-6). In COVID-19 infection, IL-6 is superior to C-reactive protein (CRP) and other inflammatory markers in predicting respiratory failure. The IL-6 is the main cytokine triggered by T cells when a cytokine storm occurs. IL-6 is the most important driver of immune dysregulation and ARDS in COVID-19 infection. The purpose of this study is to assess differences of IL-6 levels based on clinical severity and outcomes in COVID-19 patients at Dr. M. Djamil Hospital.

Method: The study took place at Dr. M. Djamil Hospital from November 2021 to November 2022. This is a retrospective cohort study in which patients were tested for IL-6 levels between January 1st, 2021 and December 31, 2021. The distribution of the frequency and proportion of each variable is included in univariate analysis; bivariate analysis determines the correlation between the independent variables (clinical severity, length of stay, and final status of hospitalization) and the dependent variable (IL-6 levels in COVID-19 patients).

Results: Patients' characteristics in this study, the majority of patients aged 18-49 years. Women and patients with moderate disease were more common. The majority of patients were treated for less than 14 days, and the final status of hospitalization the patients showed that most of the patients recovered. IL-6 levels with median (min-max) was 32.00 (1.50-589.00). The IL-6 levels were higher in clinically critical COVID-19 patients (77.20 mg/L), in patients with a shorter length of stay (14 days) (36.00 mg/L), and at final status of hospitalization were death (58.90 mg/L).

Conclusion: There were differences of IL-6 level based on clinical severity and final hospitalization status of COVID-19 patients, but not from the length of stay in COVID-19 patients at Dr. M. Djamil Hospital.

Keywords: clinical severity, COVID-19, IL-6 length of stay, outcome

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak has infected millions of people and has a high mortality rate, deeming it a global emergency.[1] The Severe Acute

Respiratory Syndrome Coronavirus-2 (SARS-Cov2) virus infection causes a variety of symptoms ranging from asymptomatic to severe. Fever, cough, difficulty breathing, other respiratory symptoms, and non-respiratory symptoms such as diarrhea, anosmia, ageusia, delirium, nausea, vomiting, and others are the most common clinical symptoms.[2] Around 80% of COVID-19 cases have mild-moderate symptoms, and 5% or more patients with critical-severe symptoms require intensive care unit (ICU) treatment, with a mortality rate of 1-2%.[3]

The pathogenesis of COVID-19 is divided into three stages: pulmonary, pro-inflammatory, and thrombotic.[4] COVID-19 infection has a diverse clinical picture in each phase, with 5-20% progressing to a severe level and requiring intensive care due to organ dysfunction. Therefore, it is important to identify patient characteristics that must be prioritized and have the potential to progress to a severe degree through hyperinflammation prevention. The challenge is determining how to detect early worsening conditions to aid in the management of COVID-19 patients. Effective markers can help with the detection, management, and prevention of serious complications.[5]

Acute respiratory distress syndrome (ARDS) and multi-organ failure can occur in patients with severe COVID-19 due to an increase in proinflammatory cytokines. Han et al discovered that lymphopenia and cytokine release syndrome (CRS) were related to disease severity.[6] Cytokine release syndromes, which cause single or multiple organ failure, have been thought to influence not only the severity but also the prognosis of COVID-19.[7] Cytokine storm is a systemic inflammatory response characterized by increased levels of proinflammatory cytokines, including IL-6, that can be triggered by a variety of factors such as infection, toxins, or idiosyncratic drug responses. Gubernatorova et al discovered that IL-6 levels had a strong correlation with the incidence of ARDS (P=0.001).[8]

Recent studies by Sabaka et al suggest using IL-6 testing in patient management and identifying patients at risk of aggravation.[9] Study by Renee et al, COVID-19 patients requiring hospitalization or experiencing acute respiratory failure had higher than normal levels of IL-6.[10] According to the findings of a recent meta-analysis, critically ill COVID-19 patients (ICU admission and/or acute respiratory failure) had nearly three times higher serum IL-6 levels.[11]

High IL-6 levels have been linked to a variety of clinical symptoms, including fever and the presence of bilateral lung involvement on computed tomography chest scans.[12] In the study by Ruan et al, higher levels of IL-6 were found in patients who died from COVID-19 when compared to survivors.[13] IL-6 levels may serve as an indicator of poor prognosis, according to Coomes et al research in Toronto.[3,14]

Sabaka et al found that IL-6 is superior to CRP and other inflammatory

markers in predicting respiratory failure in COVID-19. In COVID-19, interleukin-6 is the most important driver of immune dysregulation and ARDS.[9] During a cytokine storm, interleukin-6 is the primary toxic mediator produced by T cells.[11] The systematic role of IL-6 measurement and its ability to predict disease severity has yet to be determined.[6] Based on the foregoing information and the limited research on the effect of IL-6 on the clinical degree and outcome of COVID-19 patients at Dr. M. Djamil Hospital, the researcher wishes to investigate how IL-6 levels relate to the clinical degree and outcome of confirmed COVID-19 patients being treated at Dr. M. Djamil Hospital.

METHOD

This was a retrospective cohort study. The study took place at Dr. M. Djamil Hospital from November 2021 to November 2022. This research is part of the study "Relationship between initial CT values, inflammatory markers and onset of clinical symptoms with the outcome of treatment of COVID-19 patients at Dr. M. Djamil Hospital Padang" and has received approval from the Research Ethics Committee of Dr. M. Djamil Hospital with N0. LB 02.02/5.7/520/2022. Patients were tested for IL-6 levels at Dr. M. Djamil Hospital from January 1st 2021 to December 31st 2021.

Patients who met the inclusion and exclusion criteria were studied for IL-6 levels from January 1st, 2021 to December 31st, 2021. The COVID-19 patients over the age of 18 who were treated in the isolation room of Dr. M. Djamil Hospital and examined by IL-6 with complete medical record data including demograpfhic data, clinical degree description, and outcome were eligible for the study.

The study exclusion criteria were patients with mild clinical degrees of COVID-19 who were treated due to comorbidities; discharged patients at their request while still being treated for COVID-19; and patients with comorbid autoimmune diseases (rheumatoid arthritis, SLE, rheumatic heart disease, primary Sjogren's syndrome, fibrosis), bone dysplasia, JIA, and uveitis in JIA), chronic inflammation (Erdheim-Chester disease, Behcet's syndrome, systemic sclerosis, large cell arteritis, and type 2 diabetes mellitus), malignancy (ovarian cancer, colorectal cancer, prostate cancer, breast cancer, cancer of the bones, blood cancer, pancreatic cancer, lung cancer (non-small cell carcinoma), and lymph cancer), post-organ transplantation, patients receiving anti-IL6 therapy, and patients with extreme levels of IL-6.

RESULTS

There were 322 samples that met the inclusion and exclusion criteria. Table 1 shows the characteristics of COVID-19 patients treated at Dr. M. Djamil Hospital. The COVID-19 patients aged 18-49 years are the most common age group being treated (41.93%). Female COVID-19 patients were treated more frequently than male patients (45.34%).

Table 1. Characteristics of COVID-19 patients treated at Dr. M. Djamil Hospital (n=322)

Patient's Characteristic	N	%
Age		
18–49 years	135	41.93
50–59 years	82	25.47
60–69 years	61	18.94
≥70 years	44	13.66
Gender		
Male	146	45.34
Female	176	54.66
Clinical Severity		
Moderate	132	40.99
Severe	91	28.26
Critical	99	30.75
Length of stay		
<14 days	233	72.36
≥14 days	89	27.64
Final Status of Hospitalization		
Recovered	224	69.57
Recovered with sequelae	10	3.10
Died	88	27.33
IL-6 levels [median (min-max)]	36.00 (1.50-589.00)	

The majority of patients (40.99%) had a moderate clinical severity, while only 28.26% had severe and 30.75% had a critical severity. Most patients (72.36%) stayed for less than 14 days on average, while 27.64% stayed for more than 14 days. The final status of hospitalization of the patients revealed that the majority of them (69.57%) recovered, only 3.10% recovered with sequelae, and 27.33% died. For IL-6 levels, the median (min-max) is 32.00 (1.50-589.00).

Table 2. IL-6 Levels Based on Clinical Degree of COVID-19 Patients Treated at Dr. M. Djamil Hospital

Clinical Degree	IL-6 Levels [Median (min-max)]	P
Moderate	21.50 (1.50-528.00)	
Severe	53.00 (2.49-589.00)	0.0001*
Critical	77.20 (1.50-588.00)	

Note: *P<0.05 significant with the Kruskal-Wallis test

Table 2 shows that COVID-19 patients with critical severity (77.20 mg/L) have higher IL-6 levels than those with severe condition (53.00 mg/L) and moderate condition (21.50 mg/L). The analysis revealed significant differences in IL-6 levels based on the clinical severity of COVID-19 patients at Dr. M. Djamil Hospital.

Table 3. The IL-6 levels of COVID-19 patients treated at Dr. M. Djamil Hospital based on the length of their treatment

Length of Stay	IL-6 Levels [Median (min-max)]	P
<14 days	36.00 (1.50-589.00)	0.633*
≥14 days	35.60 (1.50-528.00)	

Note: *P<0.05 significant with the Kruskal-Wallis test

Table 3 shows that IL-6 levels were higher in patients with a length of stay of more than 14 days (36.00 mg/L) than <14 days 35.60 mg/L. The analysis revealed that there was no significant difference in IL-6 levels between COVID-19 patients at Dr. M. Djamil Hospital based on length of stay.

Table 4. IL-6 Levels Based on Final Hospitalization Status of COVID-19 Patients Treated at Dr. M. Djamil Hospital

Final Hospitalization Status	IL-6 Levels [Median (min-max)]	P
Recovered	33.90 (1.50-589.00)	
Recovered with sequelae	37.45 (9.20-173.00)	0.0001*
Died	58.90 (1.50-588.00)	

Note: *P<0.05 significant with the Kruskal-Wallis test

Table 4 shows IL-6 levels are higher at final hospitalization status were death (58.90 mg/L), recovery with sequelae (37.45 mg/L) and recovery (33.90 mg/L). The analysis found significant differences in IL-6 levels based on final hospitalization

status for COVID-19 patients at Dr. M. Djamil Hospital.

DISCUSSION

There were 322 confirmed COVID-19 patients at Dr. M. Djamil Hospital who met the inclusion criteria for this study. COVID-19 patients with a mild clinical condition were excluded because inflammatory markers were not examined. This is consistent with a study conducted in Istanbul by Esin et al, which found that in patients with mild clinical symptoms, there was no significant increase in serum IL-6 due to the small amount of cell damage caused by SARS CoV2. In these mild COVID-19 patients, the inflammatory response did not increase proinflammatory cytokines such as IL-6, IL1-, and TNF-.[15]

The characteristics of the patients in this study revealed that the majority of the COVID-19 patients treated at Dr. M. Djamil Hospital were between 18 and 49 years old as many as 140 patients (41.93%), and patients more than 70 years old as many as 46 patients (13.66%). This study is consistent with the study of Setiadi et al in Jakarta, who reported that the age range of patients treated was 40-60 years for as many as 29.6%, followed by young adults aged 19-40 years for as many as 24.2%.[16]

The cause of the large number of COVID-19 patients who are adults and young adults of productive age is the transmission of the SARS-CoV-2 virus, whose transmission that influenced by human mobility. The adult and young adult's outdoor activities, such as work and face-to-face learning, as well as domestic and international travel, provide opportunities for transmission.[16]

According to the findings of a separate study conducted by Liu et al, the average age of COVID-19 patients in China is 56 years old.[17] Khan et al discovered that 74% of patients were over the age of 50.[18] The severity of COVID-19 disease is related to age, which is caused by a decline in the immune system (immunosenescence) in old age.[18] This study supports the findings of Lee et al, who discovered that age influences the decrease in Angiotensin Converting Enzyme-2 (ACE-2) expression, implying that age has clinical implications in determining the prognosis of COVID-19 patients.[4]

According to a study conducted by Cummings et al in New York, old age is associated with high morbidity and mortality due to many comorbidities, longer length of stay, increase need for mechanical ventilation, and increase need for oxygen supplementation after hospital discharge.[19] In the elderly, cellular senescence, immunosenescence, and inflammaging cause phenotypic changes in immune cells such as telomere shortening, inhibition of immune cell proliferation, and accumulation of senescent macrophages (macrophageing), interfering with viral clearance in the respiratory tract. A decrease in the number of T cell receptors caused by aging results in the production of a small number of T cells and B cells, disrupting the adaptive immune response and making vaccinations less effective in the elderly.[20]

According to this study, there were more female patients than male COVID-19 patients treated at Dr. M. Djamil Hospital. The findings of this study are consistent with the findings of Liu et al, who discovered that female patients had 52.17% more severe cases than male patients, while male patients had 47.83% more severe cases.[17] These findings are also consistent with Shayan Kahn's research, which discovered 52.3% more female patients and 47.6% more male patients.[18]

Women have higher levels of ACE2 enzymatic expression than men, particularly ACE2 expression in the transverse colon. When compared to other symptoms, this increase in ACE2 expression causes gastrointestinal symptoms to predominate in COVID-19 infection in women.[21]

This study differs from Lee et al's study, which found that the morbidity and mortality rates of COVID-19 patients were higher in males because the ACE2 gene was located on the X chromosome, resulting in a more severe condition because of a decrease in the number of ACE2 receptors in male patients.[4] Another factor that contributes to more SARS-CoV-2 infections in men is the effect of sex hormones on immune and inflammation modulation. Estrogen boosts innate and adaptive immunity, improves vascular function, promotes regeneration, and has anti-inflammatory and antioxidant properties, whereas testosterone suppresses the immune system.[21]

According to the clinical severity of the disease, the number of patients in the moderate clinical category was 40.99%, the critical category was 30.75%, and the severe category was 28.26%. Patients treated for less than 14 days were as many as 72.36%, while those treated for more than 14 days were as many as 27.64%. According to the final hospitalization status of the patients, 69.57% recovered, 3.10% recovered with residual symptoms, and 27.33% died. Those 88 patients died with varying clinical severity, including 60 patients in critical, 15 in severe condition, and 13 in moderate condition.

According to Pal et al study in Romania, the death rate for COVID-19 patients ranged between 12.9% and 61.5%.[22] According to Goertz et al, COVID-19 symptoms were still present 90 days after recovery in patients who had been hospitalized for COVID-19, with 32% having one or two symptoms, 55% having three or more symptoms, and only 13% being symptom-free.[23]

The results of this study's examination of IL-6 levels in COVID-19 patients revealed a 92.2% increase in IL-6 levels >7 pg/ml and a 7.8% in normal IL-6 levels of <7 pg/ml. Most existing studies show that IL-6 levels in COVID-19 patients are higher than the normal range and that IL-6 levels are higher in severe cases of COVID-19 than in mild to moderate clinical cases.[24] Takashi's research demonstrates an association between serum IL-6 levels in COVID-19 patients and the likelihood of ICU hospitalization.[25]

The increase in IL-6 in COVID-19 is because this cytokine is produced by stromal cells as well as a variety of immune cells including macrophages, dendritic cells, mast cells, T lymphocytes, and B lymphocytes. In COVID-19 infection, these cytokines are also activated by IL-1 and TNF, and their secretion is influenced by TLRs, prostaglandins, adipokines, and other cytokines.[14]

Another important factor that contributes to higher IL-6 levels in SARS-CoV-2 infection when compared to other infectious or inflammatory conditions is the virus's ability to directly initiate IL-6 secretion. Protein N on the surface of the SARS-CoV-2 virus is a structural protein that can directly activate IL-6 secretion and expression (nucleocapsid). Apart from activating this protein, it also prolongs IL-6 secretion, so the amount of RNA viral load influences the severity of the patient.[14]

According to this study, IL-6 levels are higher in critical conditions (77.20 mg/L) compared to severe (53.00 mg/L) and moderate (21.50 mg/L). The analysis revealed significant differences in IL-6 levels based on the clinical severity of COVID-19 patients at Dr. M. Djamil Hospital. Herold's study found that a high increase in interleukin-6 (IL-6) above 80 pg/ml was sufficient to identify COVID-19 patients at high risk of respiratory failure.[26]

Patients with IL-6 levels of 80 pg/mL had a 92% risk of respiratory failure, which was 22 times higher than patients with lower IL-6 levels. The median time for mechanical ventilation after reaching IL-6 levels of 80 pg/mL was 1.5 days (range 0–4 days).[27] In the early stages of COVID-19 infection, monocytes and macrophages produce the cytokine IL-6, which if in excess, can cause severe lung damage (acute lung injury) and worsen the patient's condition.

Gorham's study concentrated on ICU patients with severe conditions (high SOFA score; 85% of patients were on mechanical ventilation, 68% were treated supine, and 20% were on ECMO). The overall mortality rate is 32%, indicating clinically critical COVID-19 patients with a poor prognosis. A larger cohort study of IL-6 levels in COVID-19 patients treated in the ICU is required to assess the significance and role of IL-6 in patient prognosis more specifically.[28]

In a study of 127 patients with severe COVID-19 in China, Zhu et al discovered that IL-6 levels as the sole parameter determining the severity of COVID-19 were superior to other inflammatory parameters, with an AUROC of 0.835, a sensitivity of 87.50% (95% CI=61.60-98.10), and a specificity of 74.77% (95% CI=65.60-82.50).[29] Sabaka et al discovered that patients with baseline IL-6 levels greater than 24 pg/ml had a 50% chance of developing hypoxia, with a 100% sensitivity and an 88.9% specificity; the positive and negative predictive values were 76.9% and 100%, respectively.[9] Mojtabavi et al discovered an average difference in IL-6 levels of 23.1 pg/mL (95% CI=12.42-33.79) in a meta-analysis study involving 1357 COVID-19 patients.[30]

Interleukin-6 stimulates T-cell activation and expansion, as well as B-cell

differentiation, both of which contribute to the acute phase response. When B cells are activated by antigen, these cytokines are required for B cell proliferation. They also cause B cells to differentiate into effector cells that produce IgM, IgG, and IgA antibodies. These cytokines promote the maturation of immature thymocytes into cytotoxic T cells while suppressing the induction of regulatory T cells via Th17 cells.[24]

Increased IL-6 levels, followed by excessive immune cell proliferation, cause the release of proinflammatory cytokines and chemokines, resulting in a worsening of systemic inflammation, known as a "cytokine storm." A cytokine storm damages the lungs, leading to ARDS and worsening the patient's clinical condition.[31]

The analysis revealed that there was no significant difference in IL-6 levels between COVID-19 patients at Dr. M. Djamil Hospital based on length of stay. The average length of stay for patients with moderate degrees was 12.36 days, 10.80 days for those with severe degrees, and 8.71 days for those with critical degrees. In this study, the average length of stay for recovered patients was 12.42 days, while patients with residual symptoms stayed for 13 days, and patients who died had the shortest stay, namely 6.42 days. This finding is consistent with the findings of Christel et al, who found no relationship between onset and outcome in COVID-19 patients (P=0.633).[32]

The median length of stay for patients who recovered ranged from 5 days (in the young) to 15.7 days (in the elderly), while the median length of stay for patients who died ranged from 5.7 days (in the elderly) to 12.2 days (in the elderly working age). The length of hospital stays for recovering patients increases with age, and men recover slightly slower than women. In contrast, the working-age population has the longest time between hospitalization and death, while the elderly have shorter survival times. Nursing home patients spend more time in the hospital than patients of the same age in the general population.[32]

In a separate study, Zhu et al discovered that IL-6 levels in severe COVID-19 cases were higher than those in the mild-moderate group at baseline, 5-10 days after the onset of the disease, and gradually decreased until they reached levels comparable to those in the mild-moderate group, following a 10-day course of treatment.[29] Cruz et al discovered high IL-6 levels in survivors, leading to clinical deterioration, but there was a rapid decrease in IL-6. Peak IL-6 levels in survivors occur 7-10 days after symptom onset. The critical inflammation peaks around days 7-10, accompanied by clinical worsening.[33]

Even though the patient had clinically progressed to the hypoxemic stage, IL-6 levels tended to decrease after the 10th day and were close to normal. The strongest predictor of age is IL-6.[33] Sun et al discovered a 23-fold increase in IL-6 levels in 8 patients who progressed to critical illness and respiratory failure in a retrospective study of 40 patients with severe degrees in China.[34]

High IL-6 levels can cause bilateral lung damage and pyrexia, worsening symptoms and necessitating oxygen therapy and mechanical ventilation. COVID-19 patients with high IL-6 levels stayed in the hospital for longer periods than COVID-19 patients with mild to moderate COVID-19 levels. In terms of length of stay, the average significant difference in IL-6 levels between patients with severe and non-severe COVID-19 is 38.6 pg/mL.[35] Other factors influencing COVID-19 patients' length of stay include age and the number and type of co-morbidities such as diabetes, hypertension, and cardiovascular disease.[36]

According to the findings of this study, IL-6 levels were higher at final hospitalization status death (58.90 mg/L) when compared to recovery with sequelae (37.45 mg/L) and recovery (33.90 mg/L). The analysis found significant differences in IL-6 levels based on final hospitalization status for COVID-19 patients at Dr. M. Djamil Hospital. The findings of this study are supported by Shimazui's research, which found that higher IL-6 levels (per tertile) are significantly associated with a higher 90-day in-hospital mortality rate (P=0.005).[25]

This is supported by research by Xiaohui who discovered that the IL-6 level can predict the severity of COVID-19 patients. The combined area under the curve (AUC) was 0.85 (95% confidence interval (CI) 0.821 to 0.931). According to research, there is a link between IL-6 levels and mortality. Pooled sensitivity, specificity, and AUC were 0.15 (95% CI=0.13-0.17; I^2=98.9%), 0.73 (95% CI=0.65-0.79; I^2=91.8%), and 0.531 (95% CI=0.451-0.612).[7]

The study by Abdul et al found the same correlation between IL-6 and the severity of COVID-19 patients; this is because IL-6 is an adequate predictor of disease severity in COVID-19 patients.[37] According to research conducted in Munich, high IL-6 levels can predict critical illness. In a cohort of 40 patients, increased IL-6 (>80 pg/ml) was found to be strongly associated with a 22-fold higher need for mechanical ventilation compared to patients with lower IL-6 levels.[27]

Interleukin-6 is a significant cytokine whose production is linked to a variety of inflammatory diseases.[9] Subjects infected with SARS-CoV-2 had elevated IL-6 levels, which correlated with patient symptoms such as pulmonary inflammation and extensive lung damage. Furthermore, patients infected with SARS-CoV-2 had low levels of suppressor cytokine signaling-3, which controls and stimulates the IL-6 negative feedback mechanism.[38]

Other studies have found that IL-6 levels are higher in patients with severe COVID-19, which can be used to predict the progression from mild to severe infection.[9] According to Diao et al, COVID-19 patients in intensive care had lower CD8+ T cell counts, and their total CD4+ and CD8+ T cell counts were also negatively correlated with TNF- and IL-6 levels.[39]

Recent research has revealed that higher levels of IL-6, CRP and IL-10 are more significant than other cytokines in a

subset of COVID-19 patients. This study examined the IL-6 parameter at the time of the patient's arrival at the hospital. Due to the dynamics of inflammatory processes during SARS-CoV-2 infection, Cruz et al concluded that measuring IL-6 only at the start of treatment was insufficient for accurately predicting outcomes or serving as a guideline for therapy. IL-6 kinetics analysis revealed that IL-6 levels increased transiently in patients who had received treatment.[33]

The mortality rate of COVID-19 patients can be divided into three stages based on the immune parameter of increased IL-6 levels. Stage 1 is the first four days of being sick with COVID-19, when significant viral replication occurs, resulting in viremia in the blood.[40] IL-6 levels were not significantly different between patients who recovered and those who died. Age, gender and co-morbidities such as hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease and obesity all have an impact on patient outcomes during this stage.[36,40]

Stage 2 occurs in 5-14 days when the disease's fatality rate rises due to amplification of the inflammatory response and accelerated progression to clinically severe or critical. Due to the massive production of immune cells and inflammatory cytokines, particularly IL-6, severe symptoms such as shortness of breath, sepsis, and ARDS appear at this stage. Excessive inflammatory mediators cause lung damage and impair lung function as a result of widespread inflammatory infiltration. COVID-19 patients in this stage are extremely vulnerable and will die. Survivors of COVID-19 who have a cytokine storm during this phase have sequelae after they recover.[40]

Stage 3 is the final stage, which occurs after 15 days, with a median time of 16-18.5 days from the onset of COVID-19 until the patient dies. Patients in this phase suffer severe organ injuries, particularly to the heart, kidneys, liver, and lungs; nearly all patients in this phase require life-sustaining mechanical ventilation. In this vase, IL-6 levels rise dramatically, causing vascular leakage, activation of complement pathways, and disseminated intravascular coagulation, which occurs in 71.4% of patients and leads to death from multiorgan failure.[40]

This study employed total sampling with a large sample size to discover a significant association between IL-6 levels and clinical severity and final hospitalization status, but it discovered limitations. This is a retrospective cohort study with data collected from medical records, and the patient distribution in each clinical degree is uneven. It only evaluates IL-6 levels during the first 24 hours of treatment.

CONCLUSION

The COVID-19 patients in this study were mostly women between 18-49 years old, with a moderate clinical severity of disease, a length of stay less than 14 days, and a final hospitalization status recovered. There were differences of IL-6 levels based

on clinical severity and final hospitalization status of COVID-19 patients, but not from the length of stay in COVID-19 patients at Dr. M. Djamil Hospital.

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Original Article

Continuing Monitoring in Respiratory Intensive Care Unit and Mortality in Patient Post Bronchoscopy Procedure

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Abstract

Background: Bronchoscopy is a relatively safe procedure in the diagnosis and therapy of lung disease, however in some cases complications can occur which lead to further monitoring in the intensive care or respiratory intensive care unit (RICU) and even lead to mortality. This study aimed to determine the need for intensive care unit monitoring and the risk factors that increase the need for intensive care unit monitoring followed by mortality after bronchoscopy procedure.

Method: A retrospective data of consecutive bronchoscopy procedures in Persahabatan Hospital between July to December 2021.

Results: From 410 patients underwent bronchoscopy procedures, there were 52 patients (12.6%) were admitted to RICU after bronchoscopy. From patients who were treated in RICU 3 (5.8%) of them died. Patients who died during monitoring in intensive care unit had an older mean age of 60.3 years. There were 2 (12.5%) died after bronchoscopy procedures with two or more intervention, 1 patients (3%) died in the group with one intervention. There were 2 patients (13.3%) died with two or more comorbidities and 1 patient (5.9%) died with one comorbid. In the group with diagnosis of malignancy, 3 patients (7.5%) died. Whereas in patients who were performed surgery during bronchoscopy there were 2 patients (20%) died and only 1 patient (2.4%) died without any surgery during bronchoscopy.

Conclusion: Although bronchoscopy is a relatively safe procedure but the need of monitoring in intensive care after bronchoscopy procedures were relatively high and mortality quite high compare to previous study. Further research is needed to determine the risk factors that increase the need of continuing monitoring in intensive care unit followed by mortality after bronchoscopy procedure.

Keywords: bronchoscopy, mortality, RICU

INTRODUCTION

Bronchoscopy is an important diagnostic and therapeutic procedure in the management of lung disease. The flexible fiber optic bronchoscope allows excellent visualization of the airway lumen and the luminal surface of the bronchial segments with relatively less traumatic instruments.

A rigid bronchoscope allows more therapeutic options but is limited to the trachea and main bronchi, unless it is combined with a flexible fiber optic bronchoscope. Several studies have shown that bronchoscopy is a relatively safe procedure with a very low mortality rate ranging from 0% to 0.1%.[1,2]

Although bronchoscopy is a relatively safe procedure, complications can occur in some procedures. Most of the complications occur in patients with comorbidities or interventions during bronchoscopy. Overall, both rigid bronchoscopes and flexible fiber-optic bronchoscopes are safe and effective procedures for the diagnosis and treatment of airway disorders and lung disorders.[2]

The most common reported complications, although not the same in several studies, are tachycardia/ bradycardia, bleeding, bronchospasm/ laryngospasm, cough, dyspnea, apnea, seizures, desaturation, pneumothorax and pulmonary edema. Other smaller studies reported a complication rate of 5-32%, and a mortality rate of 0-0.8%, but these studies are limited as they are from retrospective data so data regarding variable definition of adverse events and follow-up is limited.[3]

An escalation in level of care although does not necessarily reflect harm, but it could have been considered in the short term following therapeutic bronchoscopy.[4] Currently there are very few studies that discuss the need for intensive care or respiratory intensive care unit (RICU) in patients after bronchoscopy procedure. This study discusses the risk factors that increase the need of intensive care unit or RICU monitoring and the mortality of patients after bronchoscopy.

METHOD

We included patients who need intensive care unit after bronchoscopy procedures from July to December 2021 at the Persahabatan Hospital, Jakarta, Indonesia. The data collected included sex, age, diagnosis divided into malignancy and non-malignancy, the totaln number of interventions performed during bronchoscopy, the presence of comorbidities, mortality and other surgical procedures performed concurrently with bronchoscopy. All the data were collected retrospectively from electronic medical record and analyzed used SPSS.

RESULTS

Of the 410 patients who underwent bronchoscopy procedures, 52 (12.6%) patients were treated in the RICU after bronchoscopy, 47 patients underwent diagnostic bronchoscopy procedures and 5 patients underwent therapeutic bronchoscopy procedures.

Of the 52 patients, 32 (61.5%) were male and 20 (38.5%) female with a mean age of 50.3 years. There were 3 patients (5.8%) post bronchoscopy procedures in RICU died. Patients who died during treatment in the intensive care unit had an older mean age of 60.3 years compared to patients who survived, with an average age of 49.6.

Table 1. Patient's Characteristic

Variables	N (%)
Sex	
Male	32 (61.5%)
Female	20 (38.5%)
Age (mean)	50.3
Interventions during bronchoscopy	
Bronchoscopy explorative	3 (5.8%)
Bronchoscopy + 1 intervention	33 (63.5%)
Bronchoscopy + ≥2 interventions	16 (30.8%)
Diagnosis	
Malignancy	40 (76.9%)
Non-malignancy	12 (23.1%)
Comorbid	
No comorbid	20 (38.5%)
1 comorbid	17 (32.7%)
2 or more comorbid	15 (28.8%)
Status	
Decease	3 (5.8%)
Survive	49 (94.2%)
Other surgery	
No	42 (80.8%)
Yes	10 (19.2%)

There were 2 patients (12.5%) who died in the group undergoing bronchoscopy procedures with two or more. Whereas in interventions during bronchoscopy, 1 patient (3%) died in the group with one intervention during bronchoscopy.

As for mortality associated with comorbid, there were 2 (13.3%) with two or more comorbidities who died and 1 patient (5.9%) with one comorbid who died. In the group with a diagnosis of malignancy, 3 patients (7.5%) died. Whereas in patients who were performed surgery during bronchoscopy there were 2 patients (20%) died and without any surgery during bronchoscopy only 1 patient (2.4%) died.

DISCUSSION

Bronchoscopy is generally considered a safe procedure. Data on complications associated with bronchoscopy are mostly obtained through retrospective studies. In a systematic review by Ost et al, the mortality rate for bronchoscopy was low, but it was difficult to compare populations between these studies.[4]

Table 2. Mortality was associated with age, interventions, diagnosis, comorbidities and surgery

Variables	Alive	Death
Age, years (mean)	49.6	60.3
Intervention during bronchoscopy		
Bronchoscopy explorative	3 (100.0%)	0 (0.0%)
Bronchoscopy + 1 intervention	32 (97.0%)	1 (3.0%)
Bronchoscopy + ≥2 interventions	14 (87.5%)	2 (12.5%)
Diagnosis		
Malignancy	37 (92.5%)	3 (7.5%)
Non-malignancy	12 (100.0%)	0 (0.0%)
Comorbid		
No comorbid	20 (100.0%)	0 (0.0%)
1 comorbid	16 (94.1%)	1 (5.9%)
2 or more comorbid	13 (86.7%)	2 (13.3%)
Other surgery		
No	41 (97.6%)	1 (2.4%)
Yes	8 (80.0%)	2 (20.0%)

In this population, the bronchoscopy procedure was shown to be more diagnostic than therapeutic, which is in line with Suleman's study that bronchoscopies were mainly done for diagnostic purposes, while bronchoscopy for therapeutic purposes is limited due to lack of equipment and expert staff.[5] This is consistent with our study, the high rate of RICU care in patients with malignancy and all the mortality from patients with malignancy.

In this study, without assessing the complications that occurred there were 12.6% of patients that led to intensive care after bronchoscopy with an overall mortality rate of 0.7% which was quite high compared to previous studies. Facciolongo et al reported a mortality rate of 0.02% in a large prospective study at 19 hospitals performing diagnostic and therapeutic bronchoscopy. This may be due to the number of samples in this study is too small, so further research with greater samples is needed. The study also stated the low incidence of complications in the exploratory bronchoscopy group (i.e, carried out without sampling).[6]

In accordance with our study, there was no mortality in exploratory bronchoscopy without other interventions. In our study it was also shown that mortality increased with the number of interventions during bronchoscopy. Bronchoscopy accompanied by intervention in the form of lung biopsy is most often associated with increased complications during bronchoscopy procedures and increased mortality compared to other interventions. It is in accordance with the study by Jacomelli et al that most of the complications occurred in patients undergoing sample collection procedures, particularly biopsy.[7] Meanwhile, broncho alveolar lavage (BAL), which is used to diagnose infection cases, is the safest procedure and no study has ever reported complications associated with this procedure.[5]

There are still very few studies that report patient characteristics related to the safety of bronchoscopy such as indications for bronchoscopy, gender, age, comorbidities, types and procedures or interventions performed during bronchoscopy and whether there are other surgical procedures along with bronchoscopy which can cause an increased risk of treatment. RICU and death. A study by Kaparianos et al reported a mortality rate of 0.04%, that is, there were 2 deaths. One of the patients experienced hypoventilation and cardiac arrest after the end of the procedure while the other died from sudden hemorrhage after manipulation of endotracheal carcinoma. These patients had comorbidities, namely chronic obstructive pulmonary disease, hypertension and diabetes mellitus.[8] In our study, the cause of death was not known due to a lack of data.

Jin and colleagues reported three deaths following bronchoscopy. One patient died had comorbid coronary heart disease, cardiac arrest at the time of action and could not be resuscitated and two patients died of major airway obstruction

after bronchoscopy.[9] This is similar to our study of comorbidities increasing the risk of death. The study also showed that malignancy was the most common indication for bronchoscopy, but did not mention its effect on complications and mortality. Whereas in our study all deaths were in the group with a diagnosis of malignancy.

In Boyd et al's study, it was shown that there is an increased risk of side effects with increasing age, but the absolute frequency is low, so that age should not be a contraindication for bronchoscopy.[10] Meanwhile, in our study, mortality was higher at an older age, but the following factors must be considered such as comorbidities and interventions during bronchoscopy.

This study provided the characteristics of patients who need intensive care and mortality post bronchoscopy procedure, which has very little data in previous studies. However, this study has a limitation with small number of samples and no data regarding complications that occur during bronchoscopy causing treatment in the intensive care unit and causes of death.

CONCLUSION

This study showed that although bronchoscopy is a relatively safe procedure but the need of RICU care after bronchoscopy procedure needs to be considered. Therefore, health facilities that perform bronchoscopy are expected to have a special intensive room for further monitoring of patients after bronchoscopy procedure. Further research is needed with more samples and more complete data as predictors of clinical outcomes based on patient characteristics, interventions performed and complication during bronchoscopy procedure which can increase the risk of RICU care and post-bronchoscopy mortality.

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Original Article

Aromatherapy Effectivity in Controlling Anxiety, Respiration Rate, Pulse Rate, and Pain in Bronchoscopy

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Abstract

Background: Bronchoscopy is a relatively safe diagnostic and therapeutic procedure, but it is often reported as an uncomfortable experience and causes acute procedural anxiety that affects the procedure and the patient and operator's comfort. Anti-anxiety drugs have the risk of causing mild to severe side effects. Therefore, we need premedication with potent anxiolytics with minimal side effects, such as the use of aromatherapy. This study aims to analyze the effectiveness of aromatherapy as an additional premedication to reduce anxiety, respiratory rate, pulse rate, and pain in patients undergoing bronchoscopy.

Method: A clinical study with experimental quasi pre-post test control group design using consecutive sampling was performed in pulmonary patients undergoing bronchoscopy in dr. Moewardi Hospital from February to March 2020. The study subjects were randomized into three groups: lavender aromatherapy, orange aromatherapy, and control. Hospital anxiety and depression scale (HADS) score, respiratory rate, pulse, and visual analogue scale (VAS) pain score were measured before and after bronchoscopy.

Results: A total of 45 subjects of lung patients undergoing bronchoscopy participated in this study. Post hoc test differences in the HADS anxiety score of lavender and orange groups showed a significant decrease (P=0.011); (P=0.083), respectively. The decrease in the control group was not significant (P=0.622). There was a significant decrease in the respiratory rate of lavender (P≤0.0001), and orange groups (P=0.001), while the control group did not decrease (P=0.515). There was a significant decrease in pulse rate in the lavender (P=0.004) and orange (P=0.011) groups. The decrease in the control group was not significant (P=0.900). There was a significant decrease in VAS pain scores in the lavender and orange groups with each (P<0.001), whereas, in the control group, there was an increase in VAS pain scores.

Conclusion: Aromatherapy effectively controls anxiety, respiration rate, pulse, and pain in bronchoscopy patients.

Keywords: aromatherapy, bronchoscopy, HADS, respiration rate, VAS pain score

INTRODUCTION

Bronchoscopy is an endoscopic technique examination procedure for visualization of the larynx, trachea, and lower respiratory tract with diagnostic and therapeutic purposes. Bronchoscopy procedures are often reported as an uncomfortable experience and often make patients refuse to do a re-examination procedure. This becomes an obstacle in establishing the patient's diagnosis. Benchmarking the success of bronchoscopy is focused on patient satisfaction alongside the diagnostic and therapeutic value of the bronchoscopy procedure. One of the main factors affecting patient satisfaction is anxiety about the bronchoscopy procedure.[1–5]

According to Poi et al, the incidence of anxiety during bronchoscopy is 68 percent. Anxiety can increase cortisol levels, blood pressure, pulse, and respiration, affecting patient tolerance to bronchoscopy. For practitioners, anxiety in patients can hinder the success of bronchoscopy procedures. Anxiety about certain medical procedures is called acute procedure anxiety. Acute procedural anxiety is an excessive fear of medical procedures that triggers acute *distress* or interferes with completing the procedure to be performed.[1–5]

Anxiety can be reduced by preparing the patient and premedication before the bronchoscopy procedure. Premedication of sedative and analgesic drugs can increase patient satisfaction and reduce patient discomfort during the procedure. Bronchoscopy can be done under general anaesthesia or only light sedation, but the premedication given can cause side effects. Anxiety can increase the need for sedation, resulting in an increased risk of anaesthesia, including prolonged sedation, amnesia, and respiratory depression. The ideal anxiolytic is potent with minimal side effects.[1,4,6,7]

Clinical trials related to other modalities in reducing anxiety include adding hypnotherapy or music to the series of patient preparations for bronchoscopy, which have been proven to be effective in increasing patient comfort and reducing anxiety. Aromatherapy is a modality widely used in clinical trials to reduce acute procedure anxiety in patients.[1,5,8,9]

In one of the clinical trials using aromatherapy, Mogharab et al examined the effect of lavender essential oils (EO) inhalation on the anxiety of patients undergoing colonoscopy procedures. The patient's anxiety level was assessed from Spielberger's State Anxiety Inventory (STAI) questionnaire that was filled in by the patient before and after the colonoscopy. The results of clinical trials showed that inhalation of lavender EO significantly reduced anxiety levels compared to the control group.[1,5,8,9]

Aromatherapy is a form of complementary and alternative therapy that is simple, non-invasive, low-risk, and cost-effective for reducing acute procedure anxiety. Aromatherapy is the therapeutic use of certain plant EO through skin absorption or inhalation of the olfactory system. Stimulation of the olfactory system

can affect cognitive perception, mood, behavior, and physiological responses of the body. Essential oil is an aromatic oil concentrate extracted from plants by steam distillation, hydro-diffusion, or pressure. Essential oil can be extracted from various parts of plants, including leaves, petals, stems, and roots. Generally, EO is volatile or easily evaporates.[8–12]

Aromatherapy can have an effect through the sense of smell, which is a pathway from the olfactory system to the limbic system, which is the centre of emotion and memory, causing changes in perception, in this case, anxiety. This also explains why specific smells can give rise to perceptions of a situation or trigger memories related to smells. Penetration of EO through the airways has a direct effect on the autonomic nervous system and an indirect effect through neuropharmacological pathways derived from EO components. Direct or indirect effects will affect hypothalamic control of related hormones and neurotransmitters.[13–15]

The olfactory system has a combination coding system to distinguish various odors so that the olfactory receptors are specifically able to distinguish odors. In the corticomedial amygdala via the olfactory tract, the signal will be translated into an olfactory interpretation, and the body's response will appear.[12–15] When the body receives a stimulus as a stressor, there are two pathways for activating responses to the stressor. The first pathway is the sympathetic adrenomedullary system (SAM) or sympathetic nervous system (SNS) phase, which is a response to a short-term stressor characterized by the secretion of adrenaline and noradrenaline, including increased heart rate, blood pressure, sensory perception, and body metabolism. The second pathway, known as the hypothalamic pituitary adrenal (HPA) axis, responds to a more serious and long-term stressor (which lasts more than a few minutes) characterized by secreting cortisol into the bloodstream causing a more significant body response and longer duration.[16–19]

Responses to stressors also affect the brain's neurotransmission system, where GABA receptor activity will increase, accompanied by activation of NMDA antagonist receptors, and decreased serotonin levels. This affects causing the emotional perception of anxiety, which in turn is connected with the HPA axis system in causing metabolic effects, and behavioural responses and can modulate pain. Pain stimulation on bronchoscopy can be modulated through two pathways: the pain response, which is directly captured by the anterior cingulate cortex, then causes the perception of pain.[19–21]

The main components of lavender and orange EO are lynalyl acetate and linalool. The active ingredient EO is an enantiomer of volatile components known to have different psychological and physiological effects. The EO enantiomer has an affinity for binding to serotonin transporters and N-methyl-D-aspartate (NMDA) glutamate receptors. Inhibition of serotonin receptors in the hippocampus

and cingulate cortex influences dopaminergic effects through modulation of the serotoninergic system, resulting in anxiolytic and analgesic effects. NMDA receptor modulation can inhibit nerve excitation, causing a calm, relaxing, anti-agitational effect. Essential oils can also modulate gamma-aminobutyric acid (GABAergic) neurotransmission, especially GABAA receptors and increase the inhibitory tone of the nervous system.[22–27]

Lavender aromatherapy also triggers activation of the parasympathetic nerves and reduces sympathetic nerve activity, thus playing a synergistic role in response to anxiety, including triggering a decrease in heart rate, reducing respiration rate, and lowering blood pressure. This effect can improve somatic symptoms of anxiety.[27,28]

Currently, no studies are related to aromatherapy used in bronchoscopy. This study aims to determine and analyze the effectiveness of anxiolytic aromatherapy in patients undergoing bronchoscopy procedures in controlling and reducing anxiety, respiration rate, pulse rate, and pain.

METHOD

The research design was a quasi-experimental, pretest and posttest design. The research was conducted at RSUD Dr. Moewardi Surakarta from February to March 2020 until the number of samples fulfilled. The study population was patients who underwent bronchoscopy procedures at RSUD Dr Moewardi Surakarta. Sampling carried out by consecutive sampling, namely the selection of research subjects based on inclusion criteria and then included in the study until the required number of subjects fulfilled.

The inclusion criteria were age ≥18 years when sampling, had never undergone a bronchoscopy procedure before, could read and write, and was willing to participate in the study by signing informed consent. Exclusion criteria included total anosmia, allergy to aromatherapy components, history of hypertension and heart disease, taking anti-hypertensive drugs, using anti-anxiety drugs, history of head trauma, impaired consciousness, hemodynamic instability, alcohol or drug dependence, a hearing impairment that hinders verbal communication, cognitive or psychiatric disorders or a history of previous.

Subjects who met the inclusion criteria have explained the aims and objectives of the study. Subjects received education and data recording, including identity, history taking, and physical examination. Study variables (anxiety, respiratory rate, pulse, and pain) assessed twice, namely, the initial assessment, which carried out in the treatment ward, and the second about 30 minutes after the bronchoscopy procedure completed.

Anxiety assessment used the hospital anxiety and depression scale (HADS) questionnaire, respiration rate was assessed by manual calculation, pulse rate was assessed using a pulse oximetry monitor, and pain assessment was assessed using a visual analogue scale

(VAS) for pain. The aromatherapy used is lavender and orange essential oils.

Data analysis was carried out using SPSS version 19 for Windows and data presentation using Microsoft Office 2010. This study used a normality test and a different test for research data. With a meaning limit, P≤0.05 is significant.

RESULTS

The sample population in this study was 45 patients who were divided into three groups, namely the lavender EO aromatherapy treatment group 15 patients, the orange EO aromatherapy treatment group 15 patients, and 15 patients as the control group. The aromatherapy treatment procedure was given in the treatment ward ±1 hour before the bronchoscopy procedure.

Aromatherapy is inhaled through a diffuser placed beside the patient's bed. Both treatment groups received standard bronchoscopy preparation and premedication. The control group did not receive aromatherapy treatment, they only received standard bronchoscopy preparation and premedication procedures.

Characteristics of the subjects in this study consisted of gender, age, education, occupation, diagnosis, bronchoscopy results, and actions during bronchoscopy. A different test on patient characteristics was carried out to determine the homogeneity of the two sample groups as a condition for the feasibility of the experimental procedure.

Table 1 shows that the majority gender was male, with 9 patients (60%) in both the lavender, orange, and control groups. The mean age of patients in the lavender group was 56.80±6.16 years, the orange group was 56.80±6.50 years, and the control group was 55.47±6.20.

The education of patients in the lavender group is junior high school (SMP), namely 7 patients (46.7%). The Orange group is the majority of elementary schools (SD), 9 patients (60.0%), and the control group is the majority of high schools (SMA), 6 patients (40.0%). Most occupations are farmers (40%).

Most bronchoscopy results found compression stenosis. The most common action during bronchoscopy is bronchial washings. There were no significant differences in patient characteristics between the control and treatment groups, which means that the patient characteristics were homogeneous.

There was a decrease in HADS anxiety scores pretest-posttest in the lavender group -2.20±1.21; orange -1.80±1.61; control -1.12±0.83. Based on Table 2, it is known that the results of the different unpaired tests in the value of the post-pre difference obtained a value of P=0.040, which means that there was a significant difference in changes in the HADS score between the 3 groups. To find out the difference in changes in HADS scores between the treatment group and the control group partially (one by one), a post hoc test was carried out.

Table. 1 Basic Characteristics of Research Subject

Characteristic	Control	Lavender	Orange	P
Gender[a]				
Male	9 (60.0%)	9 (60.0%)	9 (60.0%)	1.000
Female	6 (40.0%)	6 (40.0%)	6 (40.0%)	
Age[b]	55.47±6.20	56.80±6.16	56.80±6.50	0.800
Education[c]				
Elemantary	5 (33.3%)	5 (33.3%)	9 (60.0%)	
JHS	4 (26.7%)	7 (46.7%)	4 (26.7%)	0.191
SHS	6 (40.0%)	3 (20.0%)	2 (13.3%)	
Employment[a]				
Laborer	3 (20.0%)	3 (20.0%)	4 (26.7%)	
Trader	1 (6.7%)	1 (6.7%)	3 (20.0%)	
Craftsmen	1 (6.7%)	0 (0.0%)	0 (0.0%)	
Tailor	1 (6.7%)	0 (0.0%)	0 (0.0%)	0.895
Pension	1 (6.7%)	1 (6.7%)	1 (6.7%)	
Farmer	5 (33.3%)	6 (40.0%)	4 (26.7%)	
No Work	3 (20.0%)	4 (26.7%)	3 (20.0%)	
Smoke[a]				
No	6 (40.0%)	7 (46.7%)	8 (53.3%)	0.765
Yes	9 (60.0%)	8 (53.3%)	7 (46.7%)	
Diagnosis[a]				
Lung Abscess	1 (6.7%)	0 (0.0%)	0 (0.0%)	
Pleural Effusion	2 (13.3%)	1 (6.7%)	1 (6.7%)	
Giant bullae sinistra	0 (0.0%)	0 (0.0%)	1 (6.7%)	
Hydropneumothorax	0 (0.0%)	1 (6.7%)	0 (0.0%)	
Mass regio colli	0 (0.0%)	0 (0.0%)	1 (6.7%)	0.790
Metastases ca	2 (13.3%)	2 (13.3%)	1 (6.7%)	
Pneumothorax	1 (6.7%)	0 (0.0%)	1 (6.7%)	
Pyopenumothorax	2 (13.3%)	1 (6.7%)	0 (0.0%)	
Mediastinal Tumour	1 (6.7%)	2 (13.3%)	1 (6.7%)	
Lung Tumour	6 (40.0%)	8 (53.3%)	9 (60.0%)	
Bronchoscopy results				
Endobronchial mass	0 (0.0%)	2 (13.3%)	1 (6.7%)	
Edema of the mucosa	0 (0.0%)	1 (6.7%)	0 (0.0%)	
Infiltrative Mass	2 (13.3%)	0 (0.0%)	1 (6.7%)	0.544
Vocal fold nodules	0 (0.0%)	1 (6.7%)	0 (0.0%)	
Compression Stenosis	6 (40.0%)	6 (40.0%)	8 (53.3%)	
Normal	7 (46.7%)	5 (33.3%)	5 (33.3%)	
Bronchoscopy Procedure				
Rinse	14 (93.3%)	12 (80.0%)	13 (86.0%)	
Rinse, Forceps	0 (0.0%)	2 (13.3%)	1 (6.7%)	0.524
Rinse, Brush	0 (0.0%)	1 (6.7%)	1 (6.7%)	
Rinses, Forceps, Brushes	1 (6.7%)	0 (0.0%)	0 (0.0%)	

Note: [a]nominal categorical data (Chi-square test); [b]normal distributed numeric data (Anova)

Table 2. Tests for Differences in HADS Scores Between the Lavender, Orange Aromatherapy Groups and the Control Group

Group	HADS (Anxiety)			
	Pretest	Postest	P	Deviation
Control	14.93±3.24	13.80±3.10	0.002[d]	-1.13±0 .83
Lavender	14.53±2.85	12.33±2.89	<0.001[c]	-2.20±1.21
Orange	15.40±2.03	13.60±2.56	0.001[c]	-1.80±1.61
P	0.691[a]	0.332[b]	---	0.040[b]

Note: The results of the observations were described with the mean±SD; [a]different test of unpaired groups passing the normality requirement (ANOVA); [b]the unpaired group differential test did not pass the normality requirement (Kruskal-Wallis); [c]the different test of paired groups passed the normality requirement (pair t-test); [d]the different test of paired groups did not pass the normality requirement (Wilcoxon-rank test). Changes are declared significant if the test results in P<0.05.

Table 3. Test of Respiration Rate Differences Between the Lavender, Orange Aromatherapy Groups and the Control Group

Group	Respiration rate			
	Pretest	Post-test	P	Deviation
Control	22.87±1.92	22.93±1.75	0.926[d]	0 .07±1.33
Lavender	23.27±2.02	21.67±1.84	<0.001[c]	-1.60±0.99
Orange	23.13±1.92	21.80±1.61	<0.001[c]	-1.33±0.98
P	0.850[a]	0.096[b]	---	<0.001[a]

Note: The results of the observations were described with the mean±SD; [a]different test of unpaired groups passing the normality requirement (ANOVA); [b]the unpaired group differential test did not pass the normality requirement (Kruskal-Wallis); [c]the different test of paired groups passed the normality requirements (pair t-test; [d]the paired group differential test did not pass the normality requirement (Wilcoxon-rank test). Changes are declared significant if the test results in P<0.05.

Table 4. Pulse Rate Difference Test Between the Lavender, Orange Aromatherapy Group and the Control Group

Group	Pulse			
	Pretest	Post-test	P	Deviation
Control	101.13±9.26	100.00±8.07	0.365[c]	-1.13±4.69
Lavender	93.07±8.15	89.87±8.35	<0.001[c]	-3.20±1.97
Orange	101.00±7.45	97.60±7.49	<0.001[c]	-3.40±2.82
P	0.015 [a]	0.003[a]	---	0.008[b]

Note: The results of the observations were described with the mean±SD; [a]different test of unpaired groups passing the normality requirement (ANOVA); [b]the unpaired group differential test did not pass the normality requirement (Kruskal-Wallis); [c]the different test of paired groups passed the normality requirements (pair t-test; [d]the paired group differential test did not pass the normality requirement (Wilcoxon-rank test). Changes are declared significant if the test results in P<0.05.

Table 5. Pain Score Difference Test Between the Lavender, Orange Aromatherapy Group and the Control Group

Group	Pain Score			
	Pretest	Posttest	P	Deviation
Control	42.00±14.24	46.00±13.52	0.083[d]	4.00±8.28
Lavender	52.67±13.87	42.67±13.35	0.001[d]	-10.00±6.55
Orange	54.67±13.02	45.33±11.87	<0.001[c]	-9.33±5.94
P	0.033[a]	0.698[b]	---	<0.001[b]

Note: The results of the observations were described with the mean±SD; [a]different test of unpaired groups passing the normality requirement (ANOVA); [b]the unpaired group differential test did not pass the normality requirement (Kruskal-Wallis); [c]the different test of paired groups passed the normality requirements (pair t-test; [d]the paired group differential test did not pass the normality requirement (Wilcoxon-rank test). Changes are declared significant if the test results in P<0.05.

Based on the post hoc test on the HADS score, it is known that the comparison of the control HADS score with lavender has a value of P=0.011. Comparison of control with orange P=0.083. The effectiveness differed

significantly between the lavender and orange groups compared to the control group in reducing the HADS score, whereas the aromatherapy treatment of lavender and orange was better at reducing the HADS score. There is no difference in effectiveness between lavender and orange P=0.622.

The difference in changes in the respiration rate of the lavender group pre-post test decreased on average -1.60±0.99; orange 1.33±0.98, while in control, there is an average increase of 0.07±1.33 (Table 3). The post hoc test compared the respiration rate of the control group with lavender with a value of P≤0.001, control compared to orange P=0.001, which means that the aromatherapy treatment group reduced the respiration rate significantly compared to the control group. Compared to the orange group, the lavender group did not differ significantly P=0.515.

The changes in pulse rate changes before the pre-post test showed that the average decrease in the lavender group was -3.20±1.97; orange -3.40±2.82; and control -1.13±4.69. Test different groups paired control group (P=0.365) means that the pulse rate decrease is insignificant. The lavender group P≤0.001, orange P≤0.001, means that the pulse rate decreased significantly in the treatment group (Table 4).

Post hoc test comparison of the pulse rate of the control group with a lavender value of P=0.004, control compared to orange P=0.011 means that the aromatherapy treatment group reduced pulse significantly compared to the control group. The lavender group compared to the orange group did not differ significantly P=0.900.

The pre-post-test pain VAS score in the lavender group -10.00±6.55; orange decreased -9.33±5.94; while in the control group, it increased by 4.00±8.28 (Table 5). Post hoc test comparison of pain VAS scores between the control group and lavender P≤0.001, control compared to orange P≤0.001 means that the aromatherapy treatment group reduced the pain VAS score significantly compared to the control group. Compared to the orange group, the lavender group did not differ significantly P=0.771.

DISCUSSION

This study found a total of 45 patients divided into 3 groups, the lavender aromatherapy treatment group, the group of people, and the control group. The most common sex in each group is male. Based on data from the National Institute of Health in 2019, there is an increase in studies regarding the role of gender in lung disease. The male sex is still dominant, but there is an increasing trend where there is an increase in the number of sufferers in the female sex, especially in chronic lung disease.

Factors that may play a role in this gender disparity include differences in the size of the lung organs in men and women, and differences in levels of the hormones estrogen and testosterone can also be factors that can affect the prevalence of

lung disease. In this study, the most common diagnosis was a lung tumour with suspicion of malignancy. Epidemiologically, lung malignancy also shows the same thing where the incidence in men is greater than in women, but the incidence of lung malignancy in women tends to increase yearly. Similar things, such as exposure to carcinogenic substances in the workplace or possible exposure to indoor air pollution, such as cooking fuel or household dust, can influence the increased incidence of malignancy in women.

The highest level of education varies in the three groups, which can be caused by demographic and cultural factors that are not evenly distributed in Indonesia. Most occupations on research subjects are farmers. According to data from the Central Statistics Agency for 2019, the number of people in Central Java who work in the agricultural sector has reached 5.16 million or around 30% of Central Java's population. Most diagnoses were lung tumours, 53.3% in the treatment group and 40% in the control group. This is in accordance with the findings of bronchoscopy, which is predominantly compression stenosis. There were no significant differences based on subject characteristics in the three groups, which means that the patient characteristics were homogeneous.

The HADS anxiety score of the lavender or orange treatment group significantly decreased compared to the control. The anxiety pretest of all groups averaged 14-15, classified as moderate anxiety. Feelings of ignorance can cause pre-bronchoscopy anxiety because all subjects have never had a bronchoscopy procedure before, so fear and anxiety arise regarding the course of the procedure, the possibility of pain appearing, and fear of the bronchoscopy results. Post-test HADS scores decreased with an average of 12-13 which is still classified as moderate anxiety.[10,21,22]

Even so, a statistically significant decrease in the score showed that aromatherapy in the treatment group effectively reduced HADS anxiety scores. Naturally, anxiety will decrease after the bronchoscopy is completed so that the score decreases in all three groups, but the decrease in the treatment group is statistically significant, while the decrease in the control group is not significant. These results are in accordance with the study of Ghiasi et al through a systematic analysis review that aromatherapy has an anxiolytic effect. Koulivand et al reviewed the effect of lavender aromatherapy on anxiety, where there were improvements in anxiety and mood in patients in ICU care.[10,21,22]

The active ingredients of citrus aromatherapy are similar to lavender, namely linalool and lynalyl acetate. Linalool inhibits acetylcholine release and alters the function of ion channels at the neuromuscular junction. Lynalyl acetate functions as a narcotic and sedative agent. The active substance also has the potential to bind to 5HT-1A receptors in the brain, thereby triggering activation of the autonomic nervous system and HPA axis to change emotional perception and reduce anxiety.[12,22,24]

The respiration rate of the treatment group decreased to the upper limit of normal breathing, which was 20 times/minute, while the control group did not differ from the pretest. Lavender and orange aromatherapy were able to reduce respiration rate better than the control group, where the lavender group compared to the orange had no significantly different effectiveness in reducing respiration rate. These results are in accordance with the study of Slamati et al, who conducted a study on the effect of inhalation aromatherapy on vital signs in ICU patients undergoing open heart surgery, where there were significant differences between the control and treatment groups regarding blood pressure, respiration rate, and pulse.[26–28]

Bikmoradi et al conveyed that inhalation aromatherapy research effectively reduced stress, anxiety, and pain and controlled vital signs in women undergoing cesarean sections. The effect of aromatherapy on the control of respiration rate arises through the work of aromatherapy in the amygdala, thalamus, and cerebral cortex, which triggers the activation of the adrenal glands which regulate the hormones adrenaline and noradrenaline, which results in a decrease in the respiratory rate.[10,11,21,22]

There was a significant decrease in pulse rate in the treatment group, where the pulse rate fell in the normal range of 60-100 beats/minute. In the control group, the pulse rate decreased but not significantly. However, it should be noted that in this study, not all groups were at the same initial or baseline conditions. This is similar to the results of Salamati et al's study, where there was a significant decrease in heart rate in the aromatherapy group compared to controls in patients with open heart surgery. When the patient inhales aromatherapy, there is an increase in blood flow rate and a decrease in systolic blood pressure, which indicates a decrease in parasympathetic nervous activity characterized by a decrease in pulse rate. This is synergistic with the effect of aromatherapy which triggers the activation of the adrenal glands in regulating the hormones adrenaline and noradrenaline.[8,9,11]

The VAS pain score in the treatment group decreased significantly, while the control group had increased pain scores. Pain stimuli can cause an increase in the pain score in the control group during bronchoscopy, which can occur when the device is inserted, or an action is taken. Research by Kim et al states that inhalation aromatherapy can reduce the need for opioid analgesics in postoperative breast biopsy patients. Sasannejad et al's study, stated that aromatherapy could reduce pain in acute migraine patients.[10,21,22]

The analgesic effect of aromatherapy is due to the role of opioidergic neurotransmission in inducing analgesia. Aromatherapy active substances can modulate GABAergic neurotransmission, especially GABAa receptors and increase the inhibitory tone of the nervous system in the anterior cingulate cortex, thereby triggering changes in the perception of pain.[11,22,24]

Limitations of this study include the condition of the subjects at baseline not being in the same condition and not carrying out objective laboratory assessments, such as assessing anxiety by measuring cortisol levels in saliva or other indicators. There is variability in the aromatherapy essential oils used which can be due to differences in species or plant varieties or in the process of making essential oils. Follow-up research accompanied by objective assessments and satisfaction index assessments can be conducted to further confirm the effectiveness of aromatherapy in patients undergoing bronchoscopy.

CONCLUSION

Based on the description above, it can be concluded that aromatherapy with the essential oils of lavender, and orange, is effective in reducing anxiety and controlling respiration rate, pulse, and pain in patients undergoing bronchoscopy procedures. There is no difference in effectiveness between lavender and orange aromatherapy.

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Case Report

Remarkable Breakthrough: Unleashing the Power of Paclitaxel and Carboplatin in Defeating Squamous Cell Carcinoma (SCC) of the Lungs - A Compelling Case Report

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Abstract

Background: This case report focuses on the evaluation of treatment efficacy in a 64-year-old male patient diagnosed with stage IVA lung squamous cell carcinoma (SCC) in the right upper lobe. The patient underwent chemotherapy using paclitaxel and carboplatin, administered in measured doses over six cycles. Close monitoring of patients was conducted throughout the treatment period, taking into account their clinical condition.

Case: The patient underwent a computerized tomography (CT) examination before starting treatment, followed by a comparison in the third month of treatment. Encouragingly, significant clinical improvement was observed with respect to the initial complaint. The patient achieved an excellent response, the tumor appearance disappeared and the previous size was assessed by Partial Response (PR) based on RECIST criteria.

Discussions: The administration of paclitaxel and carboplatin in patients with SCC gave positive results. Metered doses and scheduled administration allow for effective disease management, leading to substantial clinical improvement. The case studies highlight the potential of this treatment regimen in treating SCC, emphasizing the importance of close monitoring during therapy.

Conclusion: This case report underscores the promising results obtained with paclitaxel and carboplatin in the treatment of lung SCC. The patient's notable response, marked by clinical improvement and achieving a partial response based on RECIST criteria, exemplifies the potential of this therapeutic approach. Further investigations and clinical trials are warranted to explore the broader applicability and efficacy of this regimen.

Keywords: carboplatin, paclitaxel, squamous cell carcinoma

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide and its incidence is intrinsically linked to smoking. Most lung cancers are non-small cell lung cancers (NSCLC) which are divided into squamous and non-squamous histology. The NSCLC accounts for 85% of all lung cancers.[1]

Adenocarcinoma and squamous cell carcinoma (SCC) are the most frequent histologic subtypes, accounting for 50% and 30% of NSCLC cases, respectively.[2]

Although the incidence of lung SCC is decreasing as a consequence of changes in tobacco consumption habits, SCC is still a major health issue.[3] Patients with advanced or metastatic NSCLC have a poor prognosis. Chemotherapy with doublet platinum-based compounds is recommended as the first-line treatment for advanced NSCLC patients, but the treatment benefit is limited.[4]

The Eastern Cooperative Oncology Group (ECOG) conducted a randomized study to compare the efficacy and safety of four common platinum-based treatments (cisplatin and gemcitabine, cisplatin and docetaxel, paclitaxel and carboplatin, or paclitaxel and cisplatin). No significant difference in overall survival was found.[5]

CASE

A 64-year-old man with complaint of occasional shortness of breath since the last 2 months, which has worsened in the last week, visited our hospital in June 2022. The current patient, a smoker (1 pack/day for 42 years), was diagnosed with stage IVA lung SCC. Computed tomography (CT) of the chest revealed a tumor in the right upper lobe of the lung with mediastinal invasion and SVC narrowing. A transbronchial lung biopsy confirmed the presence of SCC. In order to treat the disease, the patient underwent chemotherapy with carboplatin (747 mg) and paclitaxel (318 mg) for six cycles.

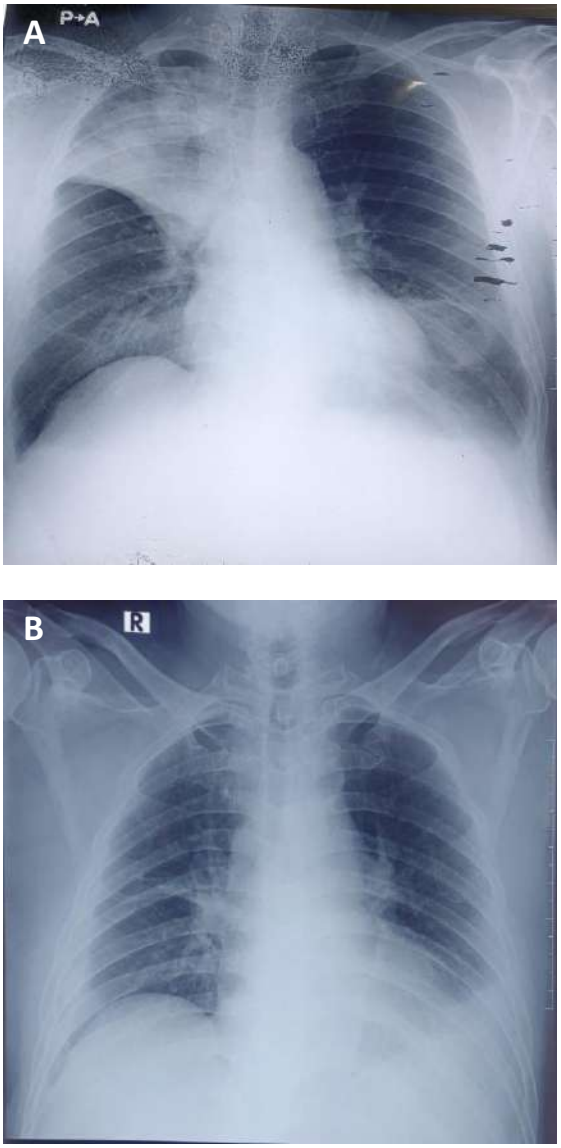

Figure 1. A) Chest X-ray at the start of chemotherapy, demonstrating a shadow in the right upper field, left pleural effusion, and an enlarged cardiac silhouette; B) Chest X-ray, four months after chemotherapy, showing improvement in the right upper lung but persistent left pleural effusion.

Upon first admission to the hospital, the patient's vital signs were as follows: heart rate 111 bpm, blood pressure 149/95 mmHg, and body temperature 36.2 °C. Percutaneous arterial blood oxygen saturation was 90% in ambient air and the patient had a respiratory rate of 24 breaths per minute. The patient could be concluded

to have ECOG Performance Status 2, based on the ECOG Performance Status Scale.

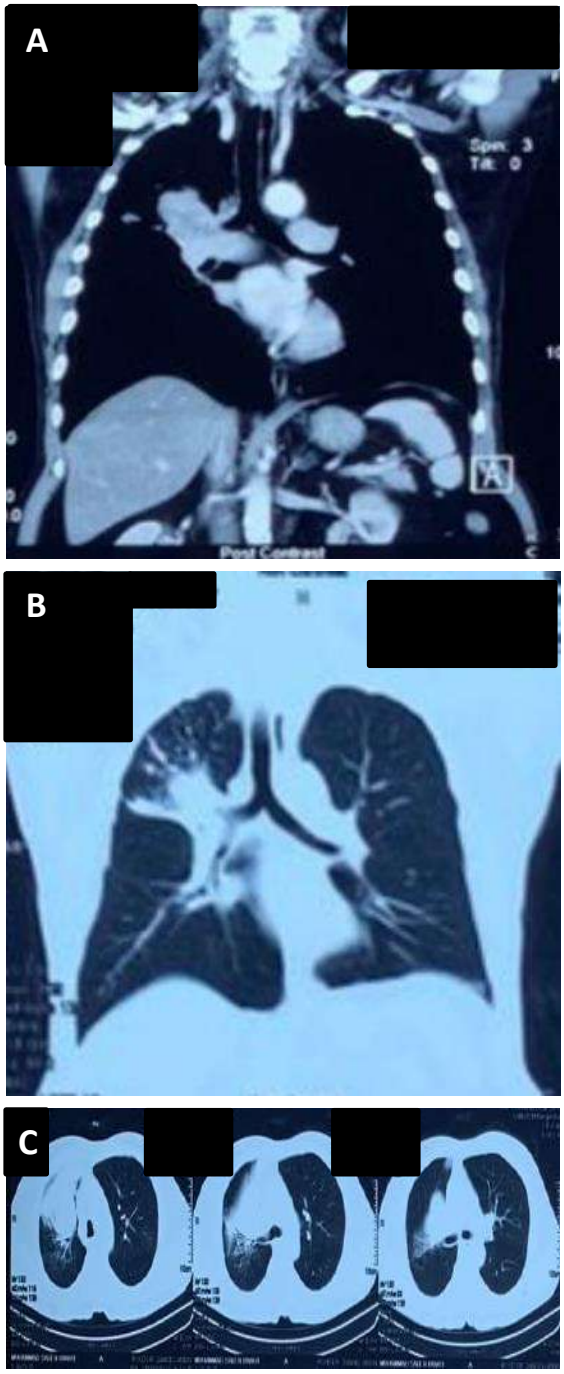

Figure 2. The initial CT scan shows a lobulated heterogeneous mass measuring 5.72 x 4.45 x 3.9 cm in the superior segment of the apical anterior lobe, with partial lung collapse and surrounding infiltrates, enlarged paratracheal and multiple subcarina lymph nodes, non-thickened pleura, and bilateral pleural effusions

After undergoing 4 cycles of chemotherapy, the patient's vital sign examination revealed a heart rate of 87 bpm, a blood pressure of 123/85 mmHg, and a body temperature of 36.4°C. Percutaneous arterial blood oxygen saturation was 97% in ambient air, while the respiratory rate was 20 breaths per minute. The patient could be concluded to have ECOG Performance Status 1, based on the ECOG Performance Status Scale.

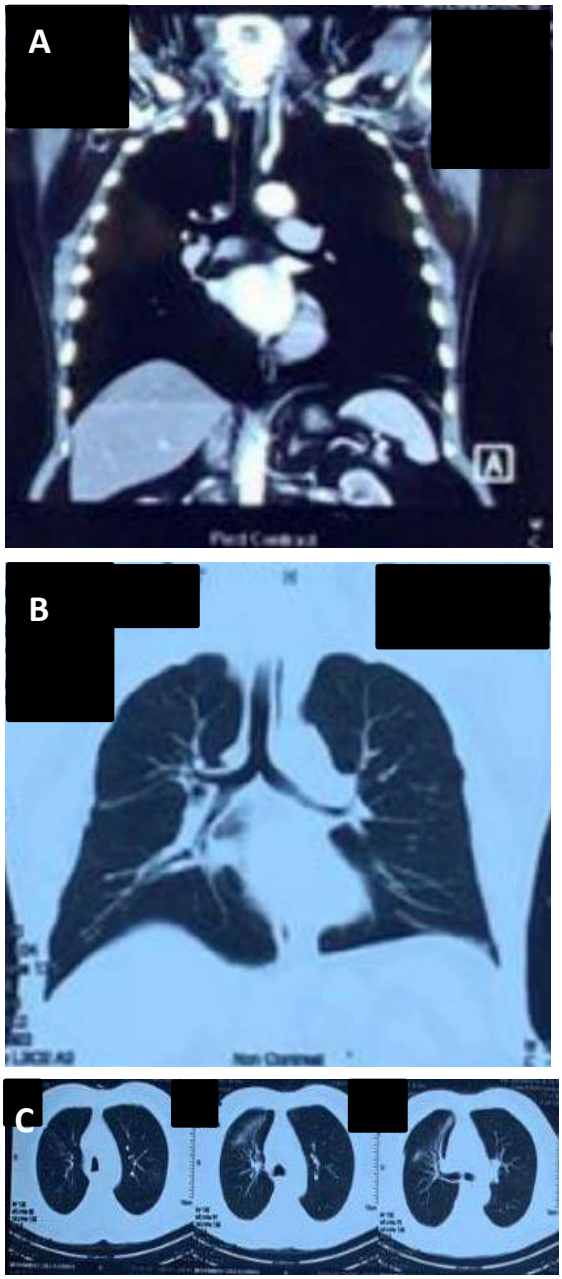

Figure 3. The second CT scan, performed 3 months after chemotherapy, does not show any lung mass, minimal fluid density in bilateral pleural cavity, fibrosis in the anterior apical segment of the right lung lobe, and lymph nodes <1 cm in the right paratracheal.

On examination, normal heart sounds were heard, but there were decreased breath sounds at the base of the left lung. The patient showed swelling of the superficial chest veins but no edema of the face or upper extremities. During treatment, the patient received 3 liters per minute (lpm) of nasal oxygen through a cannula, and therapy was adjusted according to the patient's clinical condition.

Encouragingly, clinical improvement was observed within the first week of treatment. As a result, the patient was allowed to continue treatment on an outpatient basis and scheduled routine checks at the pulmonary clinic according to the chemotherapy schedule.

Recist Evaluation

1. Subjective Evaluation. The patient admits an improvement in the symptoms before chemotherapy is started, such as improved shortness of breath, improved chest pain, improved complaints of weakness, and cough that disappears.
2. Semi-Objective Evaluation. Clinical improvement was found in these patients, with improvement in pain complained of from Numeric Rating Scale (NRS) 7-8 to NRS 3-4. Likewise, complaints of shortness of breath decreased from 24 times per minute to 20 times per minute, and also improvements in blood saturation levels started from 90% of room air to 99% of room air.
3. Objective Evaluation. In this case, the evaluation includes the initial chest X-ray, which shows a right upper field shadow, left pleural effusion, and an enlarged cardiac silhouette. The follow-up chest X-ray, four months after chemotherapy, indicates improvement in the right upper lung but persistent left pleural effusion. Additionally, the initial CT scan reveals a lobulated heterogeneous mass measuring 5.72x4.45x3.9 cm in the superior segment of the apical anterior lobe. The second CT scan does not show any lung masses.
4. Side Effects. During the administration of therapy, the patient claimed to be nauseous in the first few hours after chemotherapy, but these complaints improved after some time.

DISCUSSION

In organs other than the lungs, such as head and neck SCC, weekly carboplatin and paclitaxel are also good options as first-line therapy for recurrent/metastatic SCC.[4] The different responses to carboplatin treatment depend on individual factors and resistance mechanisms. During chemotherapy, dexamethasone is applied as an antiemetic. Evaluation was carried out after 3 cycles of chemotherapy in this patient, and many changes occurred, starting from the loss of mass in the affected lung to clinical improvement in this patient, so that it was considered a partial response (PR) according to RECIST criteria.[6] In this case, the potential efficacy and side effects of chemotherapy as a

treatment for lung cancer in this patient can be seen

While recent studies have suggested a poor prognosis for lung cancer patients, this patient showed significant improvement in symptoms and overall condition after receiving chemotherapy. It is important to highlight the benefits of chemotherapy in this case as well as the potential challenges that patients may face in managing side effects.[7,8]

Additionally, future research may explore alternative treatment options or combination therapies that could further improve outcomes for lung cancer patients. Overall, this case provides valuable insights into the management of lung cancer and the potential for positive outcomes with appropriate treatment.[7,8]

It should be noted that although the patient showed improvement in symptoms, reduced mass size, reduced number of nodules and less effusion, further evaluation is still required in the remaining few cycles to determine if the response to therapy is truly present and improving. This evaluation is crucial to understanding the extent of the disease and adapting the treatment strategy to the patient's specific needs in the future.

CONCLUSION

Further research is still required to gain a comprehensive understanding of the long-term efficacy and potential side effects associated with the combination therapy of paclitaxel and carboplatin. Continued investigation will help refine treatment strategies and improve outcomes for patients with pulmonary SCC.

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Literature Review

Immunopathogenesis of Silicotuberculosis: A Literature Review

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Abstract

Silicotuberculosis is a tuberculosis infection that emerges as a silicosis complication. A silicosis patient is 2.8 to 39 times more likely to develop pulmonary tuberculosis (TB). Moreover, the fibrotic condition caused by silicosis may exacerbate the symptoms and worsen the clinical outcome of silicotuberculosis patients. The current report suggests that the immune system plays an important role in the pathogenesis of this disease. Silicosis or silica exposure might interfere with the immunological response, especially the macrophages, which permit the *Mycobacterium tuberculosis* to infect the host. In this literature review, we will discuss the definition, epidemiology, and immunopathogenesis of silicotuberculosis.

Keywords: *Mycobacterium tuberculosis*, silica, silicotuberculosis

INTRODUCTION

A pneumoconiosis called silicosis, one of the oldest industrial diseases, is brought on by breathing in inorganic dust for an extended period that has high concentrations (>10%) of free crystalline silica (SiO_2).[1] Inflammation, the development of silicotic nodules, and fibrosis which are gradual and irreversible-define this interstitial lung disease.[2]

There are various names for this illness, including Potter's rot, Grinder's asthma, and Miner's pthisis.[2,3] Silicosis is brought on by the prolonged inhalation and deposition of silica crystals (SiO_2/silicon dioxide).[4] Hippocrates noted the link between silica dust exposure and respiratory diseases in 430 BC, and Agricol discovered it in the 16th century. Rammazini's studies in 1713 using postmortem silicotic nodules established the connection even more.[1]

Depending on the length of time and the severity of exposure to silica dust, the latency period for silicosis can last anywhere from a few years to many decades. Due to the prolonged latency period in several occupational pulmonary diseases, such as silicosis, mesothelioma, and asbestosis, the diagnosis may be delayed, which can have detrimental effects on the course of the disease.[5]

The majority of the earth's crust, 59%, is composed of the mineral silica. In order to be inhaled and reach the alveoli,

silica crystal particles typically have a diameter of less than 5 μm.[6] This size results from industrial work procedures such as cutting, crushing, and grinding materials. This is the reason why people who work in the building construction industry, glass industry, jewelry industry, gold mining, ceramics industry, and other industries frequently get silicosis.[7]

Individuals inhaling silica crystals may be at risk for cardiovascular, COPD, autoimmune, and tuberculosis (TB) illnesses.[8] Patients with silicosis can develop silicotuberculosis, a TB infection, as a secondary illness. Patients with silicosis have a 2.8 to 39-fold increased chance of contracting pulmonary TB and a 3.7-fold increased risk of contracting extrapulmonary TB.[8,9]

Understanding the immunopathogenesis of silicotuberculosis is crucial because it helps us better understand how the human immune system contributes to the development of post-silicosis TB infection.

EPIDEMIOLOGY

It is challenging to estimate the prevalence of silicotuberculosis on a global scale. In countries with poor economic levels, silicosis and silicotuberculosis are more common. This is a result of inadequate training in the use of safety equipment and compliance with occupational safety laws.[9] Silica crystal inhalation may also increase a person's risk of developing autoimmune diseases, neoplasms, cardiovascular issues, chronic obstructive pulmonary disease (COPD), and TB infections.[10]

According to a 2015 study on 3,121 employees in Iran, there were 917 cases of silicosis for every 100,000 people, and there were 172 cases of silicotuberculosis for every 100,000 people in the same group.[11] Additionally, among those who had been exposed to silica but did not have silicosis, there were 69 cases of TB infection per 100,000 people. The study found that smoking, being older than 30, and having worked for more than ten years are all risk factors for developing silicotuberculosis.[11,12]

Research conducted in the United States also showed an increase in the mean Odds Ratio (OR) of 2.48 in the group of workers who had prolonged exposure to silica.[9] Several other risk factors, such as male gender, HIV infection, smoking, COPD, migration, and the severity of silicosis can be triggers for silicotuberculosis.[13]

BASIC IMMUNOLOGY

The body's defense responses are mediated by the immune system, which is made up of many cells, tissues, and chemicals.[10] The immune system defends the body from harmful foreign substances like bacteria, viruses, cancer cells, and poisons. Innate immunity and adaptive immunity are the two main divisions of the immune system.[14]

The body's initial line of defense against infections that enter the body is innate immunity, sometimes referred to as

natural or naive immunity. The non-specific defense mechanisms of innate immunity might become active right away or several hours after being exposed to antigens.[15] The particular immune system or acquired immune system are other names for adaptive immunity. After antigen exposure, adaptive immunity requires some time to respond at its best.[14]

INNATE IMMUNOLOGY

The body's first line of defense against diseases or foreign objects is innate immunity, which has a quick response. By producing cytokines, innate immunity works to draw immune cells to areas of infection and inflammation. Small proteins called cytokines serve as intermediaries between immune cells.[14,15]

Antibodies, proteins, and glycoproteins are released as a result of cytokine synthesis, activating the complement system. Dead cells and foreign bodies found in organs, tissues, blood, and lymph are removed during this process. Antigen-presenting cells (APC), which present antigens to adaptive immunity, help the innate immune system activate adaptive immunity.[15,16]

Anatomical defenses, physiological defenses, endocytic-phagocytic defenses, and inflammatory processes make up the four types of defenses that compose innate immunity.[15] Anatomical defenses include skin and mucosa, while physiological defenses include temperature, pH, and chemical mediators. The skin and mucosa's epithelial barrier is the first line of defense in innate immunity, stimulated by microorganisms. Other defense mechanisms include phagocytic cells, lymphoid cells, plasma proteins, and complement system.[16,17]

ADAPTIVE IMMUNOLOGY

Ineffective innate immunity prevents pathogen removal, while adaptive immunity identifies antigens, eliminates pathogens, and develops immunologic memory.[17] Humoral and cellular immunity involve B lymphocytes producing antibodies for homing immunity.[17–19] T-lymphocyte activation leads to cellular immunity as APC phagocytosis and binding to MHC molecules activate T-lymphocytes, triggering cytokine production and immune system regulation.[18,19]

Table 1. Aspects of Innate Immunity Cells

Cell	Function
Phagocytes	Includes neutrophils and macrophages, function to phagocytose of foreign bodies. Granules seen in neutrophils destroy harmful organisms.
Dendritic Cells	Phagocytosis and APC have a role in mediating innate and adaptive immunity.
Mast Cells	Function to start an immediate inflammatory reaction. The connective tissue contains these cells.
Basophils	Possess the same purpose as mast cells but are found in the bloodstream.
Eosinophils	Phagocytic, able to eat parasites that are too big to fit within its cells.
Natural Killer (NK)	By producing porphyrins and granzymes that cause apoptosis, this enzyme contributes to the rejection of tumors and the killing of virus-infected cells.

In the bone marrow, hemopoietic stem cells give rise to B lymphocytes. All antigens can be recognized by B cells, which do not function as APC. In addition to producing antibodies, B cells participate in the humoral immune response. B lymphocytes generate five distinct antibody subtypes.

SILICA

Silica, a common mineral, can be crystalline or amorphous, causing lung and organ toxicity after inhalation. Quartz, tridymite, and cristobalite are crystalline forms.[19,20] The resulting silica crystal dust often has no color and smell. Silica crystals smaller than 5 μm can be breathed in until they reach the alveoli, and those larger than 10 μm can pass through the airway. Silica that is crystalline is more harmful than non-crystalline silica. Silica, a common mineral like silica, quartz, tridymite and cristobalite cause lung and organ toxicity.[20]

Piezoelectricity in crystalline silica increases cytotoxicity due to electrical polarity and the formation of reactive silica crystals, causing increased reactive oxygen species production.[21] Crystalline silica is more harmful than non-crystalline silica, causing lung and organ toxicity.[22]

SILICOTUBERCULOSIS

Silicosis is a lung condition that damages lung tissue and progresses without cure. Reaching the silicosis elimination goal by 2030 is challenging due to workplace concerns in 13 middle- to low-income countries.[23,24]

One of the most frequent comorbidities linked to silicosis is pulmonary TB, which is more prevalent in underdeveloped nations. Silico-TB is silicosis with active TB on top. According to estimates, people with silicosis had a 2.8 relative risk of getting pulmonary TB.[24] One-fourth of individuals with silicosis and coal workers' pneumoconiosis, which are frequently characterized by "eggshell calcification" of peripheral lymph nodes, have silico-TB.[25]

Severe silicosis increases TB risk; exposure to silica dust increases risk.[24,25] Experimental studies show that silica crystals inhibit macrophage function, increasing vulnerability to TB infection and increasing the reactivation risk.[25]

IMMUNOPATHOGENESIS

Respirable silica particle inhalation causes mineral deposits, inflammatory pulmonary tissue reactions, and fibrosis. The severity and pathogenicity of the disease depend on the amount and duration of exposure. Long-term exposure can lead to repeated airway injuries and deplete airway epithelial stem cells, causing pulmonary silicosis.[26]

When someone breathes in silica, their immune system is activated. Numeorus studies have concentrated on early silica exposure, lung cells, and modifications in the innate immune cell response.[27] There are five primary ways in which silica can harm an object (Figure 1). Alveolar macrophages and broncho-alveolar epithelial cells come into contact

with silica crystals that have entered the alveoli. Due to their piezoelectricity, which can result in electrical polarity, silica crystals can inflict immediate injury when they come into contact. Inflammation and lipid peroxidation of bronchoalveolar cells are the results of this.[28,29]

Alveolar macrophages will also phagocytize silica crystals. This scenario results in a respiratory burst and increased oxygen consumption, which raises the levels of ROS, reactive nitrogen species (RNS), and inducible nitric oxide synthase (iNOS).[29]

The amino acid L-arginine is changed by the presence of iNOS into L-citrulline, which interacts with superoxide to produce peroxynitrite, which harms mitochondria and deoxyribonucleic acid (DNA). After dying, macrophage cells will once again release silica crystals. Other alveolar macrophage cells will once more phagocytize silica crystals that are not completely destroyed.[29]

An inflammatory process is brought on by the interaction of silica, macrophages, and epithelial cells, which activate neutrophils and lymphocytes in the injured area. The creation of Interleukin (IL)-1, which promotes nuclear factor kappa beta (NF-κB) translocation from the cytoplasm to the nucleus and binds to DNA, is the following process. Pro-IL-1 is then translated and transcriptionally transcribed (Figure 1). Additionally, inflammatory cytokines such as leukotriene B4, Fas Ligand (FasL), macrophage inflammatory protein (MIP)-1, MIP-2, tumor necrosis factor (TNF)-, interferon (IFN), and IL-6 are released.[30,31]

Scavenger Receptor (SR)-A and Macrophage Receptor with Collagenous Structure (MARCO) on macrophages are additional receptors that can identify and phagocytose foreign objects to be eliminated from the alveoli. One of the pattern recognition receptors (PRR) is called MARCO.[28–30]

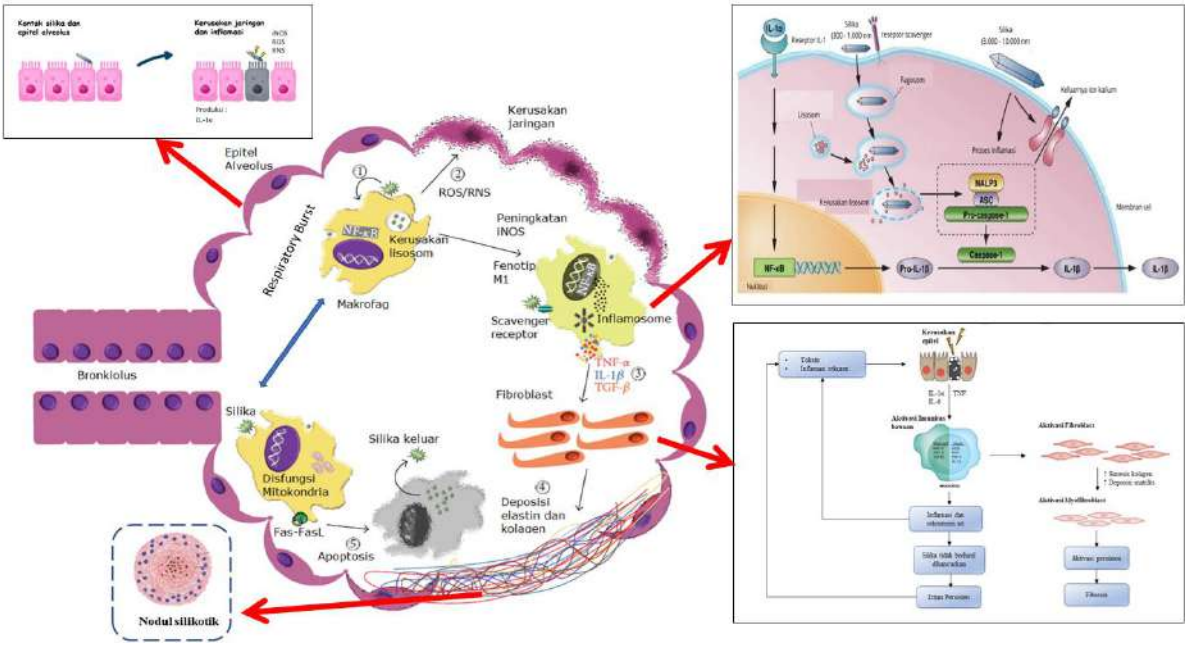

Figure 1. Immunopathogenesis of Silicosis

Macrophages that engulf silica crystals will damage the phagosome and discharge their contents into the cytoplasm. Adipose-derived stem cells (ASC), pro-caspase-1, and nicotinamide adenine dinucleotide phosphate (NALP-3) inflammasomes are all activated as a result. Pro-inflammatory IL-1 is created when inflammasomes break down pro-IL-1. IL-18 production and intracellular potassium ion release are also triggered by NALP-3 inflammasome activation.[28–30] Additionally, interactions between lymphocytes can readily activate NALP-3 inflammasomes. In this route, T cells express T-lymphocyte antigen 4 (TLA-4) IL-10, and transforming growth factor (TGF)-β.[30]

During the silicosis process, increased TNF expression results in fibroblast recruitment and proliferation. TGF causes fibroblasts to assemble in the injured area, where it induces collagen deposition and enhanced elastin production. The lung parenchyma undergoes structural alterations as a result of increased expression of metalloproteinase (MMP)-2 & MMP-9 and tissue inhibitors of metalloproteinase (TIMP)-1 & TIMP-2.[32]

Fibrosis and lung remodeling are caused by an increase in silica-induced tissue injury, extracellular matrix degradation by MMPs, and concentric aggravation of collagen deposition (Figure 1).[28,32] Nodular lesions will develop if free silica crystals are encircled by fibroblasts and collagen. These silica nodules are made up of fibroblasts and collagen surrounding an acellular zone loaded with silica in the center.[30,32]

Apoptosis induction in macrophages is a potential consequence of silica exposure. It is well known that TNF and FasL interact with cell death receptors to start the apoptotic cascade. Dysfunction of the mitochondrial caspase is the cause of apoptosis. Oxidative stress, which lowers mitochondrial potential, leads to mitochondrial malfunction.[29,30]

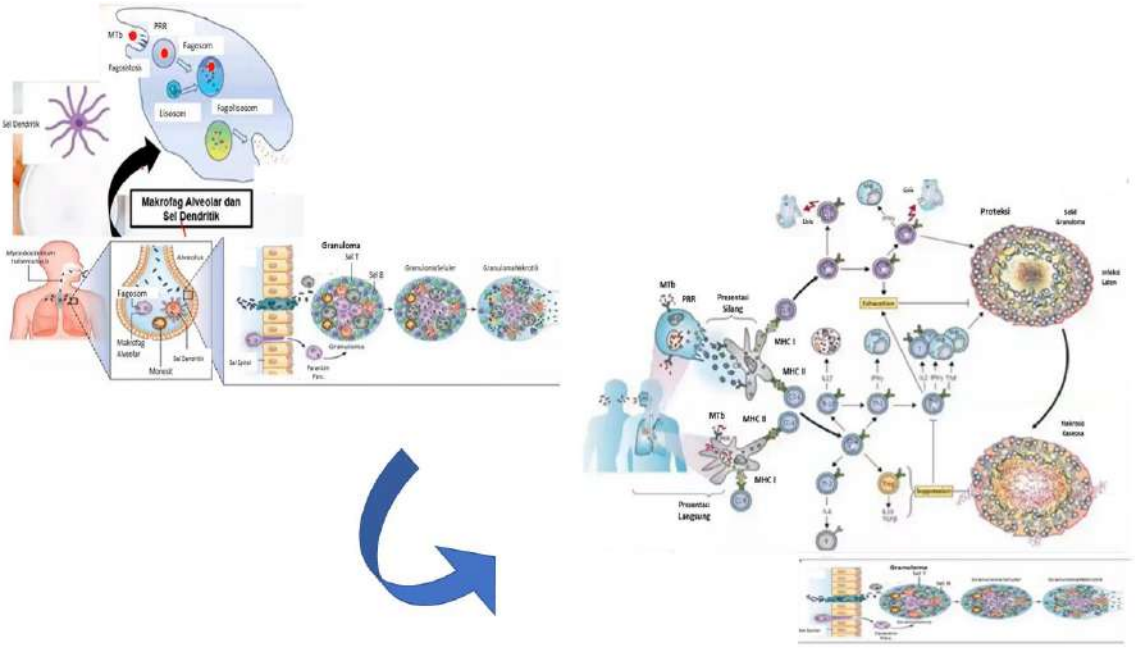

Figure 2. Immunopathogenesis of Tuberculosis

DNA fragmentation and caspase-9 and caspase-3 activation are caused by this mechanism. In addition to re-secreting silica crystals and chemotactic substances that worsen the already present inflammation, macrophage cells will undergo death.[29,30]

Dendritic cells increased as a result of the apoptosis that occurred following silica exposure, which reduced the number of alveolar macrophages. It is well established that non-specific interference with the inflammatory response lowers dendritic cell viability and activity.[33] In addition to interfering with the function of dendritic cells and macrophages, silica particles also have an impact on neutrophil cells. Similar to macrophages, neutrophils have lower vitality and phagocytic capacity.[13,33] A study found that NK cells grew more in spleens that had been exposed to silica nanoparticles.[34]

The inhalation of MTB-containing droplets or aerosolization actions is the first step in the MTB infection process, which is supported by several risk factors.[33] Human Immunodeficiency Virus (HIV) and other immunocompromising disorders, those taking long-term immunosuppressant medications, smokers, drinkers, children under the age of five, contact with active TB patients, and slum surroundings are some of the risk factors that affect MTB transmission.[35]

The number of organisms present, their concentration, and the amount of time a person spends breathing contaminated air are some of the variables that affect MTB transmission in the air.[33–35]

MTB has a complicated component structure under the microscope, and its cell wall contains 40% mycolic acid. The cell wall of MTB is made of mycolic acid, which makes it exceedingly robust and challenging to study via gram staining. MTB is characterized as an Acid Resistant Bacillus (Acid-Fast Bacilli/AFB) because of its bacillus shape and the mycolic acid component, a fatty acid with a role in cell wall impermeability. Additionally, MTB contains barriers against macrophage phagocytosis[32]

The immune system of the body is formed by MTB intake through the upper airways in a complex manner, beginning with the innate immune system and stimulating the activation of the adaptive immune system (Figure 2).[35] The mucosa in the airway will react to MTB inhalation into the airway first. Alveolar macrophages and mucosal immune cells, specifically dendritic cells, will interact at the same time (Figure 2).[35,36]

Macrophages will identify MTB as PAMPs (pathogen-associated molecular patterns) via the mucosal antigen receptor PRR. The body's battle to get rid of MTB is carried out by macrophages phagocytosing it. The three stages of this process are antigen adhesion to the cell membrane, lysosomal enzyme harvesting, and breakdown.[35,36]

Hepsoprotein (HSP) is one of MTB's defense mechanisms. A hit-shock response is the result of MTB with HSP, and it stresses the cells in the body. Additionally, MTB damages its link with lysosomal enzymes, neutralizes phagosomes by

reducing pH, and is resistant to lysosomal enzymes. The ability of macrophages to eradicate MTB reaches a threshold due to the MTB resistance mechanism. Adaptor proteins are recruited by NF-κB positive macrophage components to activate pro-inflammatory cytokines, chemokines, and other antimicrobial compounds. Additionally, through MHC I and MHC II, macrophages that serve as APC will trigger adaptive immunity.[35,36]

When adaptive immunity is engaged, all pro-inflammatory cytokines are released and assembled into solid granulomas (Figure 2). Caseous necrosis will arise by encapsulating solid granulomas.[35] The immune system performs this process because MTB is an aerobic organism that requires oxygen and nutrients to exist in the body. However, at this time, MTB can also dormant and create a latent TB infection. The reactivation of MTB and the hematogenous or lymphogenous propagation of the infection will be influenced by host risk factors.[36,37]

MTB infection is more likely to occur in those who have silicosis or have been exposed to silica crystals (Figure 3). Droplets of less than 5 μm in size that contain MTB nuclei can enter the alveoli when breathed in. The MTB will come into contact with other APC and alveolar macrophages. The PAMP structure of MTB can be recognized by APC PRRs. One PRR that is crucial to the development of bacterial infection is the toll-like receptor (TLR). The macrophages will then identify MTB and phagocytize it.[36]

With the assistance of host risk factors for silicosis and TB, this process will mark the onset of silicotuberculosis (Figure 3). Repeated occurrence of this mechanism will result in a clinical course that progresses along with the concurrent creation of silicotic nodules and caseous necrosis.[36,37]

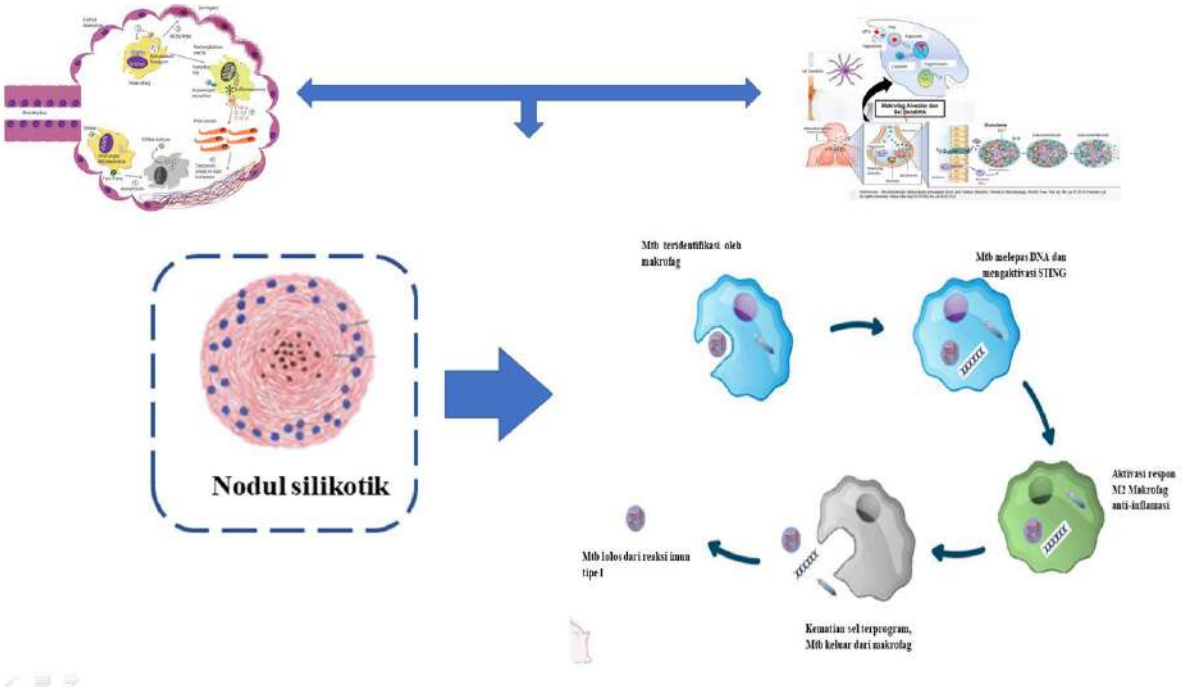

Figure 3. Immunopathogenesis of Silicotuberculosis

The cytosolic surveillance mechanism uses cyclic guanosine monophosphate (cGMP)-AMP Synthase (cGAS) to identify DNA released by MTB residing in macrophages. A type I IFN response is brought on by this process, which also activates the adaptor molecule Stimulator of IFN Genes (STING).[36]

The presence of silica crystals boosts MTB DNA's ability to polarize macrophages into the anti-inflammatory M2 phenotype. Type 2 cytokines like IL-10, which are secreted by M2 macrophages, block type I cytokines including TNF-, IFN, and IL-12. Through the production of reactive oxygen intermediates (ROI) and reactive nitrogen intermediates (RNI) in the late phase of phagosomes, the IFN cytokine is crucial in the elimination of MTB. MTB bacteria may survive when the release of IFN cytokines is inhibited (Table 2). MTB can persist in silicotic nodules in addition to macrophages.[33,34]

Through the synthesis of the eicosanoids prostaglandin E2 (PGE2) and lipoxin A4 (LXA4), surviving MTB will cause programmed cell death. Cell DNA and MTB will be released from within the cell and enter the extracellular milieu as a result of this process. Due to this mechanism, MTB can avoid the type I immune response, which is the body's main line of defense against eliminating pathogenic invaders.[37] APCs include dendritic cells and alveolar macrophage cells. These cells can identify antigens and connect to T lymphocytes in the adaptive immune system.[37,38]

Reduced macrophage viability and function are the result of macrophage apoptosis, which is the outcome of the silicosis mechanism. As a result, the MTB infection's ability to penetrate and harm the lung parenchyma increases. Both cells are prevented from delivering MTB antigens to T lymphocytes as a result of this mechanism.[39] As a result, the adaptive immune system's ability to activate normally will be compromised, which makes it impossible to stop the spread of MTB.[40]

Table 2. Immune Responses to Silica Exposure and Silicotuberculosis

Immune System	Silica	Silicotuberculosis
Macrophages	Apoptosis induction, the development of fibrotic nodules, the activation of inflammatory and chronic anti-inflammatory pathways, and the creation of ROS and RNI	Research on impaired MTB response is still needed
Dendritic cells	Lessening viability	Still requiring research
Neutrophils	decreased viability and phagocytosis	Still requiring research
Natural killer	A rise in NK	Still requiring research
Antigens	There is still conflicting evidence.	Still requiring research
CD 4+, CD 8+, δγ T cells	Apoptosis is elevated, Th1/Th2 responses are altered, T-reg is activated, and T cell inhibitory activity is decreased in response to increased FAS ligand.	Research is still needed because the evidence is inconsistent and intermittent.
B cells	B cell activity both increasing and decreasing, increased autoantibodies	Still requiring research

Further research must be carried out to determine the precise mechanism of this process. A future study is required to completely understand the role of different immune cell components in the immunopathogenesis of silicotuberculosis (Table 2).[32,39]

A mixed pathological state of silicotic nodules and caseous necrosis can result from silicosis plus MTB infection. According to certain journals, MTB can also persist in silicotic nodes and result in caseous necrosis. MTB will survive and wait to reactivate until the host immunity factor drops. This is the reason of a patient's clinical state who is suspected of having silicotuberculosis cannot be determined by radiologic evaluation. Chest pain, severe shortness of breath, and a cough with phlegm that may or may not contain blood are signs of silicotuberculosis. Complaints of coughing may be a sign that the lung parenchyma has developed cavities.[13,41]

This immunopathologic silicotuberculosis series can be used as a guide in the clinical setting to identify occupational lung disease. To determine the exact cause of silicotuberculosis cases and the process of the disease, more testing is necessary. To establish the presence of silicosis and TB, a number of supportive investigations can be carried out, including thoracic photos, computed tomography (CT-scan), and histopathological testing. By using samples obtained from bronchoalveolar lavage (BAL) testing along with histopathological investigation, recommendations can be made to confirm both diseases. Caseous necrosis or the presence of silicotic nodules might be noticed on a histopathologic examination.[13,41]

For the purpose of obtaining a histopathologic image of the silicotuberculous lung, a lung dissection study for silicotuberculosis in BALB/c mice was performed (Figure 4). To create a mouse model of silicotuberculosis, intratracheally exposed BALB/c mice were injected with MTB 107 colony-forming units (CFU).[41]

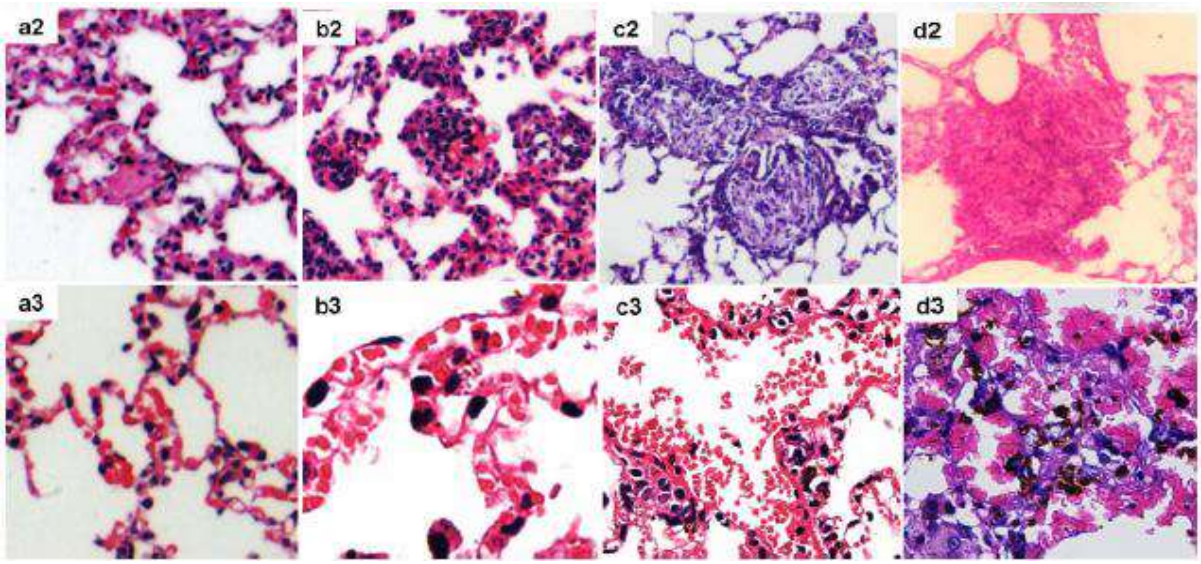

Figure 4. Silicotuberculosis histopathologic characteristics in BALB/c mice

Microscopic analysis of the lungs of mice that had been simultaneously exposed to silica and MTB revealed the development of tuberculoid epithelial cells, macrophage accumulation, and tubercle formation, as well as leukocyte infiltration around them. In the lung tissue, there was also caseous necrosis and a scattering of Langerhans cells. On the other hand, mice who received MTB injection on day 50 after silica exposure had distinct traits.[41]

The primary pathologic characteristic of lung tissue is exudation. Large fibrous nodules (tertiary silicon nodules) with thick walls can also be seen, together with concentrically and circularly ordered endothelial cell growth (Figure 4).[40]

The details in Figure 4 are represented by several microscopic pictures, including the dispersion of Langerhans cells in image part a2 and the principal silicotic nodules in image part b2. Other pictures' findings include a depiction of secondary silicotic nodules in image c2, tertiary silicotic nodules in image part d2, lung interstitial tissue in image part a3, pulmonary capillary dilatation in image part b3, and lung congestion in image part c3.[40,41]

Additionally, image part d3 shows hemosiderin and red blood cell accumulation in the lung cavities. Because airway mucosal cells are the first line of defense for the body's response to these two mechanisms, collecting examination samples by BAL is also a sensible option.[40,41]

CONCLUSION

Innate immunity and adaptive immunity, which each contain different immune cell components, make up the human immune system. The main risk factors for silicotuberculosis with recurrent silica exposure are occupational and environmental variables. One of the body's immune cells, called macrophages, plays a crucial role in the development of silicotuberculosis. Increased ROS, elastin and collagen deposition, as well as macrophage apoptosis, are all effects of silica that can directly harm lung tissue. In silicotuberculosis, anti-inflammatory M2 phenotype macrophages are activated, preventing MTB from being eliminated by macrophages. As they cannot completely remove MTB, macrophages cannot function as APCs for adaptive immunity. Future studies are therefore required to determine how additional immune cells contribute to the immunopathogenesis of silicotuberculosis.

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Literature Review

Smoking Cessation: A Review

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Abstract

Smoking is a leading cause of preventable death worldwide. Smoking damages almost all organs and body systems and reduces the overall health of a person with the highest mortality, especially due to respiratory and cardiovascular disease. Evidence shows that the symptoms and prognosis of smoking-related diseases will improve after smoking cessation. Smoking cessation is one of the most important ways to improve the prognosis of patients with respiratory ailments. Counseling and treatment can increase the chances of smokers to successfully smoke cessation. Smoking cessation therapy must include pharmacological treatment (Nicotine Replacement Therapy (NRT), bupropion, varenicline or N-acetylcysteine) combined with nonpharmacological therapy.

Keywords: bupropion, N-acetylcysteine, NRT, smoking cessation, varenicline

INTRODUCTION

Smoking is the world's leading cause of preventable disease and death. Smoking harms almost every organ of the body. Smoking causes about 90% of all lung cancer deaths and about 80% of all deaths from Chronic Obstructive Pulmonary Disease (COPD). Passive smoking is also harmful to health, especially for children.[1,2] The results of the Global Adult Tobacco Survey (GATS) 2021 saw an increase in the number of adult smokers by 8.8 million people, from 60.3 million in 2011 to 69.1 million smokers in 2021. Smoking in Indonesia has increased in the last ten years.[3,4]

Almost all smokers are aware of the dangers of tobacco and most smokers want to quit. However, nicotine contained in tobacco products is highly addictive. Without support quitting attempts only 4% of smokers who try to quit on their own will succeed. Professional support and smoking cessation therapy have been shown to more than double a smoker's chances of successfully quitting.[5–7]

Smoking cessation recommended by the World Health Organization (WHO) and Food and Drug Administration (FDA) is the best option, but limitations in drug availability and side effects make us choose other alternatives in treating patients.

Treatment using Nicotine Replacement Therapy (NRT), non-NRT and currently using n-acetylcysteine is one of the options that can help in smoking cessation efforts.[1,3,6] Of all smoking patients, few of them try to stop smoking but struggle with the negative feedback of smoking. Therefore, this study aims to review the current option for smoking cessation that is available until this day.

TOBACCO CIGARETTES

Cigarette smoke contains more than 4500 chemicals, 250 of which are known to be harmful and at least 70 of which cause cancer. Some of the chemicals contained in tobacco smoke are nicotine, tar, cyanide, benzene, cadmium, methanol, acetylene, ammonia, formaldehyde, hydrogen, arsenic and carbon monoxide.[2,8,9]

E-CIGARETTE

E-cigarettes are also called Electronic Nicotine Delivery Systems (ENDS) and Electronic Non-Nicotine Delivery Systems (ENNDS), which are methods for delivering nicotine by vaporizing a solution through a device while still providing the sensation of hand-to-mouth movements resembling smoking. There are currently four generations of e-cigarettes. The use of e-cigarettes is not considered smoking but "vaping".[8–10]

Most e-cigarette refill solutions contain propylene glycol, glycerol, ethylene glycol and polyethylene glycol mixed with flavoring agents and some nicotine. Almost all e-cigarette refill solution products contain tobacco alkaloids (such as nornicotine, anabasine and anatabine) or synthetic nicotine, they also contain formaldehyde and Tobacco Specific Nitrosamines (TSNAs) which are carcinogens such as N-nitrosonicotine (NNN), N-nitrosoanabasin (NAB), N-nitrosoanabatin (NAT) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The nicotine label levels on cartridges from several brands were found to be inconsistent with the actual levels, even ENNDS, which from several examinations contained nicotine.[11–13]

EPIDEMIOLOGY

Countries with amount smokers in 2020 are China, India, Indonesia, the United States, Russia, Bangladesh, Japan, Turkey, Vietnam and the Philippines. The top ten countries form around two-thirds of the population of world smokers, with 30% of smokers in China. Indonesia occupies order third the largest amount smokers in the world from the GATS results noted that 27.9% are smokers aged 15-24 years.[3,10,14]

SMOKING AND RESPIRATORY DISEASES

The impact of smoking affects blood circulation, heart, lungs, stomach, skin, bones, brain, mouth and throat, reproduction and fertility. Smokers in Indonesia experience 45% stroke, 81% heart attack, and 85% lung cancer. Quitting smoking improves health, saves lives and reduces financial problems.[15–17]

Lung diseases caused and affected by cigarette smoke are airway cell and epithelial damage, chronic obstructive pulmonary disease (COPD), lung cancer,

aggravation of asthma and increased risk of developing pulmonary infections. Inhaled particles from cigarette smoke are deposited in the airway depending on their size, with larger airborne particles in the upper airway and smaller particles deposited in the alveoli. Cigarette smoke causes oxidative stress resulting in chronic inflammation and inflammatory cells to the airway with activation of epithelial cells, alveolar macrophages, neutrophils and T lymphocytes.[18–20]

Smoke from cigarettes causes macrophages and epithelial cells to become active and release chemokines. C-X-C Chemokine Ligand 1 (CXCL1) and C-X-C Chemokine Ligand 1 (CXCL8) act on CCR2 to activate neutrophils and monocytes, respectively, whereas C-C Chemokine Ligand 2 (CCL2) acts on C-C Chemokine Receptor 2 (CCR2) to activate monocytes. Type 1 helper T cells and type 1 cytotoxic T cells are activated by C-X-C chemokine ligand 9 (CXCL9), C-X-C chemokine ligand 10 (CXCL10), and C-X-C chemokine ligand 11 (CXCL11), which act on C-X-C chemokine receptor 3 (CXCR3).[19–21]

Together, these cells secrete neutrophil elastase and matrix metalloproteinase-9 (MMP-9) protease, which damages the alveolar wall and causes elastin breakdown. Transforming Growth Factor Beta (TGF-) is also released by macrophages and epithelial cells, which causes the small airways to fibrosis.[19–21]

HEALTH BENEFITS OF QUITTING SMOKING

There are both short-term and long-term advantages to quitting smoking. Knowing the advantages of quitting might be a good motivator. Stopping smoking behavior will significantly lower the risk of death, from the initial 20 minutes of improved blood pressure, heart rate, and blood flow to the reduction of all causes of smoking-related mortality if it can be accomplished.[1,6,22]

The greatest method to shield your loved ones from the risks of secondhand smoke is to stop smoking. The advantages of quitting smoking for the body over time are shown in Table 1.[1,6,22]

Table 1. Benefits of Quitting Smoking[1]

Smoking Quit Period	Benefit
20 minutes	Improve blood pressure, heart rate and blood flow.
12 hours	All the nicotine in the body has been metabolized and the CO level in the blood returns to normal
24–48 Hours	Nicotine will begin to be eliminated from the body, the function of taste and smell will improve, the cardiovascular system will improve
5 days	Most of the nicotine in the body is gone.
2–6 Weeks	Accelerate the healing of infectious wounds on the body and the function of the airway cilia and lung function improve.
1 year	The risk of coronary heart disease decreases by 50%.
5 years	The risk of stroke decreases at the same rate as a non-smoker
10 years	The risk of lung cancer is reduced by 50%.
15 years	All-cause mortality and the risk of coronary heart disease decreased to the same level as non-smokers.

Table 2. Nicotine Withdrawal Effects[23]

Nicotine Withdrawal Effects	Time (After Quitting Smoking)
Anxiety	1-2 weeks
Easily offended, frustrated and angry	≤4 weeks
Sleep disorders/insomnia, impatience, difficulty concentrating and depression	≤4 weeks
Appetite increases, weight increases	≤10 weeks

NICOTINE DEPENDENCE

Nicotine is the substance responsible for a person's dependence on tobacco products. Nicotine is a class of alkaloids produced by tobacco that is very fat soluble so that it is easily absorbed in the oral mucosa, lungs, digestive mucosa and skin. Nicotine can cross the placenta and excreted through breast milk. Cigarettes generally contain 6-8 mg of nicotine. The main characteristics of drug dependence include the use of drugs that cause psychoactive effects and the reward pathway system that influences user behavior.[24,25]

The potential for a drug to cause dependence is generally determined by the speed at which the drug penetrates the brain. The faster the drug penetrates the brain, the greater the potential for the drug to cause dependence. When smoking a cigarette, nicotine enters the bloodstream and reaches the brain faster than drugs given intravenously.[23–25]

Nicotine is a selective agonist compound of Nicotinic Acetylcholine Receptors (nAChR) which plays an important role in the cognitive function of the human body. The effect of nicotine dependence is an important role of the neurotransmitter dopamine in an area in the brain called the Ventral Tegmental Area (ATV) which is where nAChR releases dopamine. Dopamine will stimulate a sense of happiness for smokers.[23–25]

The more a person smokes, the more they will be exposed to nicotine. The brain will adapt to certain levels of nicotine. As the adaptability increases, the number of nAChR units increases. ATV regions and neurons in the brain will be activated increasingly. In addition, nAChR is stimulated by nicotine resulting in the hoarding of dopamine in the brain reward system will reach peak levels followed by a decrease in nicotine levels. This decrease in nicotine levels will reach the point of withdrawal syndrome which can only be eliminated by smoking again.[23,25,26]

EXAMINATION OF NICOTINE AND CARBON MONOXIDE LEVELS IN SMOKERS

Several biomarkers can be used to determine a person's smoking status, namely through examination of nicotine levels, cotinine levels (another form of nicotine) and thiocyanate levels in plasma, urine and saliva, blood carbon monoxide levels (COHb) and examination of expiratory air carbon monoxide (CO) levels using a portable CO meter (smokerlyzer). Examination to assess nicotine dependence can use the Fagerstorm Test.[1,27]

Table 3. Methods for Smoking Cessation[28]

Method	How to Stop Smoke
Stop instantly	Today patient still smoking, tomorrow patient completely stop. This method needs pharmacological therapy to reduce the effect of nicotine separation.
Delay	Postpone moment cigarette first, 2 hours each day from the day before. Amount smoked cigarettes not counted. Example: Day 1: 09.00; Day 2: 11.00; Day 3: 13.00; Day 4: 15.00; Day 5: 17.00; Day 6: 19.00; Day 7: 21.00-last
Subtraction	The amount smoked cigarettes every day was reduced in a manner gradually with the same amount up to 0 bars. For example, smoking an average of 28 cigarettes cigarette a day. Stop smoking planned in 7 days. Day 1: 24 sticks; Day 2: 20 sticks; Day 3: 16 sticks; Day 4: 12 sticks; Day 5: 8 sticks; Day 6: 4 sticks; Day 7: 0 sticks

Therapy

The World Health Organization (WHO) recommends 2 methods of approaches that can be taken to help individuals quit smoking, namely the 5A and 5R. The 5A approach is used in patients who are ready to quit smoking. This approach consists of 5 components Ask, Advice, Assess, Assist and Arrange which have been summarized to make it easier for clinicians to educate patients. The 5S approach is used for smokers who don't want to quit smoking which consists of Relevance, Risk, Rewards, Roadblocks and Repetition. The smoking cessation program that is usually implemented in Indonesia is the 4T approach, namely Ask, Study, Help and Follow up.[1,8,18,29]

Worldwide guidelines for smoking cessation recommend immediate quitting and do not support gradual reduction and delays in quitting attempts. Hawley et al's study showed that 49% of the immediate cessation group successfully quit compared to 39.2% of the gradual cessation group. Participants who chose gradual cessation were significantly less likely to quit than those who chose immediate cessation. These smoking cessation methods are described in Table 3.[30,31]

Pharmacotherapy

Every smoker, whether they are ready to quit or not, should be given access to pharmacotherapeutic techniques since medication can encourage patients to cut back on smoking and raise the possibility that they will eventually try to quit. Nicotine Replacement Therapy (NRT) or Non-Nicotine Replacement Therapy, which includes bupropion hydrochloride and varenicline tartrate, are pharmacotherapies for quitting smoking that have been approved by the Food and Drug Administration (FDA).[22,30,31]

The patient's comorbidities and adverse effects, as well as the drug's accessibility, should be taken into account while choosing pharmacologic therapy. Compared to smokers in general, patients with respiratory diseases have a stronger and more immediate need to stop smoking. Because of this, doctors must be proactive and persistent in encouraging their patients to stop smoking and offering them treatments to do so.[22,27,30]

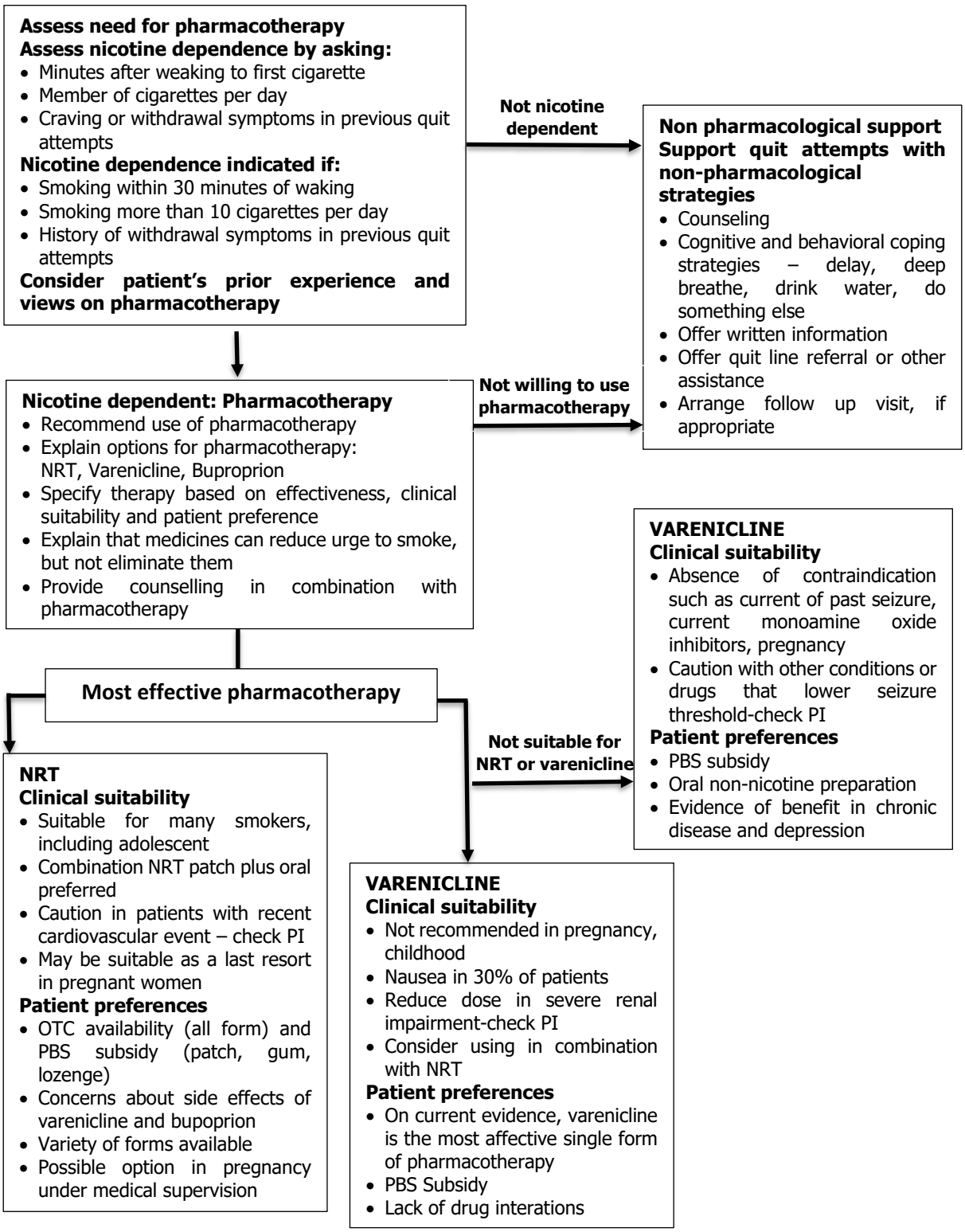

Figure 1. Smoking Cessation Algorithm[22]

The use of large doses of N-acetylcysteine (NAC) is an option and has been studied because the availability of pharmaceutical therapy is limited in Indonesia. In a 4-week study employing NAC, Harlivasari et al. from the University of Indonesia had a success rate of 37.7%.[22,27,30]

Table 4 . Nicotine Replacement Therapy (NRT)[22]

Drug	Dose	Giving	Side effects
Nicotine *patch* 21 mg 14 mg 7 mg	Initial dose 21 mg on ≥10 cigarettes/day 14 mg on <10 cigarettes/day After 6 weeks, consider lowering the dose Use ≥3 months	Installing a new *patch* every morning Location rotation to prevent skin irritation If you have insomnia or sleep disturbances, don't use it when going to sleep	Skin irritation Trouble sleeping
Nicotine *lozenges* 4 mg 2 mg	If the first cigarette ≤30 minutes after waking: 4 mg If the first cigarette >30 minutes after waking: 2 mg Use ≥3 months	Position it between the gums and cheek, let it dissolve slowly 1 fruit every 1-2 hours (max 20/day)	Mouth irritation Notch Chest pain Nausea
Nicotine *gum* 4 mg 2 mg	If the first cigarette ≤30 minutes after waking: 4 mg If the first cigarette >30 minutes after waking: 2 mg Use ≥3 months	Chew briefly until the mouth feels tingling, then position the gum in the cheek until the tingling is gone. Discard gum after 30 minutes of use, 1 piece per hour (max 24/day)	Mouth irritation Jaw cramps Chest pain Notch Nausea
Nicotine inhaler 10mg/cartridge	10mg/ml Each cartridge has about 80 puffs Use ≥3 months	Puff to mouth/throat until the urge to smoke subsides Do not inhale into the lungs. Replace cartridge if the nicotine taste is gone. Use 1 cartridge every 1-2 hours (Max: 16/day)	Mouth and throat irritation Cough if inhaled deeply
Nicotine nasal spray 10mg/ml (10 ml per bottle)	10mg/ml 0.5 mg per spray Each bottle has 200 sprays Use ≥3 months	Spray 1 spray in each nostril Spray every 1-2 hours (max: 80/day)	Nose and throat irritation Rhinitis Sneeze Cough, watery eyes

Nicotine Replacement Therapy (NRT)

The first medicine for treating smoking cessation is called nicotine replacement therapy (NRT). The majority of the nicotine in cigarettes is temporarily replaced by NRT use, which lowers the desire to smoke and eases withdrawal symptoms. This makes it easier to stop smoking altogether once you start. NRT medications include lozenges, chewing gum, nasal and oral sprays, and skin patches that deliver nicotine slowly but no faster than smoking to the brain.[28,32]

When NRT is used, the urge to smoke lessens and nicotine is released right away. There is proof that all types of NRT increase the likelihood of quitting. The likelihood of giving up smoking rises by 50% to 60%. Other NRT formulations may be coupled with nicotine patches. The type of substance, skin irritation from using patches, and irritation of the oral mucosa from using gum and pills are all side effects

of using NRT. Heart palpitations and chest pain were the most severe side effects that studies have documented.[28,32]

Non-Nicotine Replacement Therapy

Vareniklin is a nicotinic partial agonist. It was found that varenicline reduced the urge to smoke to a lesser extent than bupropion. Varenicline binds to the α4β2 nAChR subtype with high affinity and selectivity which can reduce withdrawal symptoms. Varenicline was shown to be more effective than NRT and bupropion monotherapy. Combined use of varenicline and NRT has been shown to increase the success of smoking cessation attempts.[22,28]

Table 5. Non-NRT[22]

Drug	Dose	Side effects
Varenicline	The initial dose is 0.5 mg/day Maintenance dose 1 mg 2x a day For 3 months	Nausea, Headache, Insomnia
Bupoprion	Initial dose of 150 mg/day Then increase to 150 mg twice daily for 3 months	Dry mouth, Insomnia, Headache, Nausea, Vomiting, Restlessness

Bupropion is the first licensed non-nicotinic pharmacological therapy for smoking cessation. Bupropion was first approved as an antidepressant in other countries. Bupropion works by blocking norepinephrine and dopamine. Bupropion has similar efficacy in NRT and is equally effective in smokers. Combination therapy between bupropion and NRT is more effective than bupropion alone or NRT alone. Bupropion is contraindicated in smokers who have a current seizure disorder or previous history of seizures, bulimia, anorexia nervosa and who take monoamine oxidase inhibitors.[33,34]

N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is a widely available drug with mechanisms of increasing intracellular glutathione levels, antioxidant, modulating oxidative, immunoinflammatory, glutamatergic, and neurotrophic pathways. N-acetylcysteine can currently be used as a smoking cessation therapy and is easy to apply because it is readily available. Nicotine stimulates nACh in the central nervous system, which can increase the release of several neurotransmitters such as dopamine, glutamate and serotonin. The use of NAC can reduce nicotine-dependent behavior, which is modulated by glutamate. The pathway is by replacing glutamate levels by inhibiting GluR2/3 receptors which can reduce the return of nicotine craving.[27,30]

Harlivasari et al's study used a randomized placebo-controlled trial in smokers conducted from January to December 2018 from the University of Indonesia. A total of 90 smokers received treatment divided into two groups, namely NAC 2x1200 mg and placebo for 4 weeks. In the NAC group, it was 37.7% while the placebo group was 6.7%. There were statistically significant improvements in Fagestorm score and exhaled CO values at the end of the study. N-acetylcysteine proved to be safe and well tolerated in

patients for smoking cessation. N-acetylcysteine had no significant side effects, only pruritus, nausea, headache and high blood pressure, so NAC can be applied to people in Indonesia.[27,30,35]

CONCLUSION

Smoking is the leading cause of preventable death worldwide. Counseling/ non-pharmacological approaches and pharmacotherapeutic interventions can improve smoking cessation success. World Health Organization suggests 2 models of approaches that can be taken to assist individuals in quitting smoking, namely 5A and 5R. Nicotine Replacement Therapy or Non-Nicotine Replacement Therapy pharmacotherapy options are bupropion and varenicline. The use of N-acetylcysteine can be used as a pharmacological therapy option in smoking cessation efforts.

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Literature Review

The Solitary Pulmonary Nodule: Is It Benign or Malignant?

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Abstract

Solitary pulmonary nodules (SPN) are round-shaped opacities with or without firm borders and ≤3 cm in diameter. 40% of solitary pulmonary nodules in high-risk populations are malignant and >10 mm in diameter. With the high incidence of pulmonary cancer, diagnosing pulmonary nodules is essential for clinicians. This review aims to discuss more solitary pulmonary nodules based on multiple recommendations for diagnosis and management. Malignancy probability assessment is the first step in evaluating each patient with new pulmonary nodules, as it significantly affects the prognosis of the disease. The assessment depends on the risk factors present in the patient, which are cigarettes, age, history of cancer, and family history. Radiological evaluation is the second phase in pulmonary nodule evaluation. Predictors of malignant nodules that should be assessed are nodule size, growth rate, nodule morphology, location, and enhancement. Many guidelines have been published regarding treating solitary pulmonary nodules, including the Fleischner Society, ACCP, and BTS guidelines.

Keywords: benign, malignant, pulmonary nodule management, solitary pulmonary nodule

INTRODUCTION

Solitary pulmonary nodules (SPN) are defined as round-shaped opacities with or without firm borders and ≤3 cm in diameter. Spherical lesions with a more than 3 cm diameter are associated with lung masses and can be indicated as lung cancer until proven otherwise histologically.[1] Solitary pulmonary nodules are generally lesions due to benign abnormalities such as infections, inflammations, and vascular and congenital abnormalities. However, 40% of solitary pulmonary nodules in high-risk populations are malignant and >10 mm in diameter. With the high incidence of pulmonary cancer, diagnosing pulmonary nodules is essential for clinicians.[2]

The initial identification process in cases of malignant nodules significantly affects the prognosis of the disease.[3] The initial step in the nodule assessment is the evaluation of clinical parameters such as signs and symptoms, the patient's age, smoking history, exposure to carcinogens, family history of cancer, clinically related

lung disease, and previous history of the disease. The next step is the evaluation of the radiological picture. The main parameters assessed in the radiological evaluation are the nodule's size and speed of growth. Other parameters that can be assessed are spiculated, lobulation, vascular convergence, and pleural retraction.[2]

Supporting examinations are also needed to identify cases of pulmonary nodules. Some modalities that can be done include Thin-section Computerized Tomography (CT), Magnetic Resonance Imaging (MRI), Positron emission tomography (PET), and PET/CT integration to help diagnoses become more accurate in nodule characterization. Clinical follow-up is still needed to help establish a diagnosis in cases of small nodules, and a definitive diagnosis still requires a tissue biopsy.[2,3]

Pulmonary nodules can be divided into solid and subsolid with different morphological and pathological features based on density.[1] Most subsolid nodules are transient and arise due to infection or bleeding. Granulomas, lymph nodes, primary malignancies, or metastases can cause solid nodules. Subsolid nodules are more likely to exhibit indolent growth patterns, and subsolid nodules diagnosed with malignancy have a high overall cure rate.[4,5]

In a systematic study, 712 lung cancer cases with ground-glass opacity manifestations were stage I adenocarcinomas with a five-year survival rate of 100%.[4] In contrast, malignant solid nodules have a worse prognosis than malignant subsolid nodules with rapid growth and earlier metastases.[3]

With the complications associated with the biopsies or repeated "unnecessary" CT scans of the chest, a systematic approach becomes essential in evaluating these nodules.[6] Many guidelines have been published regarding the treatment of solitary pulmonary nodules. The Fleischner Society guidelines are guidelines for pulmonary nodules found incidentally.[7]

Meanwhile, the American College of Chest Physicians (ACCP) and British Thoracic Society (BTS) guidelines do not distinguish between incidental and screening-detected nodules. There are some differences between the three guidelines. The Fleischer Society recommendations emphasize the initial inspection, whereas the ACCP and BTS guidelines include the evaluation and treatment.[2]

This literature review discusses more solitary pulmonary nodules based on multiple recommendations for diagnosis and management.

DEFINITION, EPIDEMIOLOGY, AND RISK FACTORS OF SOLITARY PULMONARY NODULE

The Fleischner Society defines solitary pulmonary nodules as a single nodule, round-shaped, well-defined with an opaque appearance and a diameter of less than or equal to 3 cm, and surrounded by normal lung parenchyma without other abnormalities such as enlarged lymph nodes, atelectasis, or pleural effusions.

Lung masses with a diameter of >3 cm are considered lung cancer until proven otherwise.[1]

Pulmonary nodule is seen in 150,000 Americans annually. Thoracic CT scans in clinical practice increased pulmonary nodule detection. In 2006 and 2012, U.S. thoracic CT scans detected 3.9 to 6.6/1000 lung nodules yearly. Baseline screening found 20% of nodules in a 2012 systematic study. Eight randomized controlled studies reported a 3%–30% prevalence, while 13 cohort studies reported 5–51%. Most studies report <5-10% malignant nodules, meaning 90-95% are false positives.[4] It poses a challenge for clinicians and radiologists to eliminate the diagnosis of malignant nodules, but they want to avoid invasive examinations and procedures.[8]

Malignancy probability assessment is the first step in evaluating each patient with new pulmonary nodules. The assessment depends on the risk factors present in the patient, including the following.

Cigarette

Smoking causes lung cancer and 85% of cancer fatalities. Smoking number and duration affect lung cancer risk. According to the meta-analysis, men's lung cancer risk increased with the number of cigarettes they smoked daily: <10 cigarettes (4.97 times), 10-20 (8.93 times), and > 20 (14.61 times). Smoking duration also increases lung cancer risk, 0-20 years 1.23 times, 20-30 years 2.98 times, 30-40 years 7.84 times, 40-50 years 12.82 times, and >50 years 28.94 times.[2] Passive smokers were also at risk for malignancy.[9]

Age

Older age is associated with an increased likelihood of malignancy in patients with pulmonary nodules. The majority of cancer cases (>50%), including lung cancer, are found at the age of >70.[1] SPN is a rare finding in the pediatric population and, as a result, when the finding is incidental, it is difficult to narrow down the differential diagnosis, especially for the untrained eyes.[10]

History of Cancer

Individuals who have survived lung cancer have a heightened likelihood of developing subsequent primary lung cancer. According to research on patients with early-stage non-small cell lung cancer (NSCLC) who underwent resection surgery, second lung cancer was nearly 7x higher during the initial year following the surgery. The risk remains 4x higher after ten years. Patients with squamous cell carcinoma or other cigarette-related malignancies (pancreatic or bladder cancer) are at a heightened risk of developing primary lung cancer.[1]

Family History

The familial background of an individual is a noteworthy determinant of risk. Individuals who have a first-degree family history of lung cancer are at a twofold increased risk of developing lung cancer. Individuals with multiple family

members diagnosed at a young age are at an increased risk.[1]

Another risk factor for lung cancer, such as exposure to carcinogens (asbestos, uranium, radon), has been described in studies. Prolonged exposure to coal dust or mineral dust (silica or beryllium) can also cause the appearance of lung nodules.[11] Emphysema and chronic obstructive pulmonary disease were also evaluated as risk factors for lung malignancy.[12,13]

CLASSIFICATION OF SOLITARY PULMONARY NODULES

The categorization of pulmonary nodules is based on their density (Figure 1), which classifies them as either solid or subsolid. Subsolid pulmonary nodules can be classified into two categories: non-solid or pure ground glass nodules, which do not obstruct broncho-vascular structures, and part-solid nodules, which consist of ground-glass opacity with solid components. The pulmonary parenchyma underlying subsolid nodules remain observable. The term ground-glass opacity is commonly used to describe this phenomenon.[3] Solid nodules are the most common type, with radiodensity characteristics in the form of homogeneous soft tissues.[1]

Granulomas, lymph nodes, primary malignancies, or metastases can cause solid nodules. Subsolid nodules are predominantly transient and manifest as a result of infection or hemorrhage. If subsolid nodules persist, they result in adenocarcinoma pathology. Non-solid nodules can be non-invasive, minimally invasive, or lepidic-predominant adenocarcinomas. The majority of part-solid nodules, meanwhile, are invasive adenocarcinomas. Most of the nodules detected by screening have solid characteristics.[4]

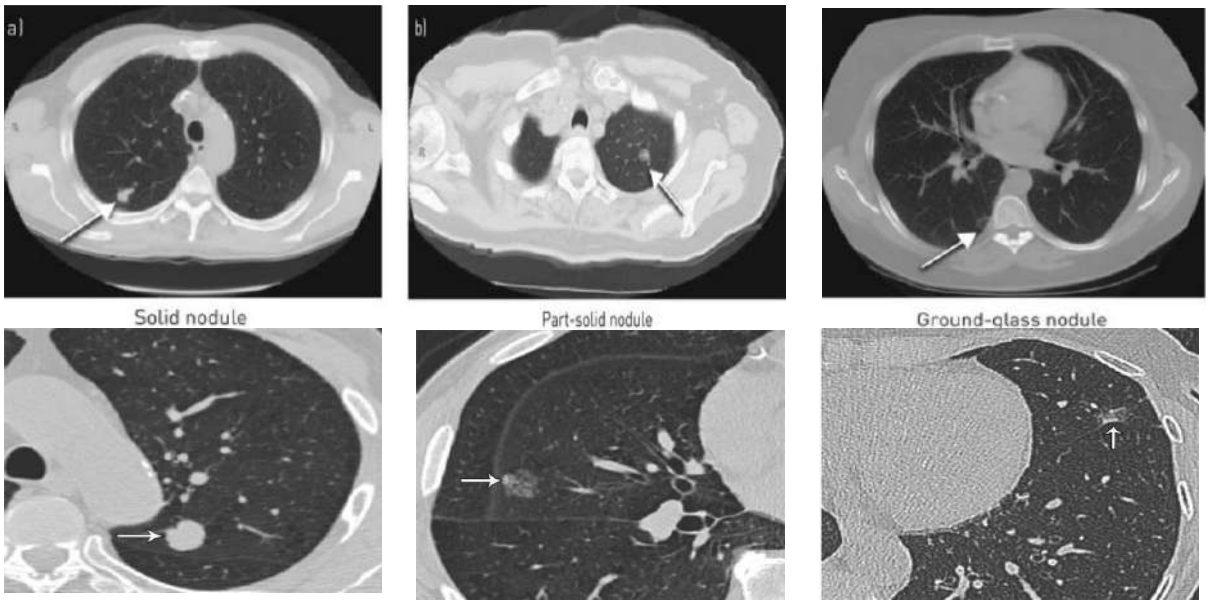

Figure 1. Classification of pulmonary nodules by density
(A) solid nodule; (B) part-solid nodule; (C) ground-glass nodule.[14]

According to Henschke et al's research, the probability of malignancy is higher in sub-solid or part-solid nodules than in solid nodules. Most pulmonary solid nodules are benign. The majority of solid nodules, approximately 80%, are granulomas and intrapulmonary lymph nodes. Hamartomas account for approximately 10%, while the remaining 10% are attributed to other benign lesions.[15]

Based on their clinical presentation, SPNs can be divided into three groups: incidental SPNs, symptom-associated SPNs, and screen-detected SPNs. This classification method is helpful since the clinical presentation affects the likelihood that the nodule is malignant. An SPN can be seen on imaging performed for nonpulmonary clinical indications, termed an incidental SPN.[16]

Symptom-specific SPNs are those identified after chest imaging that was explicitly done to determine the origin of respiratory complaints. Screen-detected SPNs are SPNs that are found on a screening LDCT (low-dose computed tomography).[16]

DIAGNOSIS OF SOLITARY PULMONARY NODULES

Non-solid nodules tend to grow slowly. Overall, malignant non-solid nodules have a high cure rate.[4] Due to their rapid growth and early metastasis, malignant solid nodules have a worse prognosis than non-solid ones. Therefore, the early identification of malignant solid nodules significantly affects the prognosis.[3] Radiological evaluation is the second phase in pulmonary nodule evaluation. Assessment of lung cancer risk is based on nodule size and growth rate. Other imaging features have been identified as predictors of benign and malignant nodules.[1]

Using screening CT scans, men are more likely than women to have an SPN of 18.8% versus 16.3%, respectively. Men still had more SPN findings than women when a chest X-ray was used for screening, with incidence rates of 2.5% and 1.6%, respectively. On the other hand, in the non-smoking group, women did have a higher incidence of having an SPN than men.[17]

Predictors of Benign Nodules

Several benign nodule predictors exist. Perifisural nodules are solid nodules in contact with the fissure or pleural surface. These nodules are considered benign nodules and most likely describe intrapulmonary lymph nodes. After long-term follow-up, no patients with these nodules developed lung cancer.[3]

Calcified pulmonary nodules are rarely cancerous. However, some preliminary research indicated calcification in 10% of lung cancer cases. Thus, the calcification pattern should be prioritized. Diffuse, central, laminated, and popcorn calcification patterns indicate benignity. In contrast, punctate, eccentric, and amorphous calcification patterns cannot rule out malignancy.[1]

The BTS guideline advised not investigating small, homogenous, well-defined perifissural and subpleural nodules. However, the Fleischner Society Guideline states that perifissural and subpleural locations do not rule out malignancies. Other risk factors, such as morphology and clinical condition, should be considered when determining treatment.[1]

Predictors of Malignant Nodules

Size

Malignancy is closely correlated with nodule size. The current guideline proposes a low-risk indicator (<1%) of <6 mm based on high-risk patients' lung cancer screenings. The threshold works for single and multiple solid nodules. The second clinically relevant threshold is >8 mm in diameter. According to the NELSON study, solid nodules of 8 mm had a 9.7% chance of lung cancer, whereas those of 5-8 mm had a 1% chance.[1]

The Fleischner Society classified pulmonary nodules into acinar, which usually measures 5-8 mm and shows consolidations in the acinus. Opacities ≤3 mm, are called micro nodules.[18] A CT scan is needed to detect nodules under 1 cm.[19] Wahidi et al. examined several studies that compared nodule size with malignancy frequency.[20]

Solitary pulmonary nodules <5 mm have a malignancy rate of less than 1%, even in the high-risk category, while 5-10 mm and >2 cm nodules had 6-28% and 64-82%, respectively. Pulmonary nodules >10 mm have a 33-60% probability of cancer, according to other research.[20] Malignancy is more likely in lesions larger than 3 cm.[21]

Growth Rate

Pulmonary nodules are often cancerous. Incidentally detected nodules should be compared with previous imaging data. Nodules may not need further investigation if they are stable. CT surveillance for pulmonary nodules is based on the rapid growth of lung cancer lesions. Volume-doubling time (VDT), the most sensitive marker of nodule growth, is rarely used in clinical practice. One VDT shows 26% nodule diameter growth. Most lung cancers have a VDT of 400 days, with the highest malignancy risk at 100 days. However, a VDT of >400 days does not exclude the possibility of malignancy.[1]

In the NELSON research, VDT >600 days had 0.8% malignancy risk, 400-600 days 4%, and <400 days 9.9%. Cruickshank et al. found that lung cancer VDT averages 139 days. Bronchial carcinoma VDT is 1-18 months. VDT <20 days suggests infection. VDT over 500 days predicts malignancy 98% negatively. BTS guidelines recommend VDT for lung nodules over 6 mm.[18,21]

Since only 1% of malignant nodules maintain growth stability or size for two years, solid pulmonary nodule growth stability is measured over two years. Adenocarcinoma in situ and minimally invasive cancer had VDTs of 457-812 days, while sub-solid nodules grew slower. Sub-solid nodules require extended follow-up.[21]

Morphology and Location

Nodule morphology can also predict cancer. Spiculated nodule margins have

consistently been linked to lung cancer risk.[22] Lung cancer has been associated with lobulated margins, as in Figure 2.[3] Upper lobe lung cancer is the most common location. Pleural retraction, vascular convergence, and air bronchogram are less common malignancies characteristic.[1]

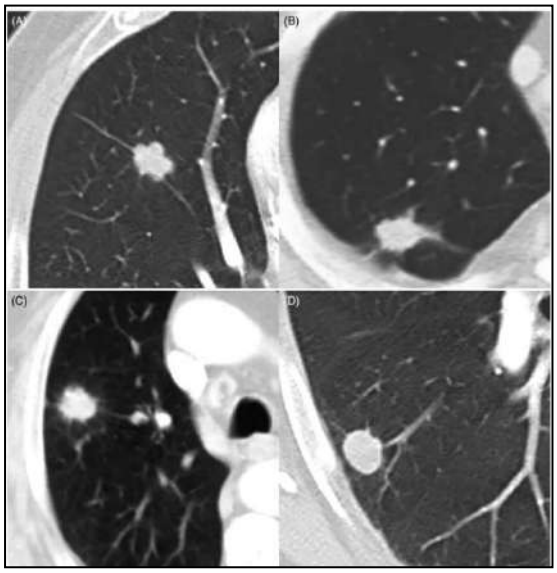

Figure 2. The morphology of the margin of a solitary pulmonary nodule. (A) lobulation, (B) irregular, (C) spiculated, (D) well-defined round-shaped. [21]

There is calcification or fat attenuation in pulmonary nodules. Calcified solitary pulmonary nodules are most likely benign.[15,18] Non-contrast CT images reveal calcifications with >200 HU attenuation. Calcification characteristics include dense central nodules, solid diffuse, laminated, popcorn, punctate, and dendriform structures. Pulmonary hamartomas exhibit calcification resembling popcorn, whereas the first three forms indicate benign lesions. Calcified nodules are also present in primary central lung carcinoid, metastasis, and primary bronchogenic carcinomas.[21]

Amorphous, punctate, and reticular calcifications characterize primary lung cancer calcification. Dystrophic calcifications result from granulomas or tumor necrosis. Mucinous adenocarcinoma may first calcify. In malignant solitary pulmonary nodules, calcifications may present in larger sizes and are usually stippled and eccentric.[15,18] Pulmonary metastasis from bone malignancies is usually also characterized by solid calcifications.[15] Calcification rate in carcinoid cancers is approximately 8-35%.[21]

Fat in the solitary pulmonary nodule indicates benign lesions like pulmonary hamartomas, lipoid pneumonia, and lipomas.[18,23] CT scans show fat in 50% of pulmonary hamartomas.[17] Imaging criteria for benign pulmonary nodules include nodule stability for at least two years or calcification with specific characteristics like in Figure 3 (calcification in all nodules, central/bull's-eye calcification, eggshell calcification). A 30-150 HU density test confirms fat in the nodule and reliably identifies benign lung lesions.[18,23]

The cavity is an air-filled space that appears as a lucency or low attenuation picture in lung consolidation, mass, or nodule. Cavities occur in benign lesions like infections and inflammation and malignant single lung nodules like squamous cell carcinoma.[18,21,24]

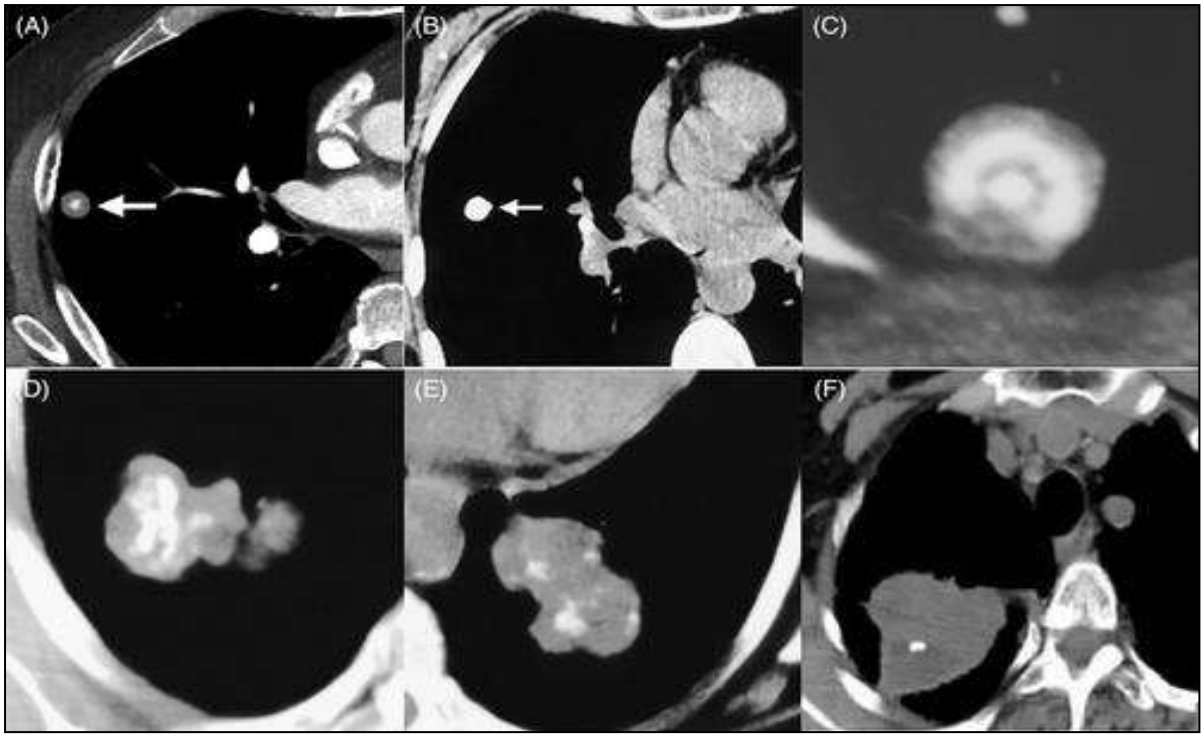

Figure 3. Calcification descriptions in pulmonary nodules. (A) central or "bull's eye" calcifications in benign granulomas; (B) diffuse calcification in benign granulomas; (C) laminated calcification in benign granulomas; (D) popcorn calcification in pulmonary hamartoma; (E) punctate calcification in malignant carcinoid tumor; (F) eccentric calcification in primary pulmonary adenocarcinoma.[21]

Pulmonary tuberculosis abscesses, histoplasmosis, aspergilloma, Wegener granulomatosis, Churg-Strauss syndrome, and rheumatoid arthritis can create benign lesion cavities. Central necrosis causes malignant lesion cavities. Wall thickness indicates cancer risk. Malignant tumors have thick, uneven walls, while benign lesions have thin, smooth walls. 95% of cavity nodules with walls thicker than 15 mm are malignant, while 92% with walls thinner than 5 mm are benign. Because 51% are benign and 49% are malignant, the 5-15 mm cavity wall thickness cannot tell whether the nodule is cancerous or benign.[18,21,24]

Air bronchograms show an air-filled bronchus surrounded by a solid, airless lung, frequently due to illness. The air bronchogram sign is common in malignant solitary pulmonary nodules such as adenocarcinomas.[21]

Solitary pulmonary nodules are usually circular or oval. Round solid nodules are less likely to be malignant, although subsolid round nodules are more likely to be malignant.[24] Perifisural nodules (PFN) are linked to intrapulmonary lymph nodes. Intrapulmonary lymph nodes (IPN) are commonly characterized by fissures or interlobular septa associated with solid nodules featuring smooth borders and shapes such as triangular, polygonal, oval, or lentiform.[18,24]

Perifisural nodules are frequently below the carina and 15 mm from the fissure or pleura. Atypical IPN is a nodule with a less evident fissure or a lesion with a convex and rounded side. PFN, a benign solid lung nodule, can double in size like

malignant ones. However, spiculated or fissure-crossing PFN should be followed.[18,24]

One-third of pulmonary nodules metastasize in the lower lobes, but most are in the upper lobes, notably the right. Nodules in the upper lobes of the lung had a 1.9-fold higher risk of malignancy, with the right upper lobe having the highest rate at 45%. In smokers, higher airflow in the right upper lobe during inspiration increases carcinogen exposure. 60% of pulmonary nodules are peripheral, mainly subpleural. Granulomas and IPNs also prefer subpleural locations. Perifissural nodules are oval or triangular solid nodules near the pleural fissure that are usually benign and do not need further imaging. Perifissural nodules with considerable risks, such as irregular spiculated margins and fissure distortion, require further imaging.[24]

A nodule's margin also influences its malignancy. Benign lesions have smooth, rounded edges. 21% to 33% of smooth-edged nodules had lung cancer or metastases.[24–26] Malignant cells invade the lung interstitium, causing irregular borders like spiculated or lobulated nodules.[24] The spiculated edges are observed, commonly called corona radiata or sunburst signs. Fibrosis is attributed to tumors in the lymphatic channels or pulmonary blood arteries. Spiculated edges have a 90% positive predictive value for cancer. Lobulated edges are moderately cancerous.[18,24]

Nodules with lobulation grow irregular patterns. It is linked to cancer. Lobulated edges within part-solid nodules may indicate the likelihood of invasive carcinoid tumors. Benign lobulation is a result of connective tissue hyperplasia and scar shrinkage. CT scans must distinguish satellite micro nodules from nodule edges. Benign nodules exhibiting lobulation are associated with hamartomas and granulomatous diseases that display a "notch sign".[24]

Enhancement

Enhancement after intravenous iodine contrast injection distinguishes benign from malignant nodules. Swensen et al. discovered that an enhancement value of >15 Hounsfield units (HU) had 98% sensitivity, 58% specificity, 68% positive predictive value, and 96% negative predictive value for malignancy. MDCT increased the enhancement value threshold. Yi et al found a 99% sensitivity and 54% specificity for cancer detection at >30 HU.[1]

Small Nodule

The previously described characteristics of malignancy help differentiate between benign and malignant nodules. However, these characteristics are usually absent in small lung nodules, making diagnosis more difficult. Increased nodule size makes the lesion more regular, with more apparent signs of edge lesions and invasion of surrounding tissues. Siegelman et al found that lung cancer tumor boundaries were rougher than benign lesions. Chu et al found that tumor-lung boundary roughness increased with nodule size, probably due to

tumor cell infiltration into peripheral tissue.[3]

Solid lung cancer growth is a gradual process. Tumor cells accumulate slowly, and lesion size increases continuously. According to the theory, tumor density becomes more homogeneous on CT scans as lesion size increases. Recent studies have found that more small nodules (especially those with a diameter <1 cm) have heterogeneous densities. Lung cancer is suspected if the density of such nodules increases and becomes homogeneous.[3]

In general, nodule characteristic changes in follow-up using a CT scan effectively differentiate the nature of small solid nodules. Knowing the regular changes in small solid nodules will make identifying suspected malignant nodules easier during follow-up.[3]

DIAGNOSIS OF SPN BASED ON RADIOLOGY EXAMINATION

A fluorodeoxyglucose (FDG) PET/CT improves lung nodule diagnosis by providing anatomical and morphological information from CT components. Yi et al compared PET/CT and High-Definition Computed Tomography (HDCT) for solitary pulmonary nodules. PET/CT outperformed HDCT with 96% sensitivity, 88% specificity, and 93% accuracy. Thus, PET/CT was recommended as the first imaging method for lung nodules.[2]

Fluorodeoxyglucose PET/CT can distinguish benign from malignant solid lung nodules and avoid unnecessary procedures. Malignant solid nodules had higher Standardized Uptake Values (SUVs) than benign ones. Slow-growing malignant tumors have minimal FDG absorption. Pneumonia, TB, amyloidosis, and sarcoidosis also absorb FDG. FDG-PET paired with CT is less specific for malignancy in populations with endemic lung infections, according to a meta-analysis by Deppen et al.[27]

MRI has better soft tissue contrast and spatial resolution; however, motion, respiratory artifacts, and low proton density can affect it. Using gadolinium chelates and new approaches has enhanced MRI lung cancer detection and staging. Diffusion-weighted and perfusion MRI sequences provide morphological and functional information. CT, FDG PET/CT, and MRI characterize nodules non-invasively.[2] The MRI results can also help follow the patients without sufficient PET-CT results.[28]

Artificial neural networks (AI) power deep learning (DL) can detect lung nodules well. Gong et al. found lung nodules with 93.6% sensitivity and one false positive per scan using 3D deep convolutional neural networks. Conventional approaches cannot attain 90% sensitivity. DL research currently classifies lung nodules by histology. Ciompi and Nishio classified nodules with DL models. DL models had 68% classification accuracy versus 55.9% for conventional approaches.[2] Radiomics quantitatively extracts medical picture features (volume, shape, density) for clinical decision-making. Radiomics enhances cancer diagnosis, prognosis, and prediction.[2,29,30]

MANAGEMENT OF SOLITARY PULMONARY NODULE

Accurate measurement is crucial in the management and decision-making process of lung nodules. It can help estimate baseline risk, appropriate management algorithms, and optimize follow-up for lesion growth during subsequent examinations. The evaluation of lung nodules begins with distinguishing solid and subsolid lesions using appropriate techniques.[2]

Fleischner Society

The Fleischner Society advises low-dose radiation CT with a 1.0 mm-section thickness and rigorous comparison of previous CT images for appropriate interpretation. The Fleischner Society criteria for accidental nodules have been revised. The minimal size criteria for solid nodule follow-up have been increased, and periods rather than intervals are recommended.[7]

The Fleischner Society (Table 1) categorizes risk into high-risk (>5%) and low-risk groupings. High-risk variables include older age (>55 years), heavy smoking (>30 pack-years), large nodule size, uneven or spiculated borders, and upper-lobe placement. High-risk patients have emphysema, lung fibrosis, family history, and carcinogen exposure.[2]

The ACCP Guideline

The ACCP recommends serial CT scans based on nodules and patient conditions, as shown in Table 2. This guideline suggests sampling intermediate-risk nodules with or without surgery, considering patient preferences and surgical risks.[2]

Table 1. Treatment Guideline for Lung Nodule according to The Fleischner Society[7]

Initial size	Solitary		Multiple	
	Low Risk	High Risk	Low Risk	High Risk
Solid Nodul				
< 6 mm (<100 mm^3)	No routine follow-up	Optional CT in 12 months	No routine follow-up	Optional CT in 12 months
6-8 mm (100-250 mm^3)	CT in months 6-12, consider CT in months 18-24	CT in months 6-12, consider CT in months 18-24	CT in months 3-6, consider CT in months 18-24	CT in months 3-6, consider CT in months 18-24
> 8 mm (>250 mm^3)	Consider CT in month 3, PET/CT, or tissue sampling	Consider CT in month 3, PET/CT, or tissue sampling	CT in months 3-6, consider CT in months 18-24	CT in months 3-6, consider CT in months 18-24
Ground-glass				
< 6 mm (<100 mm^3)	No routine observation		CT in 3-6 months. If stable, consider CT in 2 and 4 years.	
≥6 mm (>100 mm^3)	CT in 6-12 months to confirm persistence, then CT every 2-5 years		CT in 3-6 months. Further treatments are based on the suspicious nodule.	
Partly-solid				
< 6 mm (<100 mm^3)	No routine observation		CT in 3-6 months. If stable, consider CT in 2 and 4 years.	
≥6 mm (>100 mm^3)	CT in 3-6 months to confirm persistence. If there is no change and the solid component is still <6 mm, annual CT is suggested for 5 years.		CT in 3-6 months. Further treatments are based on the suspicious nodule.	

Table 2. Treatment Guideline for Lung Nodule from ACCP[2]

Initial size	Solitary and Multiple	
	Low Risk	**High Risk**
Solid Nodul		
≤4 mm	Follow-up optional	Follow-up in 12 months. If there is no change, no follow-up is required.
5-6 mm	Follow-up in 12 months. If there is no change, no follow-up is required	Follow-up in 6-12 months. If stable, follow-up in 18-24 months.
6-8 mm	Follow-up in 6-12 months. If there is no change, follow up in 18-24 months.	Follow-up in 3-6 months. If there is no change, follow up in 9-12 and 18-24 months.
>8 mm	Low risk: CT or FDG-PET surveillance Moderate risk: PET or functional imaging High risk: Biopsy or refer for a surgery	
Ground-glass		
≤5 mm	No Follow-Up	
>5 mm	Annual CT surveillance for ≥3 yr	
Part Solid		
≤8 mm	Repeat CT at 2, 12, 24 month	
>8 mm	Repeat CT at 3 months. If persistent: PET-CT, biopsy, or resection	

Table 3. Treatment Guideline for Lung Nodule from BTS[2]

Initial size	Solitary and Multiple	
	Risk <10%	**Risk ≥10%**
Solid Nodul		
<5 mm	No follow-up	No follow-up
5-6 mm	Follow-up CT scan 1 year If stable: a) Based on the volumetric: discharge; b) Based on the 2D non-automated diameter value: follow-up 1-year If unstable: a) VDT >600 days: discharge; b) VDT 400-600 days: consider CT surveillance or biopsy; c) VDT ≤400 days: further examinations and definitive treatments.	
6-8 mm	Follow-up CT scan in 3 months. If stable, follow-up 1 year and estimate VDT. Treatment is based on the recommendations for nodules of 5-6 mm.	
>8 mm	CT surveillance, according to the recommendation for 6-8 mm	PET/CT with risk assessment using the Herder model; a) <10%: CT surveillance; b) 10-70%: biopsy; c) >70%: Surgical resection or non-surgical treatment.
Ground-glass		
≤5 mm	No Follow-Up	No Follow-Up
>5 mm	Follow-up CT at 3 months to confirm the persistence	
	Annual CT x 4 yr	Consider Follow-Up CT, biopsy, non-surgical treatment, or resection.
Part Solid		
Any	Repeat CT at 1, 2, 4 year	Repeat CT, biopsy, or surgical resection.

Risk factors are low (<5%), moderate (5-65%), and high (>65%). Nonsmoking, age <40, no cancer history, well-defined borders, and middle or lower lobe location are low-risk factors.[2]

Smoking >30 pack-years, age >60, history of cancer, spiculated nodule margins, and upper lobe location are high-risk factors. Moderate risk features combine the other two groups.[2]

The BTS Guideline

Brock and Herder risk models and volumetric analysis determine a nodular doubling time in the BTS recommendation. Brock evaluates solid and subsolid nodules; meanwhile, Herder's risk stratification. Computed tomography (CT) should evaluate nodules that exceed the size of 5 mm or 80 mm^3. Stable solid nodules require a one-year follow-up. VDT results guide unstable solid nodule management. PET/CT is essential for controlling nodules with a Brock model malignancy risk of 10% and a diameter or volume of 8 mm or 300 mm^3.[2,19]

The Herder model uses FDG uptake (none, mild, moderate, high) and additional risk factors (age, smoking, cancer history, suspicious nodule morphology) to predict nodule malignancy risk. Based on PET/CT malignancy risk, nodules are treated with CT, tissue samples without surgery, excision surgery, or non-surgical therapy.[2,19] Treatment guidelines for lung nodules can be seen in Table 3.

CONCLUSION

The early detection of lung nodules significantly impacts the prognosis of the disease. The increased utilization of thoracic CT scans in routine clinical settings has led to increased case detection, enabling prompt intervention. Several variables affect the likelihood of malignancy in solitary pulmonary nodules, including clinical and metabolic evaluation, evaluation of nodule characteristics from CT scan images, nodule size, and growth rate. Determining the likelihood of malignancy presents a formidable challenge, yet it remains a crucial step in devising a course of action for subsequent monitoring and treatment.

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Literature Review

Re-expansion Pulmonary Edema

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Abstract

Re-expansion pulmonary edema (RPE) is a rare complication of pleural puncture (thoracentesis) and chest tube insertion. The incidence of RPE is low (1%), but mortality can be up to 20%. The main pathophysiological mechanism is pulmonary edema due to increased permeability and increased hydrostatic pressure in the pulmonary capillaries. Risk factors include duration of lung collapse (>3 to 7 days), size of pneumothorax (>30%), volume of aspirated air or fluid (>1.5 to 3 L), excessive negative intrapleural pressure, diabetes mellitus, and chronic hypoxemia. Prevention includes limiting the volume of aspirated air or fluid (<1.5 L), air or fluid evacuation in a controlled manner, and preventing excessive negative intrapleural pressure. Treatment is supportive care through cardiovascular and respiratory monitoring, oxygen and decubitus positioning.

Keywords: re-expansion pulmonary edema, pathogenesis, clinical management

INTRODUCTION

Pleural effusion and pneumothorax are common conditions. In the United States, each year there are 1.5 million patients with pleural effusion and 40.000 patients with pneumothorax, which causes pleural puncture (thoracentesis) and chest tube insertion to be common medical procedures.[1,2] The collapsed lung due to pneumothorax or pleural effusion after a chest tube insertion or pleural puncture in some circumstances leads to re-expansion pulmonary edema (RPE), which is a condition that rarely occurs but can be fatal.[2]

A case of RPE was first reported in 1853 when Pinault removed 3 L of pleural fluid from a patient with pleural effusion. A case report of RPE in a pneumothorax patient was initially reported by Carlson in 1958. The prevalence of RPE is relatively low (less than 1%), however, there are differences from various studies with a prevalence range between 0.3% and 32.5%. This is due to different definitions (clinical versus radiological), small sample sizes, and different patient populations.[2,3]

Mortality from RPE has been reported to be as high as 20%, nonetheless, recent studies in patients with pneumothorax have shown lower rates, making it difficult

to determine the prognosis in patients with RPE. The pathophysiology and contributing factors of RPE are not fully understood, and prevention is the best medical approach. Prevention is one of the reasons for expert agreement on the amount of fluid that can be removed in a pleural puncture for one attempt (1 to 1.5 L).[3] This literature review will discuss RPE, especially in patients with pleural effusion and pneumothorax.

PATHOGENESIS AND PATHOPHYSIOLOGY OF RPE

The pleural cavity consists of the parietal pleura lining the chest wall, diaphragm and mediastinum, and also the visceral pleura lining the lung. In normal conditions, there is fluid between the two pleural layers. The volume of pleural fluid in a normal individual is 0.26 mL per kilogram of body weight. Pathological conditions can increase the volume of the pleural cavity both in the form of increased fluid volume (effusion) and the entry of air into the pleural cavity (pneumothorax). This leads to impaired lung development and requires invasive management such as pleural puncture and chest tube insertion.[1]

Pneumothorax causes an increase in intrapleural pressure. The increase in intrapleural pressure that occurs is not very large, and usually the upper lobe of the lung is more affected because the pressure gradient at the apex is greater than the basal lung. Pleural effusion will cause a greater pressure gradient at the lowest part of the lung, so that in an upright state, the lower lobe of the lung, which is the dependent part, will be more affected than the upper lobe of the lung.[4]

The mechanism of RPE is not well known and study on this subject is limited. Data from existing studies indicate that two important mechanisms cause RPE, namely impaired permeability at the alveolar-capillary barrier and increased hydrostatic pressure in the lung microvasculature.[5,6]

The pathological processes that occur are changes in the lung microvasculature, tissue damage by oxygen free radicals, increased local cytokine production, decreased surfactant function in the collapsed lung, decreased pulmonary lymphatic vessel flow, and excessive negative pressure in the pleural cavity during lung expansion.[5,7]

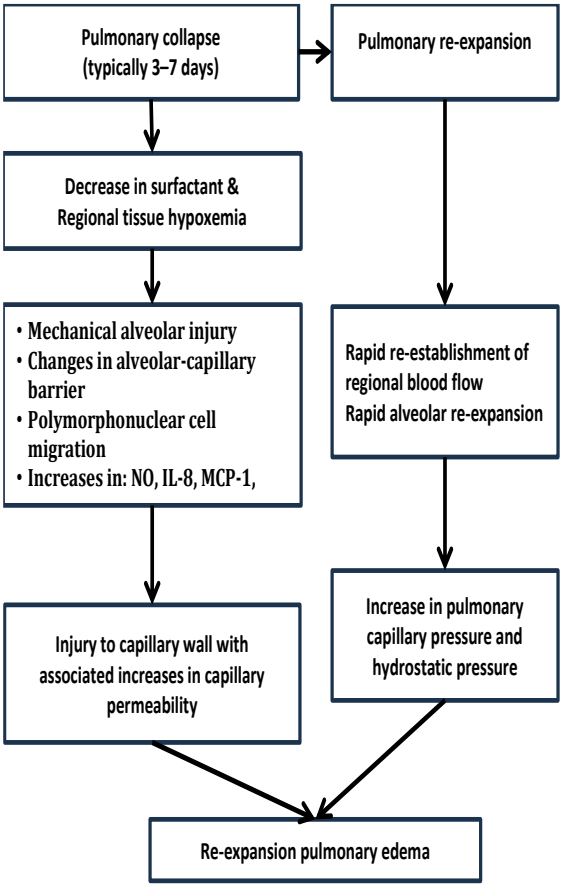

Figure 1. Pathophysiology of RPE[5–8]

Table 1. Components of diagnosis RPE[2,6,7]

Category	Description
Anamnesis	1. Abnormalities or space-occupying lesions of the thoracic cavity that cause lung collapse for more than 3-7 days
	2. Air or liquid aspiration within the previous 24-48 hours
Examination finding	1. Coughing for more than 20 minutes, pink or pollen sputum, chest discomfort, shortness of breath, tachycardia
	2. Rales on the ipsilateral, sometimes bilateral, rarely contralateral only
	3. Signs of hemodynamic instability, hypoxia, and hypovolemia
Radiologic examination	1. Unilateral radiologic abnormalities in the collapsed lung, sometimes bilateral, rarely contralateral only
	2. Alveolar filling pattern (infiltrates and consolidation) on thoracic radiographs
	3. Ground glass opacity, consolidation and thickened septa on CT scan
	4. Resolution of radiological features after a few days (in non-fatal cases)

CLINICAL MANIFESTATION

The diagnosis criteria for RPE have not yet been established. The clinical diagnosis of RPE requires a critical review of the history of the disease, clinical symptoms and signs, and radiological findings (Table 1).

Risk Factors

The mechanism of RPE is not well known and is multifactorial, so several risk factors may underlie the process. The duration of lung collapse is a major risk factor for RPE. Lung collapse of more than 3–7 days increases the risk of RPE compared to lung collapse of less than 72 hours. A possible mechanism is that pathological changes in the lung microvasculature take several days to have a significant effect on permeability when lung re-development occurs. Risk factors for RPE include:[7,8]

1. Duration of lung collapse (>3–7 days)
2. The large size of pneumothorax (>30%), tension pneumothorax
3. Concurrent effusion with pneumothorax
4. Age less than 40 years old
5. Aspiration fluid volume (>1.5–3 L)
6. Excessive negative pressure on the pleural cavity
7. Chronic hypoxemia
8. Diabetes mellitus

MANAGEMENT OF RPE

Prevention

The RPE is difficult to prevent due to its unknown etiology and pathophysiology, as well as the multifactorial risk factors. The risk of RPE remains, although all interventions have been implemented. Identification of risk factors and the possibility of RPE occurring in patients must be carried out. Identified risk factors must be adequately managed so that the risk of RPE can be reduced as much as possible. Patients with hypoxemia or high risk for RPE should be monitored and given oxygen during and after the procedure.[6]

Clinical Management

The primary management in the case of RPE is close respiratory and cardiovascular monitoring plus oxygen administration. Such conservative

management is sufficient in the majority of RPE cases.[9] The lateral decubitus strategy of placing the affected side in a dependent position can reduce intrapulmonary shunts and improve oxygenation.[6,7,10] Patients who do not improve with conservative management require respiratory support using non-invasive ventilation with continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP).[7,9]

Mechanical ventilation with tracheal intubation and positive end-expiratory pressure (PEEP) may be considered in patients who are worsening or unstable. Hemodynamic support with vasopressor or inotropic drugs may be required in such patients.[7,10] Patients who continue to have respiratory failure after maximal management may be considered for differential ventilation.[6,7,10] The benefits of steroid administration have not been supported by strong evidence while diuretic administration can be detrimental because it aggravates the hypovolemia that occurs, so if it is needed, it is given under close supervision.[6,9]

Experimental treatments such as the administration of prostaglandin analog misoprostol and non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen and indomethacin at the onset of RPE diagnosis to obtain cytoprotective and anti-inflammatory effects have been reported but to date have not been supported by strong evidence.[3,6,10]

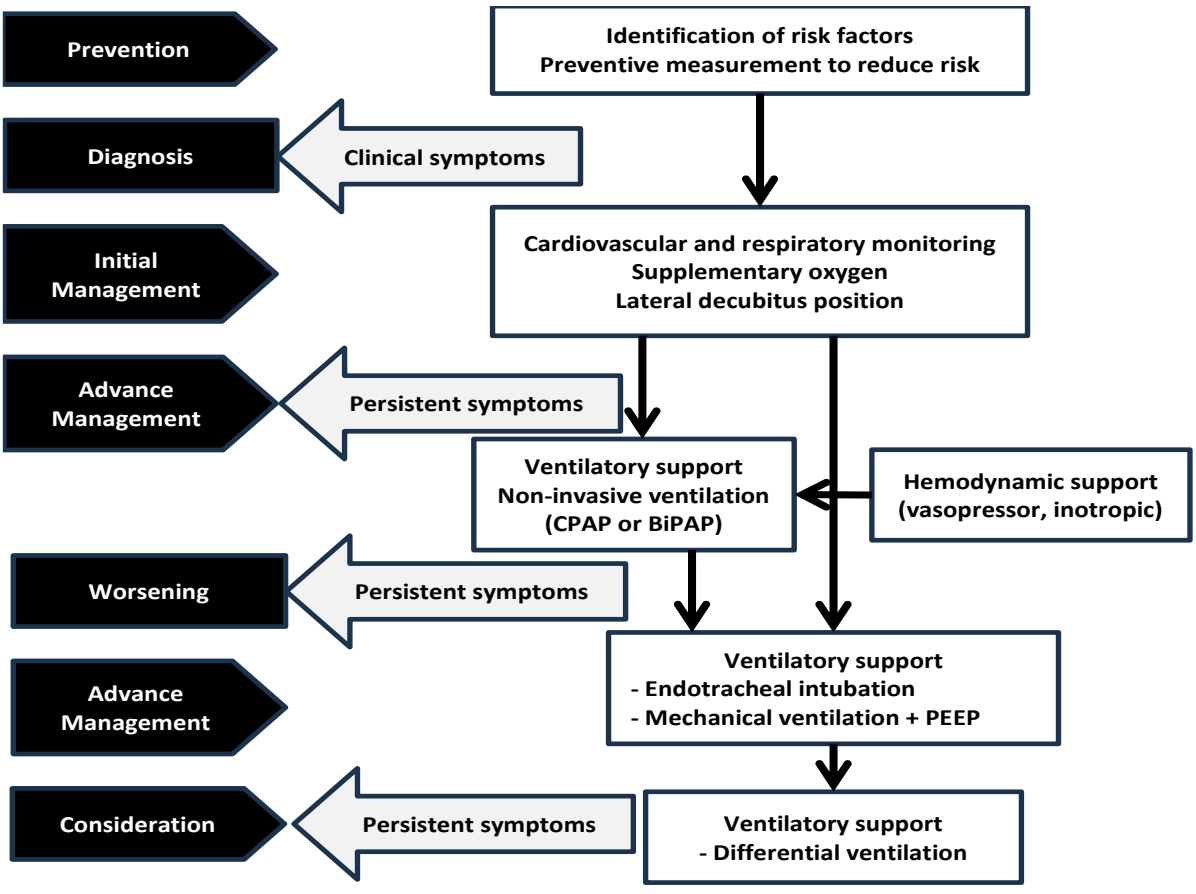

Figure 2. Comprehensive Management of RPE[3,6,7,9,10]

Administration of anti-IL-8 antibodies to reduce the inflammatory process that occurs during the development of collapsed lung and administration of alpha lipoic acid (ALA) as an antioxidant gave positive results in experimental animals, however, there is no evidence of benefit in humans.[3,6,10]

CONCLUSION

The RPE is a rare complication but is related to many cases encountered in the clinic, namely pleural effusion and pneumothorax. Identification and management of risk factors are important to minimize the risk of RPE. Most cases of RPE can be managed with cardiovascular and respiratory monitoring, as well as oxygen administration alone. Respiratory and circulatory support via non-invasive ventilation or mechanical ventilation and vasopressor/inotropic administration can be given in severe RPE.

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