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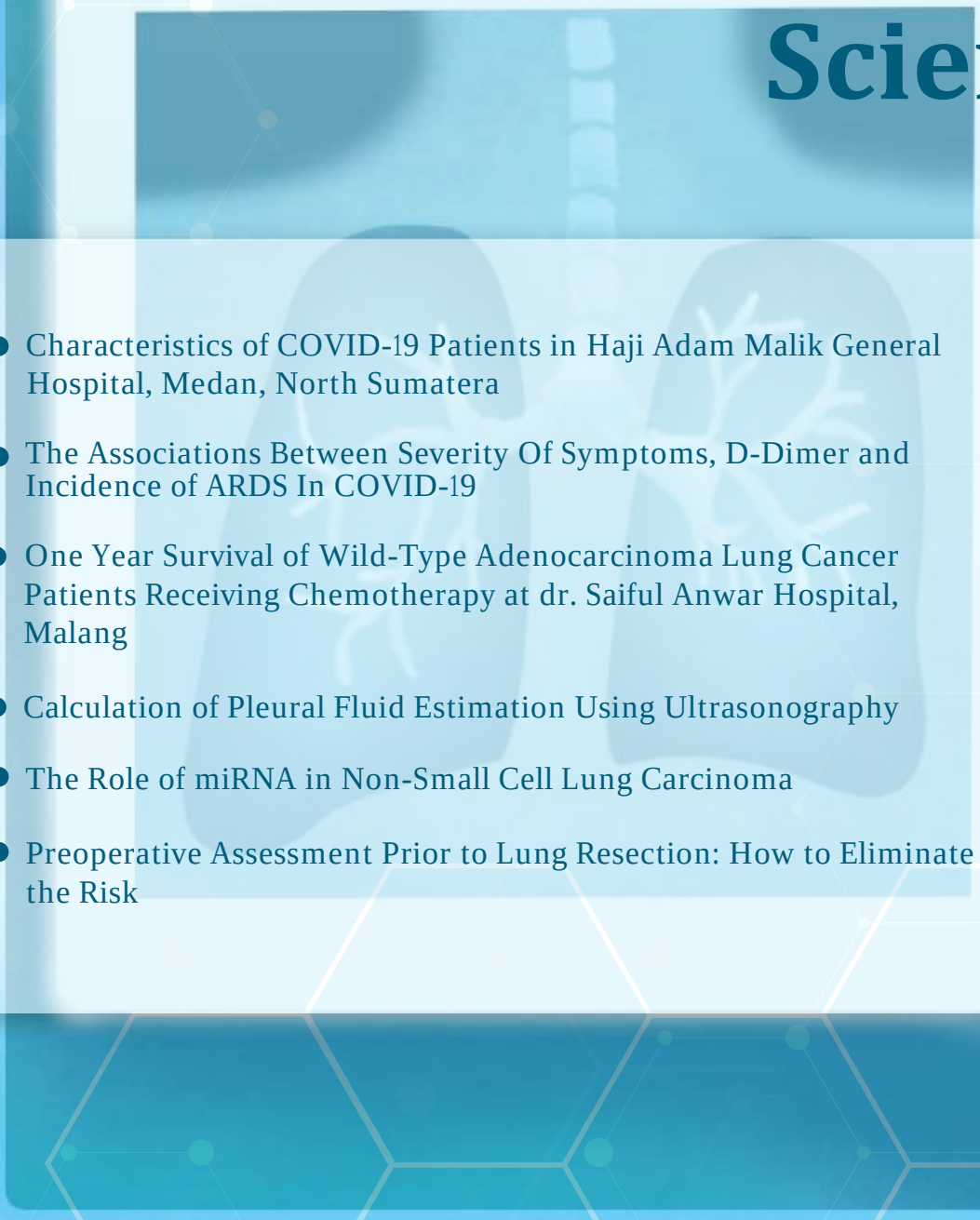



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Original Article

# Characteristics of COVID-19 Patients in Haji Adam Malik General Hospital, Medan, North Sumatera

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## Abstract

**Background:** Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The increase in the number of COVID-19 cases was happening quite quickly and has spread between countries so that COVID-19 has become a pandemic in the world. This study aimed to determine the characteristics of COVID-19 patients at Haji Adam Malik General Hospital Medan.

**Method:** This was a descriptive study. Data were taken from the medical records of 110 hospitalized patients with positive RT-PCR results for COVID-19 from December 2020 to April 2021. The inclusion criteria for the case samples were patients diagnosed with COVID-19 based on RT-PCR and the exclusion criteria were incomplete medical records. Characteristic analysis was carried out using the Kruskal Wallis test.

**Results:** The most common comorbidities found in patients with severe COVID-19 were diabetes mellitus and HIV. The most common comorbidity found in moderate-level COVID-19 patients was pregnant women. The most common chest X-rays finding in severe and critical levels was bilateral infiltrates. Recovered patients were mostly obtained at moderate level, while deceased patients were mostly observed at critical levels.

**Conclusion:** Characteristics of COVID-19 patients at Haji Adam Malik General Hospital were classified based on the degree of disease by age, lymphocyte value, N/L ratio, levels of CRP, D-dimer, procalcitonin, fibrinogen, ferritin, and comorbidities as well as the appearance of infiltrates in both lung fields.

**Keywords:** COVID-19, characteristics, degree of disease

## INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a disease caused by infection of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2), which was first reported in Wuhan, Hubei Province, China. SARS CoV-2 was identified as the pathogen of COVID-19 in January 2020.[1] On 12 March 2020, WHO declared COVID-19 as a new pandemic with very fast

human-to-human spread, causing the number of COVID-19 cases to increase rapidly throughout the country.[2,3] As of 7 September 2020, the Ministry of Health of the Republic of Indonesia has reported 26,763,217 confirmed cases and 876,616 death cases with a mortality rate of 3.3% globally.

In previous studies conducted in various countries, the most commonly discussed characteristics of COVID-19 patients were age, gender, comorbidities, clinical manifestations, laboratory examinations and chest X-rays (CXR). Based on age, Jiang et al in 2020 prior to several studies in various hospitals in China observed that the most prevalent group of age for COVID-19 was 49-56 years old.[4] According to Liu et al in 2020 at Wuhan Central Hospital, most of the progressive disease were reported in patients over 66 years of age whilst stable cases were reported in younger patients.[5]

According to Li et al in a meta-analysis on 2020, the percentage of male among COVID-19 patients was higher than female, which was 60%.[5] According to Chen et al in 2020, about 51% of the patients had decreased blood hemoglobin level, 24% had increased leukocyte level, and 35% had a decline in platelet level. In addition, 36% of the patients had elevated D-Dimer values, 6% had increased procalcitonin levels, 63% had elevated ferritin level, and 86% of the patients had elevated CRP.[6]

Based on CXR ecamination, 75% of the patients had bilateral pneumonia, 25% had unilateral pneumonia while 14% of the patients had ground glass opacity appearance on CT-Scan examination.[6]

Based on these studies and the rapidly increasing rate of COVID-19 infection as mentioned above, we intended to identify the characteristics of COVID-19 patients, based on age, gender, comorbidities, laboratory examinations, CXR examinations and the treatment outcome of COVID-19 patients in H. Adam Malik General Hospital, Medan.

## METHOD

This was a descriptive study using secondary data obtained from medical records of inpatients diagnosed with COVID-19 at Haji Adam Malik General Hospital. This study was conducted from December 2020 to April 2021.

The samples in this study were 106 samples taken through inclusion criteria, namely patients diagnosed with COVID-19 based on RT-PCR test, and exclusion criteria, namely insufficient medical record data.

This study used two variables. The dependent variable was the outcome. The independent variables were age, gender, laboratory examination results such as lymphocyte count, prolymphocyte neutrophils, D-Dimer, C-Reactive Protein (CRP), Procalcitonin (PCT), fibrinogen and ferritin, comorbidities such as diabetes mellitus, hypertension, Human Immunodeficiency Virus (HIV), heart disease, kidney diseases, malignancy, other lung diseases (Chronic Obstructive Pulmonary Disease/COPD or

Tuberculosis/TB), pregnancy, CXR results, and the treatment outcome, either dead or recovered.

The data obtained were processed by SPSS software and analyzed using Kruskal Wallis test. This study had acquired an approval from the medical research ethics committee of the Faculty of Medicine, Universitas Sumatera Utara, Medan.

## RESULTS

There were 106 samples in this study taken from the medical records of patients diagnosed with COVID-19 from December 2020 to April 2021.

Table 1. Characteristics of Samples Based on Gender

| Gender | N | Percentage |
|---|---|---|
| Male | 58 | 57.7 |
| Female | 48 | 45.3 |
| Total | 106 | 100.0 |

Table 2. Mean Age of the Samples (In Years) Based on COVID-19 Severity

| Severity | Mean±SD | Median (Min–Max) |
|---|---|---|
| Moderate | 46.92±15.71 | 48 (19-79) |
| Severe | 56.47±14.76 | 58 (30-79) |
| Critical | 58.50±9.35 | 60 (32-73) |

Table 3. Characteristics of the Samples Based on Laboratory Examinations

| Parameter | Mean±SD | Median (Min–Max) |
|---|---|---|
| Lymphocyte | 1.79±2.75 | 1.3 (0.30-29) |
| NL Ratio | 8.01±11.17 | 3.7 (0.61-65.02) |
| CRP | 0.9569±0.62 | 0.7 (0.70-2.80) |
| PCT | 1.86±8.25 | 0.06 (0-50.65) |
| D-Dimer | 931.29±1133.12 | 416 (100-4483) |
| Fibrinogen | 467.11±165.38 | 438.50 (142–900) |
| Ferritin | 941.61±1174.65 | 597.50 (7.31-10621) |

Table 4. Mean Lymphocyte Count and N/L Ratio ($10^3$/µL) Based on COVID-19 Severity

| Parameter | Severity | Mean±SD | Median (Min – Max) |
|---|---|---|---|
| Lymphocytes | Moderate | 2.13±24 | 1.59 (0.64–29) |
| | Severe | 1.41±0.92 | 1.19 (0.30–3.38) |
| | Critical | 0.72±0.33 | 0.57 (0.34–1.26) |
| N/L Ratio | Moderate | 3.70±3.39 | 2.75 (0.61–22.82) |
| | Severe | 8.87±8.24 | 6.48 (1.71–36.83) |
| | Critical | 25.2±17.05 | 18.79 (4.60–65.02) |

Table 5. Mean Value of CRP, PCT, D-dimer, Fibrinogen and Ferritin (ng/L) Based on COVID-19 Severity

| Parameter | Severity | Mean±SD | Median (Min – Max) |
|---|---|---|---|
| CRP | Moderate | 0,82±0,35 | 0,69 (0,01-2,8) |
| | Severe | 1,39±0,95 | 0,70 (0,69–2,80) |
| | Critical | 1,08±0,90 | 0,7 (0,7–2,80) |
| PCT | Moderate | 0,72±5,19 | 0,04 (0,0–45,08) |
| | Severe | 5,49±14,84 | 0,15 (0,02–50,66) |
| | Critical | 3,19±9,56 | 0,31 (0,02–40,73) |
| D- Dimer | Moderate | 624±763 | 340 (100–4001) |
| | Severe | 1750±1661 | 950 (290–4483) |
| | Critical | 1435±1318 | 799 (190–4001) |
| Fibrinogen | Moderate | 429±138.64 | 409 (142–900) |
| | Severe | 541±172.29 | 535 (275–900) |
| | Critical | 551.88±211 | 494.50 (201–900) |
| Ferritin | Moderate | 620.53±597.89 | 364.60 (7.32–2001) |
| | Severe | 1191.83±794.16 | 1125 (83.16–2001) |
| | Critical | 2043±2212 | 1893 (207–10621) |

Table 6. The Characteristics of Comorbidities, Radiological Examination Results, and Outcome Compared to the COVID-19 Severity

| Characteristics | Severity | | |
|---|---|---|---|
| | Moderate | Severe | Critical |
| Diabetes Mellitus | | | |
| Yes | 9 (12%) | 9 (52.9%) | 3 (16.7%) |
| No | 66 (88%) | 8 (47.1%) | 15 (83.3%) |
| Hypertension | | | |
| Yes | 23 (30.7%) | 8 (47.1%) | 12(66.7%) |
| No | 52 (69.3%) | 9(52.9%) | 6 (33.3%) |
| HIV | | | |
| Yes | 0 (0%) | 2 (11.8%) | 0 (0%) |
| No | 75 (100%) | 15 (88.2%) | 18 (100%) |
| Heart Disease | | | |
| Yes | 10 (13.3%) | 3 (17.6%) | 8 (44.4%) |
| No | 65 (86.7%) | 14 (82.4%) | 10 (55.6%) |
| Kidney Disease | | | |
| Yes | 2 (2.7%) | 3 (17.6%) | 7 (38.9%) |
| No | 73 (97.3%) | 14 (82.4%) | 11 (61.1%) |
| Malignancy | | | |
| Yes | 2 (2.7%) | 0 (0%) | 1 (5.6%) |
| No | 73 (97.3%) | 17 (100%) | 17 (94.4%) |
| TB | | | |
| Yes | 1 (1.3%) | 0 (0%) | 0 (0%) |
| No | 74 (98.7%) | 17 (100%) | 18 (100%) |
| COPD | | | |
| Yes | 3 (4%) | 0 (0%) | 2 (11.1%) |
| No | 72 (96%) | 17 (100%) | 16 (88.9%) |
| Pregnancy | | | |
| Yes | 9 (12%) | 0 (0%) | 1(5.6%) |
| No | 66 (88%) | 17 (100%) | 17 (94.4%) |
| Chest X-ray | | | |
| Bilateral infiltration | 73 (97.3%) | 17 (100%) | 18 (100%) |
| Diffuse infiltration | 1 (1.3%) | 0 (0%) | 0 (0%) |
| Nodule and focal infiltration | 1 (1.13%) | 0 (0%) | 0 (0%) |
| Outcome | | | |
| Recovered | 69 (92%) | 13 (76.5%) | 4 (22.2%) |
| Mortality | 6 (8%) | 4 (23.5%) | 13 (72.2%) |
| Discharge on request | 0 (0%) | 0 (0%) | 1 (5.6%) |

## DISCUSSION

The result of this study showed that most of the patients were male (54.7%) compared to female (45.3%). According to Ahmed and Dumanski in their study on 2020, this could be affected by angiotensin converting enzyme 2 (ACE2), which was a functional receptor that enabled the invasion of SARS-CoV-2 into the alveolar epithelium. It played an integral part in the renin-angiotensin-aldosterone system (RAAS) in humans. In general, RAAS activity in men is higher than in women.[7]

In this study, the mean age of COVID-19 patients in severe and critical conditions were 60 and 56 years, respectively. Liu et al. stated that the mean age of the patients in severe and critical levels were higher than patients in moderate level of the disease. A study from Wu et al. expressed that this could be due to the decline of immune system in the elderly which increased the risk of ARDS and mortality.[8]

The results of this study mentioned that the lowest lymphocyte count in moderate disease was 0.64 × $10^3$/µL and the highest lymphocyte count was 0.30 × $10^3$/µL. In severe disease, the lowest and highest lymphocyte count were 0.30 × $10^3$/µL and 3.38 × $10^3$/µL, respectively. The lowest lymphocyte count in critical disease was 0.34 × $10^3$/µL while the highest was $10^3$/µL. Cytotoxic $CD8^+$ T Cells (CTLs) and $CD4^+$ Helper T (Th) Cells boost the host ability to eliminate pathogens. However, prolonged stimulation may cause T cells to become fatigue, which will decrease the function of the cells as immune system and worsen the patient's condition. Several studies had found a decrease in the number of lymphocytes, including total T cells, CD4+ and CD8+ T cells, memory and regulatory T cells and B cells in COVID-19 patients.[9]

The increment of CRP value was promoted by the overproduction of inflammatory cytokines in COVID-19 patients. Cytokines play a role in defense against microbes; however, an exaggerated immune response can damage lung tissue.[10] According to Zavareh et al., serum CRP concentrations could be used as an indicator of COVID-19 disease progression and severity.[11]

The median PCT value in this study for moderate, severe, and critical COVID-19 patients were 0.04 ng/mL, 0.15 ng/mL and 0.31 ng/mL, respectively. This was also similar with a study from Feng et al. which mentioned that PCT increased significantly due to cytokine storm which was chracterized by elevated concentrations of interleukin (IL)-1ß, Tumor Necrosis Factor (TNF)-α and IL-6, interferon gamma-induced protein-10, and macrophage inflammatory protein 1-α which were mostly increased in severe and critical COVID-19 patients.[12]

Our study found that the mean D-dimer values in moderate, severe, and critical COVID-19 patients were 340, 950 and 799 ng/mL, respectively. This result was identical to previous study conducted by Mahardika et al, which pointed out that the D-dimer value increased to 807.7 ng/ml. This, according to Yu et al., was due to the escalation of abnormal blood coagulation which was correlated with an increase of D-dimer value. Elevated D-dimer value is an indirect manifestation of inflammatory response, equal to inflammatory cytokine which can cause an imbalance of coagulation and fibrinolysis in the alveoli, that may promote fibrinolysis and increase D-dimer levels.[13]

The mean fibrinogen values for moderate, severe, and critical COVID-19 patients were 429, 541, and 551 ng/ml, respectively. These results were similar with a prior study conducted by Nugroho et

al., which obtained that the mean fibrinogen value in critical COVID-19 patients was higher compared to severe COVID-19 patients which was less than 500. Another study by Nugroho et al., also mentioned that the mean value of fibrinogen was higher in patients who died or after the COVID-19 treatment than before treatment.[14]

In this study, it was shown that the mean ferritin levels in moderate, severe and critical patients were 620, 491 and 2041 ng/mL.[15] Similar with our study, Zhou et al. also found that there was an increase of 377-1435 ng/mL on ferritin levels. This was also in line with prior study conducted by Carubbi et al., which pointed out that hyperferritinemia was strongly correlated with inflammation in patients infected with SARS-CoV-2. Ferritin was used as a parameter to predict disease severity and the rate of cytokine storm. A complex feedback mechanism between ferritin and cytokines in controlling pro-inflammatory and anti-inflammatory mediator exists because cytokines induce ferritin expression, however, ferritin also induces the expression of pro- and anti-inflammatory cytokines.[16]

This study found that diabetes melitus was observed in 9 (12%) moderate COVID-19 patients, 9 (52.9%) severe patients and 3 (16.7%) critical patients. On the other hand, Hussain et al., expressed that hypoglycemic state (<3.9 mmol/L) mobilized pro-inflammatory monocytes and escalated thrombocyte reactivation. These contributed to higher cardiovascular mortality in patient with diabetes mellitus. Diabetes is a chronic inflammation characterized by several metabolic and vascular disorders which affect our body's response to pathogens. Hyperglycemia and insulin resistance increase Advanced Glycation End Product (AGEs) and pro-inflammatory cytokines, synthesis of oxidative stress and support the production of adhesion molecules that promote tissue inflammation. This inflammation process will worsen the patient's condition. Uncontrolled diabetes indicates that lung epithelial cells will be exposed to higher glucose levels and will significantly increase infection and replication.[17]

The results of this study mentioned that hypertension in COVID-19 were seen in 23 patients (30.7%) of moderate disease, 8 patients (47.1%) of severe disease and 12 patients (66.7%) of critical disease. According to Zhang et al., this was influenced by direct damage mediated by the ACE2. Another study in China showed that SARS-CoV-2 infection was caused by viral protein binding to ACE2 receptor upon protein activation. ACE2 is a monocarboxylate peptidase that is known to cleave several peptides in renin-angiotensin system. Since its discovery in 2000, ACE2 has been considered as blood pressure protective factor. Binding of SARS-CoV-2 to ACE2 inhibits the physiological function of ACE2, which will lead to harmful effects of hypertension such as multi-organ dysfunction.[18]

This study obtained only 2 severe COVID-19 patients (11.8%) with HIV prior to hospitalization. According to Rebeiro et al., there were 36 death cases (14.3%) of

COVID-19 patients. Study had shown that HIV patients with multiple morbidity and older age were important factors in morbidity and mortality in HIV patients coinfected with COVID-19.[19]

In this study, there were 10 moderate COVID-19 patients (13.3%) with cardiovascular morbidities, also 3 patients (17.6%) in severe disease and 8 patients (44.4%) in critical disease. Zhou et al. stated that pre-existing cardiovascular diseases caused harmful effects to COVID-19 patients. This was due to the frequently reported coronary heart attacks concomitantly with acute cardiac events and poor outcomes in influenza and other respiratory viral infection.[13] Prior study conducted by Zhou et al., observed high troponin I elevations in hospitalized patients who had died during treatment.[15]

This study also obtained 2 moderate COVID-19 patients (2.7%) with coexisting renal disease, 3 patients (17.6%) with the same comorbidity in severe disease and 7 patients (38.9%) in critical disease. A study from Gagliardi et al. pointed out that SARS-CoV-2 attacked mainly on target cells through several steps. The two main pathophysiologies for renal injury were the direct cytopathic effect of SARS-CoV-2 on renal epithelial tissue and cytokine storm syndrome. Hypoxia, persistent hypotension, rhabdomyolysis, excessive coagulation activation, cascade and microcirculation abnormalities predisposed to advanced acute renal failure.[20]

Non-lung cancer malignancy was inspected in 2 moderate COVID-19 patients (2.7%) while lung cancer coexisted in 1 critical COVID-19 patient (5.6%). According to Lee et al., patients who had cancer and were not on regular treatment had a higher rate of COVID-19 infection, which concluded that inward COVID-19 patients did not correlate with disease severity as the pandemic had caused an inadequate treatment for cancer patients in health facilities and thus influenced this study.[21]

Tuberculosis (TB) was only found in 1 COVID-19 patient (1.3%) with moderate disease, none was found in severe or critical disease. As there was only one sample in this study who had tuberculosis comorbidity, the authors suggest that more specific studies are needed before this study.[22]

Sheerin et al. mentioned that although viral infections of the respiratory tract and TB harmed the host's immune system, there was still insufficient evidence on the correlation between SARS-CoV-2 coinfection with *Mycobacterium tuberculosis* and the immune system, prior to clinical COVID-19 disease severity and TB with or without symptoms.[22] According to Widyaningsih et al., more studies from different countries were required to understand the correlation between TB and COVID-19 prognosis.[23]

In this study, COPD was observed in 3 patients (4%) with moderate COVID-19 and 2 patients (11.1%) with critical disease when administered to the hospital. The identical result was also discovered by Antunez et al., who obtained that 7.16% of COVID-19 patients had COPD comorbidity. According to Antunez et al., one of the

reasons for this low prevalence of COVID-19 in COPD patients was the use of inhaled corticosteroids, beta agonist or anti-cholinergic drugs, especially tiotropium.[24]

On their study, they also mentioned that glycopyrronium and formoterol were proven to be effective in reducing cellular susceptibility to coronavirus infection in vitro. This may be due to the inhibition of coronavirus receptor expression, less endosome activity, and minimal inflammatory response. We understand that the basic treatment for COPD patients includes long-acting muscarinic antagonist (LAMA) and/or long-acting beta agonist (LABA).[24]

We found 9 pregnant patients (12%) who were admitted with moderate COVID-19 and 1 pregnant patient (5.6%) with critical COVID-19. There was no pregnant patient in severe COVID-19. Hapshy et al. reported that about 13.9% pregnant women with COVID-19 in New York were admitted in critical condition. Hapshy et al. expressed that this might be due to inadequate data and literature on the correlation of coronavirus in pregnancy. There was insufficient evidence about the risk of COVID-19 infection during the peripartum and antepartum periods.[25]

Also, current evidences contradicted each other, and there were no long-term studies during pregnancy. The unique physiology in pregnancy and several unknown factors in pregnant patients make the pregnant women to be less infected, however, they are still have to be classified as a high-risk population.[25]

In this study, there were 73 moderate COVID-19 patients (97.3%) with bilateral infiltrates on CXR, 17 patients (100%) with the same CXR results in severe COVID-19 and 18 patients (100%) in critical condition. We also obtained 1 patient (1.3%) in moderate COVID-19 with diffuse infiltrates who also had tuberculosis comorbidity and 1 patient (1.3%) in moderate COVID-19 with nodules and infiltrates on CXR who also had lung cancer.[26]

According to Chamorro et al., false positive results on CXR might be caused by insufficient inspiration, breast mass, and incorrect positioning of the patients, which caused the scapula and soft tissue to be more prominent.[26] However, Wong et al. suggested that CXR could be used to evaluate the progression of COVID-19 disease in the lungs, especially in critical ill patients admitted to the intensive care unit.[27]

Our study obtained 59 moderate COVID-19 patients (92%), 13 severe COVID-19 patients (76.5%) and 4 critical COVID-19 patients (22.2%) who recovered. Most of the patients died in the critical stage, which was 13 patients (72.2%). Salter et al., in their cross-sectional study on medical records also stated that there was an increase in disability related to disease severity which was correlated with mortality from COVID-19. Knowledge before COVID-19 could increase the therapeutic efficiency in COVID-19 patients, so that a more intensive evaluation can be carried out on COVID-19 patients.[28]

## CONCLUSION

There were some characteristics of COVID-19 patients at Haji Adam Malik General Hospital that we described based on age, lymphocyte count, N/L ratio, levels of CRP, D-dimer, procalcitonin, fibrinogen, ferritin and comorbidities as well as lung infiltrates.

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Original Article

# The Associations Between Severity Of Symptoms, D-Dimer and Incidence of ARDS In COVID-19

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## Abstract

**Background:** Severe acute respiratory injury caused by COVID-19 (ARDS) is a serious emerging complication. ARDS results from a cytokine storm that occurs in the second week of the disease course and acute-onset hypoxemia can be seen with bilateral infiltrates on chest radiograph. This study aimed to relate the severity of symptoms and D-dimer level to the incidence of ARDS in COVID-19 at H. Adam Malik Hospital as the referral center for COVID-19 in North Sumatra.

**Method:** This was a descriptive study with a retrospective cohort design. The sample of this study was secondary data from medical records of positive RT-PCR COVID-19 patients from November 2020 to April 2021. The inclusion criteria were patients with moderate to critical COVID-19 cases with D-dimer examination taken from the first day of admission. Subjects were then followed up until discharge from the hospital to assess for ARDS episodes which were confirmed by the results of PaO2/FiO2 in arterial blood gases and bilateral infiltrations in chest X-Ray. The exclusion criteria were incomplete medical records.

**Results:** The association between the severity of symptoms and the incidence of ARDS, 1 of which was found to be moderate, 19 cases were severe and 20 were critical. However, there was a statistically significant correlation between the severity of symptoms and the incidence of ARDS (P=0.0001).

**Conclusion:** There was a significant correlation between the severity of symptoms and the D-dimer value on the incidence of ARDS.

**Keywords:** ARDS, COVID-19, D-dimer

## INTRODUCTION

ARDS is a condition resulting from the destructions of epithelial, endothelial, and alveolar cells which lead to fluid accumulation in the interstitial and alveolar space.[1,2] Pathologically, the lung parenchyma of patients diagnosed with COVID-19 shows diffuse alveolar damage with fibrin-rich hyaline membranes and several multinucleated giant cells.[3] These

manifestations will interfere with the diffusion process across the alveolar-endothelial membrane and contribute to hypoxemic state of ARDS.[4] Later, after the hyperinflammatory reaction occurs intensively in acute phase, this alveolar damage will form scar and fibrosis that appear to be more severe in COVID-19.[3] Therefore, early treatment or early recognize of the onset of ARDS is necessary to reduce the risk of morbidity and mortality among all degrees of COVID-19.

Cytokine storm is the basic mechanism of ARDS in COVID-19. Cytokine hypersecretion during COVID-19 was influenced by several factors.[5] Demographic characteristics including gender, older age, smoking habits, and comorbidities have been identified as predisposing factors for ARDS.[6] Furthermore, inflammatory markers in laboratory findings might predict the development of ARDS in COVID-19. This study aimed to investigate the association between D-dimer and severity of symptoms in patients diagnosed with COVID-19 at H. Adam Malik General Hospital.

## METHOD

This was a descriptive study with a retrospective cohort design conducted in 2020-2021 at the Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sumatera Utara. All research procedures have been approved by the Ethics Committee of Faculty of Medicine, Universitas Sumatera Utara.

The sample of this study was secondary data from medical records of positive RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) COVID-19 patients from November 2020 to April 2021 at H. Adam Malik General Hospital Medan as the referral center of COVID-19 in North Sumatera, Indonesia.

The inclusion criteria were patients with moderate to critical COVID-19 cases confirmed by RT-PCR swab for SARS-CoV2. Subsequently, the D-dimer examination was carried out through blood tests taken from the first day of admission. The samples were then followed up until discharge from the hospital to assess for ARDS episodes which were confirmed using Berlin Criteria consisted of $PaO_2/FiO_2$ <300 mg/mL in arterial blood gases, bilateral infiltrations on chest X-Ray (CXR), and clinical progression within the last 7 days. The exclusion criteria were incomplete medical records.

All collected data were entered and analyzed using a statistical analysis program for Windows. Data were presented in categorical data with a D-dimer cut off value of 500 mg/dL. Chi square test was used to analyze the correlations between D-dimer and severity of symptoms on the incidence of ARDS.

## RESULTS

Most subjects recruited in this study were male (36.3%), age >40 years (82.4%), and had smoking history (61.55%). The most common complaints were shortness of breath (42,9%), cough

(21,9%), loss of smell (7,69%), loss of taste (3,3%) and fever (39,6%). Further clinical characteristics were described in Table 1.

Table 1. Clinical characteristics of all subjects recruited in the study

| Characteristic | N | % |
|---|---|---|
| Gender | | |
| Male | 58 | 63.7 |
| Female | 33 | 36.3 |
| Age | | |
| ≥40 years | 75 | 82.4 |
| ≤40 years | 16 | 17.6 |
| Smoking History | | |
| Smoker | 56 | 61.5 |
| Never smoker | 35 | 38.5 |
| Clinical symptoms | | |
| Shortness of breath | 39 | 42.9 |
| Cough | 29 | 21.9 |
| Loss of smell | 7 | 7.69 |
| Loss of taste | 3 | 3.3 |
| Fever | 36 | 39.6 |

The severity of symptoms was categorized based on the latest COVID-19 guideline in December 2020 from The Ministry of Health of the Republic of Indonesia. In this study, 1 subject (1.1%) had moderate symptoms, 19 subjects (20.9%) had severe symptoms and 20 subjects (22%) had critical symptoms. That one subject with moderate symptoms developed ARDS after the second week of hospitalization. All of the 19 subjects with severe symptoms developed ARDS after 2 weeks. On the other hand, all subjects with severe symptoms developed ARDS within the first week of hospital admission. Furthermore, this study showed a significant correlation between severity of symptoms and the incidence of ARDS in COVID-19 patients (P=0.0001).

Table 2. Correlation between severity of symptoms and the incidence of ARDS

| Severity Symptoms | ARDS | | Non-ARDS | | P |
|---|---|---|---|---|---|
| | N | % | N | % | |
| No Symptom | 0 | 0 | 0 | 0 | 0.0001 |
| Early | 0 | 0 | 0 | 0 | |
| Moderate | 1 | 1.1 | 40 | 44 | |
| Severe | 19 | 20.9 | 11 | 12.1 | |
| Critical | 20 | 22.0 | 0 | 0 | |

D-dimer were measured by immunofiltration in the Clinical Pathology Department of H. Adam Malik General Hospital with a cut-off value of 500 mg/dL on the first day of hospital admission. Of all subjects with ARDS, 33 subjects had increased D-dimer and 7 subjects had normal D-dimer. Statistically, there was a significant correlation between D-dimer and the incidence of ARDS in COVID-19 patients.

Table 3. Correlation between D-dimer and the incidence of ARDS

| D-dimer | ARDS | | Non-ARDS | | P |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Increased | 33 | 36.2 | 20 | 22.0 | 0.000 |
| Decreased | 7 | 7.7 | 31 | 34.1 | |

## DISCUSSION

COVID-19 is a pandemic viral infection with clinical manifestations that vary according to immune status. The Ministry of Health of the Republic of Indonesia has complied specific guidelines for COVID-19 and described the severity of symptoms in COVID-19. Mild symptoms are described as upper respiratory tract infections without signs of pneumonia or gastrointestinal syndrome. Moderate symptoms are described as pneumonia with symptoms including cough and shortness of breath with oxygen saturations >93%. Severe symptoms

showed the severe pneumonia with oxygen saturation below 93% while critical symptoms are diagnosed when severe symptoms progress to ARDS or sepsis.[1] In this study, there were no subjects with asymptomatic and mild symptoms because there was no indication of hospitalization.

In subjects with severe and critical symptoms, cytokine storm had occurred and disrupted oxygen diffusion process in the alveolar-endothelial compartment. This process manifested as hypoxemia.[7] If the immune status was inadequate to deal with this condition, this process would continuously occur and caused ARDS.[4] This was line with the study of Emanuelerezaghi et al which stated that there was a significant association between severity of symptoms and the incidence of ARDS.[6,8]

D-dimer is a residual product of fibrin and represents the activation of coagulation and fibrinolysis. The coagulation cascade is activated in the hyperinflammatory process.[9] The severe inflammatory process induces damage to the blood vessels around the lungs and activates the coagulation pathway.[10] The severity of inflammation is accompanied by a large amount of fibrin remnants in the blood vessels, where these fibrin remnants are referred to as D-dimers.[9] In the case of COVID-19, ARDS is related to the high risk of thrombosis depicted as elevated D-dimer.[11] He at al pointed out that high D-dimer on the first admission was associated with poor prognosis in COVID-19 patients.[12] This was similar with our study that exhibited significant correlation between D-dimer and the incidence of ARDS in COVID-19. Higher dose of anti-coagulation drug are required in critically-ill patients diagnosed with COVID-19 to prevent life-threatening thrombotic complications.[11]

## CONCLUSION

There was a significant association between the severity of symptoms and high level of D-dimer with the incidence of ARDS in COVID-19 patients at H. Adam Malik General Hospital.

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Original Article

# One Year Survival of Wild-Type Adenocarcinoma Lung Cancer Patients Receiving Chemotherapy at dr. Saiful Anwar Hospital, Malang

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## Abstract

**Background:** Lung cancer is one of the most common malignancies that leads to mortality. In Indonesia, lung cancer ranks first in men and third in women. The most common histological type of lung cancer is adenocarcinoma. Adenocarcinoma lung cancer is divided into 2 types, namely EGFR mutations and no mutations (wild-type). Chemotherapy is the treatment of choice for advanced wild-type adenocarcinoma lung cancer. This study aimed to assess the one-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy.

**Method:** This study used a cross-sectional study design.Data were taken from the medical records of cancer patients at Dr. Saiful Anwar Hospital Malang in 2018-2019. Data were processed and analyzed by chi-square test.

**Results:** Of the 54 subjects, 24 patients received carboplatin/ pemetrexed (44.4%), 15 patients received carboplatin/paclitaxel (27.8%), 9 patients received carboplatin/gemcitabine (16.7%), 2 patients received pemetrexed (3.7%), and 4 patients received gemcitabine (7.4%). The chemotherapy drug regimen had no correlation with one-year survival (P=0.899).

**Conclusion:** There wasno significant difference between one-year survival andchemotherapy drug regimens. This study required a larger sample to minimize bias.

**Keywords:** adenocarcinoma, wild-type, chemotherapy, survival rate

## INTRODUCTION

Lung cancer is one of the most common cancers and causes many deaths. Based on cancer profile data from the World Health Organization (WHO), lung cancer in Indonesia ranks first in men, around 21.8% of the 103,100 deaths due to cancer in 2014, while in women it ranks third around 9.1% of the 92,200 deaths along with trachea and bronchial cancer. Smoking is the main cause of lung cancer in Indonesia.[1]

WHO divides lung cancer into 2, non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). The NSCLC accounts for about 80% of lung cancer cases and is divided into 3 subtypes, namely adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[2] Adenocarcinoma is the most common case, accounting for about 40% of all lung cancer cases. Approximately 70% of patientsdiagnosed with lung cancer present with an advanced stage (stage 3 or 4).[3]

Adenocarcinomas are divided into 2 types based on genetic information: adenocarcinomas with mutations such as epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) rearrangement mutations and adenocarcinomas without mutations.[4] EGFR mutations are common in adenocarcinoma lung cancer and EGFR tyrosine kinase inhibitors (EGFR-TKI) are the first line therapy to improve patients survival.[5] Lung cancers that do not activate the EGFR mutation are called wild-type.[6]

Chemotherapy is a therapeutic option for patients with wild-type adenocarcinoma.[7] The recommended first-line chemotherapy regimen is platinum-based chemotherapy such as cisplatin or carboplatin in combination with taxanes (paclitaxel or docetaxel), antimetabolites (gemcitabine or pemetrexed), or vinca alkaloids (vinorelbine). Second-line chemotherapy regimens such as docetaxel, gemcitabine, paclitaxel, or single agent pemetrexed may be used for advanced patients who failed with platinum-based first-line chemotherapy.[3]

Several studies have shown that in wild-type adenocarcinoma, chemotherapy is more effective than EGFR-TKI. A study conducted by Tomasini et al in 2017 stated that chemotherapy for wild-type adenocarcinoma patients had a survival rate of 8.38 months and a 1-year survival rate of 37.8%, while the survival rate for EGFR-TKI was 4.99 months and the 1-year survival rate was 28%.[5]

Study by Kawaguchi et al in 2014 also verified that chemotherapy had a higher survival rate for wild-type adenocarcinoma, which was 10.1 months compared to 9.0 months for erlotinib. Another trial conducted by Kimura et al in 2016 pointed out that the carboplatin/pemetrexed combination has become the standard for wild-type adenocarcinoma lung cancer because of its good efficacy, controllable toxicity and 12.7 month survival.[8]

Based on the description above, study on one-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy has not been widely carried out, especially in Malang. Therefore, this study was conducted to determine the one-year survival rate of wild-type adenocarcinoma lung cancer patients receiving chemotherapy at Dr. Saiful Anwar Hospital Malang.

## METHOD

This was an observational cross-sectional study using secondary data taken from medical records at Dr. Saiful Anwar Hospital Malang in 2018-2019. The data obtained were entered in a google form

and put together in Ms. Excel. Data werethen analyzed using chi-square test. This study was approved by the ethical clearance board of Dr. Saiful Anwar General Hospital, Number: 400/192/K.3/302/2021.

## RESULTS

This study used data from medical records of wild-type adenocarcinoma lung cancer patients at dr. Saiful Anwar Hospital Malang who received chemotherapy in 2018-2019. There were 54 subjects that met the inclusion and exclusion criteria. The characteristics of the subjects can be seen in Table 1.

Table 1. Characteristics of wild-type adenocarcinoma lung cancer patients receiving chemotherapy at dr. Saiful Anwar Hospital Malang in 2018-2019

| Characteristic | N | % |
|---|---|---|
| Gender | | |
| Male | 37 | 68.52 |
| Female | 17 | 31.48 |
| Age | | |
| ≤60 years | 35 | 64.81 |
| ≥60 years | 19 | 35.19 |
| History of smoking | | |
| Active smoker | 34 | 62.96 |
| Passive smoker | 4 | 7.41 |
| Non-smoker | 12 | 22.22 |
| No data | 4 | 7.41 |
| Drug regimen | | |
| Carboplatin/pemetrexed | 24 | 44.44 |
| Carboplatin/paclitaxel | 15 | 27.78 |
| Carboplatin/gemcitabine | 9 | 16.67 |
| Pemetrexed | 2 | 3.70 |
| Gemcitabine | 4 | 7.41 |

Based on the history of smoking, we obtained the one year survival. There were 3 subjects survived more than a year among those who had a history of being an active smoker, while 31 subjects survived only less than 1 year. Among the non-smoker patients, there were 2 subjects who survived more than 1 year, and 10 subjects survived less than a year. For patients who were passive smokers and not recorded in the data, none of them could survive more than 1 year.

Table 2. Correlationofone-year survival to gender, age, smoking history, and drug regimen

| Characteristic | N | P |
|---|---|---|
| Gender | | |
| Male | 37 | 0.667* |
| Female | 17 | |
| Age | | |
| ≤60 years | 35 | 0.813* |
| ≥60 years | 19 | |
| History of smoking | | |
| Active smoker | 34 | |
| Passive smoker | 4 | 0.658* |
| Non-smoker | 12 | |
| No data | 4 | |
| Drug regimen | | |
| Carboplatin/pemetrexed | 24 | |
| Carboplatin/paclitaxel | 15 | |
| Carboplatin/gemcitabine | 9 | 0.899* |
| Pemetrexed | 2 | |
| Gemcitabine | 4 | |

Note: *P>0.05 indicates that there is no significant difference between variables, while P<0.05 indicates a significant difference between variables.

In terms of the drug regimen given, one year survival was also observed in patients. Among those who received carboplatin/pemetrexed combination, only 3 out of 24 patients survived more than 1 year, while the same survival rate was observed in only 1 from 15 patients received carboplatin/paclitaxel combination and also in only 1 out of 9 patients who received the combination of carboplatin/ gemcitabine. No patients who received

pemetrexed or gemcitabine as a single agent could survive more than 1 year.

In this study, the analysis was carried out by Chi-Square test using the SPSS version 25 which assessed the correlations between one year survival to gender, age, smoking history and drug regimens. The results were shown in Table 2.

There were no significant differences between gender and one-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy (P=0.667). The similar result was also found in age (P=0.813), smoking history (P=0.658), and drug regimen (P=0.899).

This study also performed an analysis using the Kaplan-Meier curve to assess the one-year survival of wild-type adenocarcinoma lung cancer patients who received chemotherapy. One year survival in patients who received carboplatin/pemetrexed was 12.5% with a median of 207 days. In patients who obtained carboplatin/paclitaxel it was 6.7% with a mean of 153 days while inthose received carboplatin/gemcitabine it was 11.1% with a mean of 198 days.

Table 3. One-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy in 2018-2019

| Therapy | Mean (days) | One-year survival (%) |
|---|---|---|
| Carboplatin/pemetrexed | 207 | 12.5 |
| Carboplatin/paclitaxel | 153 | 6.7 |
| Carboplatin/gemcitabine | 198 | 11.1 |
| Pemetrexed | 12 | 0 |
| Gemcitabine | 48 | 0 |

In this study, patients receiving single-agent pemetrexed and gemcitabine chemotherapy had a one-year survival of 0% because none of these patients survived more than 1 year with a median survival of 12 days for pemetrexed and 48 days for gemcitabine. Table 3 represents the summary while Figure 1 exhibits the *Kaplan-Meier* curve.

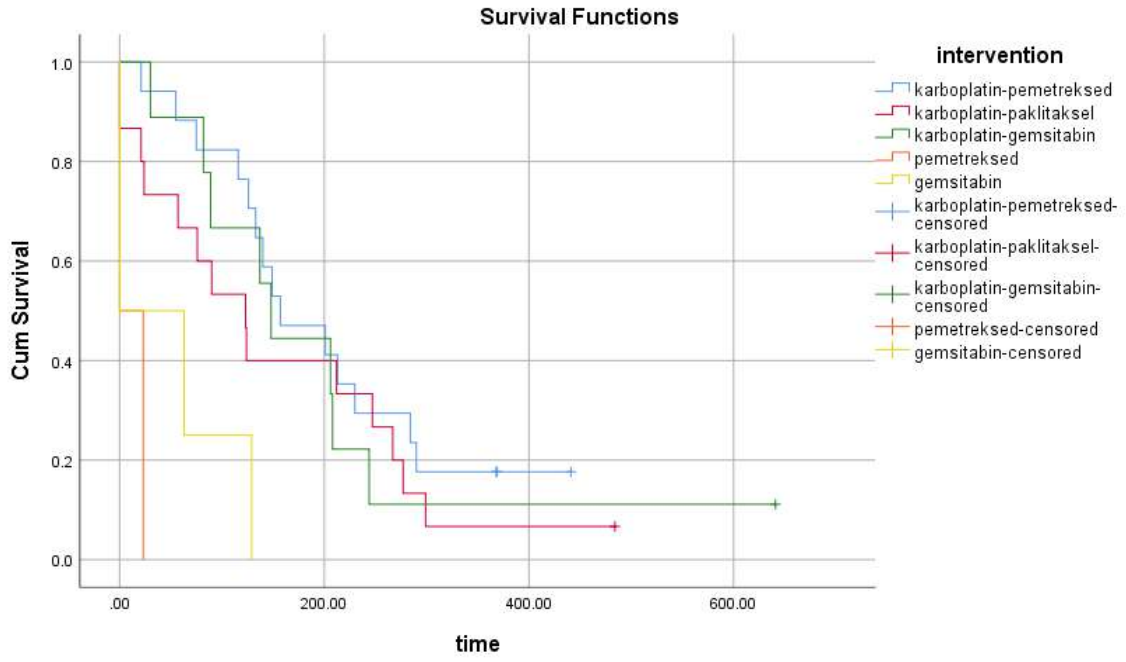


Figure 1. Kaplan-Meier curve comparison of one-year survival of wild-type adenocarcinoma lung cancer patients receiving chemotherapy at dr. Saiful Anwar Hospital Malang in 2018-2019.

## DISCUSSION

The data used in this study pointed out that there were 54 medical records in Dr. Saiful Anwar Hospital Malang for wild-type adenocarcinoma lung cancer patients who received chemotherapy in 2018-2019. Adenocarcinoma lung cancer can affect both male and female patients. In this study it was found that more cases occurred in male patients. This is in accordance with a study in Indonesia which stated that adenocarcinoma lung cancer was more common in men than women.[9] Reinforced by data from WHO, cases that occurred in Indonesia on 2014 consisted of 25,322 cases in men and 9,374 cases in women.[1]

Study conducted by Wicaksono et al in 2020 concluded that males and smokers were more at risk of developing wild-type adenocarcinoma lung cancer.[10] This study also obtained more patients with a history of active smoking. Based on the age, most of the subjects this study were less than 60 years old, similar to the study from Soetandyo et al in 2020.[9] However, the opposite was observed in the study of Laily et al in 2020 which obtained that more lung cancer patients were the age of more than 50 years.[11]

Based on the chemotherapy drug regimen, 48 patients were given the combination of chemotherapy and 6 patients received single-agent chemotherapy. Combination chemotherapy is the mainstay of therapy whereas single agent chemotherapy is directed to patients who are elderly or have less than 2 appearances.[12] In our study, the carboplatin/pemetrexed combination was the most widely used. This was based on the guidelines which stated that carboplatin/pemetrexed was the main choice of first-line therapy for wild-type adenocarcinoma lung cancer because it had good efficacy and lower side effects.[13]

In this study, there were more male subjects and subjects with a history of active smoking developed wild-type adenocarcinoma lung cancer. In general, lung cancer tends to occur in men because more men smoke.[14] Previous studies on both adenocarcinoma lung cancer with EGFR mutations and wild-type adenocarcinoma have shown better outcomes in women than in men.[15]

Similar results were obtained in this study, the percentage of female patients who survived more than 1 year was greater than that of men. The study of Tseng et al in 2017 also revealed that active smokers had poorer survival among adenocarcinoma lung cancer patients with both EGFR mutations and wild type. This study also expressed similar results based on history of smoking: the percentage of patients who did not smoke had a one-year survival greater than the active smokers and passive smokers. Although between men and women, the smoking history did not produce a significant difference.[15]

Elderly patients had poorer survival than younger patients.[16] This was because elderly patients tended to experience changes in physiological conditions and decreased immunity, such as slowed and reduced cilia which might facilitate

infection, and also hypertrophy of the mucus glands and dilated bronchi.[17] However, this study observed the opposite result in elderly patients who had a greater one-year survival than younger patients, although there was no significant difference in the results.

Based on the chemotherapy drug regimen, carboplatin/pemetrexed had the highest survival at 12.5% with a median of 207 days, followed by carboplatin/ gemcitabine with 11.1% and a mean of 198 days. Furthermore, carboplatin/paclitaxel had a one-year survival of 6.7% with a mean of 153 days, whereas the single agents, each pemetrexed and gemcitabine had a 1-year survival of 0%. The selected platinum-based regimen used carboplatin only. Carboplatin is an option when the side effects of cisplatin are intolerable. Carboplatin causes side effects of hematotoxicity, while cisplatin can cause nausea, vomiting, neutropenia, anemia, thrombocytopenia, peripheral neuropathy, and tinnitus.[18]

Previous studies have shown that carboplatin/pemetrexed had good efficacy, controlled toxicity and survival of 12.7 months so that this combination could be a standard therapy in wild-type adenocarcinoma lung cancer.[8] A study by Joerger et al in 2009 stated that there was no significant difference between carboplatin/pemetrexed and carboplatin/ gemcitabine. Both combinations also had side effects of neutropenia and thrombocytopenia. Moreover, there were grade 3 and 4 haematological toxicity in carboplatin/gemcitabine.[19]

Our study obtained the identical results which did not observe a significant difference between chemotherapy drug regimens on one-year survival. This was due to no further research on the side effects of each drug was conducted in this study and the sample distribution was uneven (from all data, there were only 5 patients who survived more than 1 year).

## CONCLUSION

In this study, the incidence of wild-type adenocarcinoma lung cancer was most common in men, age less than 60 years, and had history of active smoking. Most of the patients received carboplatin/ pemetrexed combination chemotherapy. One-year survival did not show significant differences between variables such as gender, age, smoking history, and chemotherapy drug regimen.

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Literature Review

# Calculation of Pleural Fluid Estimation Using Ultrasonography

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## Abstract

Pleural effusion is an abnormal accumulation of fluid in the pleural space due to an imbalance in increased pleural fluid production and decreased absorption. An ultrasound device can be used to guide the procedure to evacuate the pleural effusion fluid, increasing the procedure's accuracy and lowering the risk of complications. Several calculation methods can be used to calculate the volume of fluid in both an upright sitting position and a supine position. Ultrasound is nearly 100% more accurate than chest X-ray in detecting pleural fluid.

**Keywords:** pleural effusion, ultrasound, diagnostic

## INTRODUCTION

Pleural effusion is an abnormal accumulation of fluid in the pleural space caused by increased pleural fluid production and decreased absorption. Pleural effusion is a secondary effect of other diseases, with an estimated incidence of 320 cases per 100,000 people worldwide. Data collected at Kariadi Hospital Semarang in 2002 discovered an incidence of 12 cases with various different causes.[1,2]

Another study at H. Adam Malik General Hospital Medan in 2011 found a total of 136 cases, and Persahabatan Hospital Jakarta found 229 cases of pleural effusion within three years of research. According to the most recent research at Sanglah Hospital Denpasar, there were approximately 107 cases of pleural effusion caused by infectious and non-infectious diseases.[1,2]

The evacuation of pleural effusion can be guided using ultrasound (USG) as a supplementary assessment to reduce the incidence of complications by 70-80%. Complications can range from minor to fatal, such as bleeding, tearing of the the intrathoracic organs, and pneumothorax.[3,4]

Calculating the estimated effusion volume is also useful for determining whether fluid evacuation should be done through a puncture, a chest tube, or simply through the use of medications.[3,4] To determine the quantity of pleural fluid, several published calculating techniques may be used.[5,6]

## OVERVIEW OF THORACIC ULTRASOUND IN PLEURAL EFFUSION

Ultrasound is generally more sensitive than chest X-ray in detecting pleural fluid. When compared to an upright chest X-ray, the minimal amount of fluid that can be detected by ultrasound is 100 percent more accurate, with a fluid amount of only 5 ml. The benefits of using ultrasound include the fact that it does not emit radiation and that it allows the patient to be examined while still in bed. Another important function of ultrasound is to serve as a guide in performing punctures, biopsies, and markers in order to create a pleuroscopy pathway.[4–6]

Pleural effusion images on ultrasound can be classified into several types, including anechoic effusion, which appears as a black image on the screen because it lacks certain components, or simple effusion. An echogenic effusion, on the other hand, produces a floating reflected image as well as a gray or white screen image. This image represents the amount of protein, fibrin, blood, or pus that moves with each heartbeat. The last is complicated effusions, which are recognizable as fibrin threads that form bonds and cause fluid to collect in distinct sacs.[7,8]

On thoracic ultrasound, normal lung features range from three main points that appear on examination, namely lung sliding, lung pulse, and curtain effect. The friction between the parietal and visceral pleura causes lung sliding. Loss of the lung sliding feature is common in cases of pneumothorax, post-pleurodesis, or malignancy infiltrating the lung. A lung pulse is a rhythmic movement of the visceral pleura caused by motions from the beating heart, which is more noticeable in a collapsed lung. While the image of a healthy diaphragm appears as a white line that limits the thoracic cavity and abdominal organs in normal lungs, breathing movements cause the lungs to move up and down, covering the boundaries of the diaphragm line as if it were a curtain, a phenomenon called the "curtain effect".[7]

There are two methods for performing ultrasound in effusion examinations: brightness mode (B-mode) and motion mode (M-mode). Brightness mode, also known as B-mode, is a type of thoracic ultrasound examination that looks at the sound waves produced by the probe and reflected back by the organs in the thoracic cavity. The M-mode examination is a method for observing the movement of an organ in the thoracic cavity that has been adjusted for time. It is commonly used in cases of pneumothorax.[9,10]

The sitting position measurement method must be performed in an upright position forming a 90-degree angle. The probe's position should form a longitudinal line along the chest wall. The fluid was measured on the dorsolateral side of the intercostal space while the probe was upright. The examination is performed at maximum inspiration, and images for measurement are recorded while the patient holds his breath. The probe's position should not be flat or at an angle,

as this will cause the liquid's size to appear larger.[4]

## CALCULATION OF PLEURAL FLUID VOLUME IN SITTING POSITION

The fluid measurement method for the sitting position is ideally placed in the posterior axillary line. At the end of expiration, an overall ultrasound examination was performed in the posterior axillary line with a convex probe of 3-5 MHz. The distance between the visceral pleura and the chest wall (image 1B) and the distance between the lung base and the apex of the cupula diaphragm were used as parameter values (image 1C). The probe will be moved up and down from the intercostal space as a marker of the initial location of the detected pleural effusion.[11]

The formula for calculating fluid volume in an upright sitting position can be done using the Goecke 1 formula: EV = H × 90. The estimated volume of effusion fluid (EV) was obtained from calculating the chest wall craniocaudal distance on the screen in centimeters (cm) multiplied by 90 as a constant (image 1B). The second formula that is most often used is Goecke 2: EV= (H+D) × 70, which is the estimated effusion fluid (EV) resulting from the calculation of the chest wall craniocaudal distance on the screen in cm plus the lung's basal distance to the diaphragm's center (D) multiplied by 70 as a constant (image 1C). According to a study of 42 patients, the estimated amount of fluid compared to the drained fluid was closest to the Goecke 2, with a correlation coefficient of around 0.87. [4,11,12]

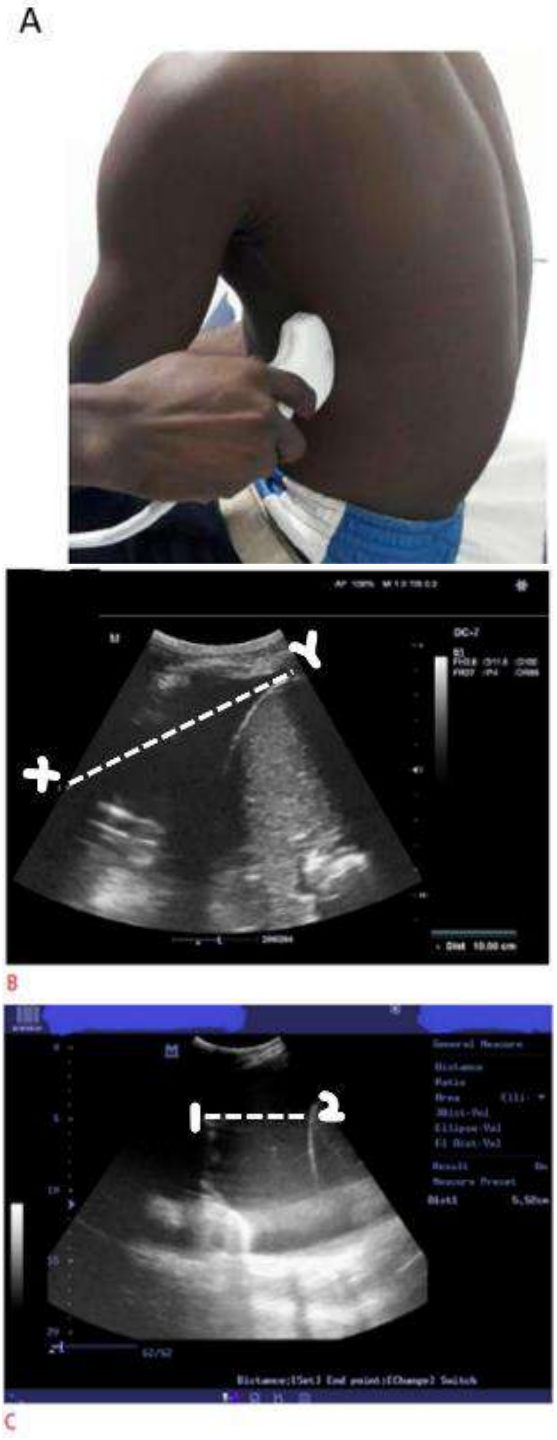


Image 1A: Patient in an upright sitting position and how to place the probe. 1B and 1C: Distance measurement of pleural effusion. **Goecke 1**: the distance between **(X)** the visceral pleura and **(Y)** the chest wall and **Goecke 2:** the distance between the base of the lung (1) and the apex of the cupula of the diaphragm/mid diaphragm (2).[4]

Due to the accumulation of fluid in the lower part of the thoracic cavity, formulas calculated in an upright sitting position are considered to be a better parameter in calculating the pleural fluid. The problem is that the amount of fluid is occasionally calculated to be greater than the exact volume.[4,11,12]

The USTA method, which calculated the volume of pleural effusion in patients who had undergone cardiac surgery, was the next study to calculate the volume of pleural fluid using the upright sitting method. On postoperative days 1, 3, 5, and 7, patients will have routine chest X-rays, and images on examination of the lateral position will be confirmed by ultrasound in patients with obtuse costostophrenic angles. In this study, the distance between the height of the upper limit and the mid-scapula was measured in an upright sitting position. The formula for fluid volume (ml) = (15.06 x D) + 21.45 is obtained by the distance D (mm) measured at the end of expiration as the distance between the mid-height of the diaphragm and the visceral pleura in a collapsed lung.[13]

The value of a simplified equation is then calculated in this study by multiplying the distance D by 16, as the formula for the approximate amount of liquid. There was no significant difference between the average calculation of the estimated fluid before the puncture and the actual amount of fluid after the puncture. Patients who have been taking vitamin K derivative drugs for about 12 hours will be subjected to a fluid evacuation procedure if their INR values are close to normal (2.0). With fluid volumes greater than 1000 ml, this formula may overestimate the fluid amount due to lower lobe atelectasis. Because this study only included patients with a distance D greater than 30 mm, the approximate value for the amount of fluid less than 500 ml could not be calculated accurately.[13]

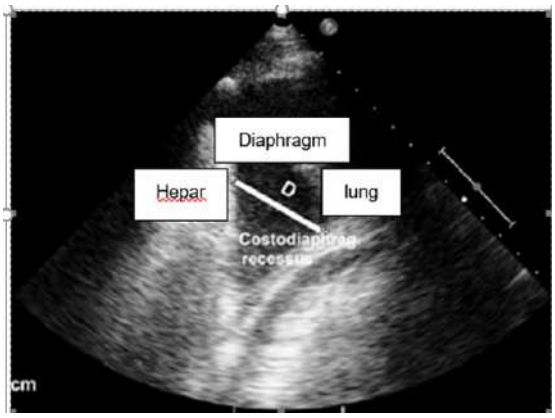


Image 2. Calculation of fluid volume using Usta method. D is the distance between the mid-diaphragm and the collapsed lung.[13]

## CALCULATION OF PLEURAL FLUIDS VOLUME IN SUPINE POSITION

Fluid volume measurement can also be calculated in the supine position using several formulas. The first formula is Eibenberger: EV = (47.6 x (A)) - 837 which obtains an estimate of the volume of effusion in milliliters (ml) by measuring the perpendicular distance in millimeters (mm) of the lung surface to the posterior chest wall during maximum inspiration (image 3B) by placing the probe in a transverse position multiplied by 47.6 and the result is reduced by 837. The calculation of the pleural fluid volume in the supine position is often performed in patients who are unable to sit down properly. The free fluid will move towards the back and the lower side of the body, forming a sickle.[4,12,14]

The transverse ultrasound probe was placed in the posterior axillary line. According to studies, the predicted fluid volume on ultrasound has a significant correlation coefficient with a true figure of about 0.8 compared to a radiological reading of about 0.5. The effusion measured on an ultrasound screen at a depth of 20 mm has a mean value of around 380 ml and a standard deviation of 130 ml.[4,12,14]

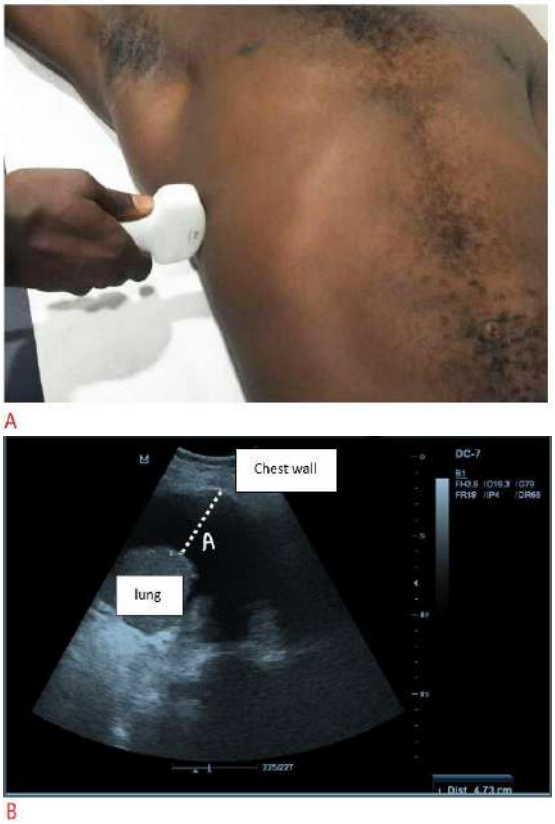


Image 3A**:** Patient in an supine position and how to place the probe. 3B**:** A line is a perpendicular distance between visceral pleura and parietal pleura in the chest wall.[4]

According to the formula calculation, an effusion depth of 40 mm yields an approximate volume of 1000 ml with a standard deviation of 330 ml. The predictive error value for ultrasound is estimated to be around 224 ml, as compared to 465 ml for chest X-ray. The ratio of the patient's thoracic cavity and the elevation of the diaphragm space affect this value, which can cause a deviation in the result.[4,12,14]

The Balik formula, EV = A x 20, is used to calculate the volume of pleural effusion by measuring the A value as the perpendicular distance between the lung surface (visceral pleura) and the chest wall (parietal pleura) at the end of expiration (in millimeters) multiplied by 20 by placing the probe in the transverse position. In comparison to the Einberger method, Balik's method is a relatively simple calculation. The correlation coefficient for both types of calculations is around 0.72.[15]

The study found that the values on the right and left sides of the chest differed significantly. Because the left side has a heart, the calculated volume of the left chest was closer to the actual volume after the fluid was removed. In the intensive care unit, Balik evaluated 81 patients. The study was limited to patients with pleural spaces greater than 10 mm, making the decision to take the fluid easier.[15]

Vignon had performed a study to determine the approximate fluid content of the pleural space. He had compared two methods for calculating pleural fluid volume. The first formula used (depth of pleural effusion) 2 x effusion height from upper to lower limit, and the second formula used (maximum cross-sectional area) x effusion height from upper to lower border. The research weaknesses were the difficulty in determining the size of the effusion and the small examination area in

the intercostal space. This study also discovered a simple formula for calculating fluid volume by calculating that the effusion width greater than 45 mm in the right hemithorax and greater than 50 mm in the left hemithorax equals the actual amount of fluid, which is approximately >800 ml. The study's limitation is that it only collects pleural fluid from patients with an interpleural distance of 25 mm or greater, so fluid volume cannot be calculated in cases with smaller distances. In addition, no other examinations were used in this study to compare the estimated pleural fluid volume.[16]

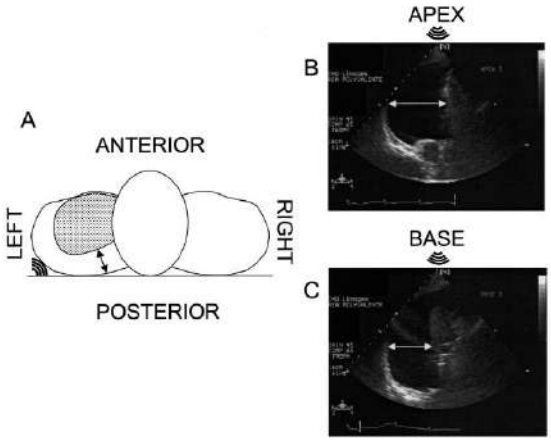


Image 4. Calculation of fluid volume by the Vignon method. (A) the patient at supine position with the probe placed on the right dorsolateral position, (B) The interpleural distance at the lung apex, (C) The interpleural distance at the lung bases (arrows distance was calculated at the end of expiration).[16]

The next calculation method for pleural effusion in the supine position is the Roch method, which is mostly performed on patients in intensive care. In this study, the ultrasound probe was attached to the posterior axillary line between the ninth and eleventh ribs to see the diaphragm, and then the probe was moved up to see the position of the fluid. The fluid was characterized by the appearance of an anechoic image above the diaphragm. The fluid image is limited by the parietal pleural layer on the surface and the visceral pleura on the inside. Identification of the lung image behind the fluid and breath movements will change the interpleural distance. The measurement of fluid volume will be carried out at the end of expiration and the measurement distance that is used as a benchmark is divided into three types, namely lung-diaphragm (LD), posterior chest-lung distance (PLD) and posterior chest-lung distance in the 5th intercostal space (PLD5).[17]

The lung-diaphragm distance was taken on a longitudinal image with the probe placed on the chest wall at the posterior axillary line, then the distance between lung thickness and diaphragm was marked as the diaphragm lung distance (LD). The distance between the lung and the posterior chest wall at the lung bases was measured when the lower side of the lung was visible. The probe was placed 30 mm above it and the probe was rotated 90°.[17]

The image of the effusion was seen as a convex shape between the chest wall and the lung. The anteroposterior size between the lung and the lower posterior chest wall was marked as (PLD). The distance between the lung and the chest wall in the fifth intercostal space was measured by the transverse position, i.e., the anteroposterior thickness of the fluid in the chest wall to the lung was assessed as PLD5.[17]

Calculations with PLD and PLD5 have a significant correlation with the actual volume of the fluid between 0.56-0.68 while in the LD distance the value was only 0.24 because LD images would not always appear in patients even though the fluid volume was more than 1200 ml. This condition was mostly caused by the tendency of the fluid to occupy the lowest chest wall position in the posterior. PLD distance can be used to predict the amount of pleural fluid more than 500 ml if the distance was >5 cm with the positive predictive value >90%.[17]

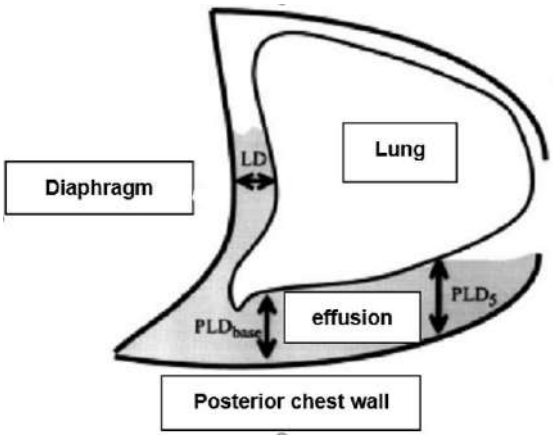


Image 5. Formula calculated by Roch method. LD: Lung-diaphragm; PLDbase: posterior chest-lung distance; PLD5: posterior chest-lung distance at 5th intercostal space.[17]

Pleural effusions in supine position can also be calculated by the formula found by Remerand et al This study found that the symptoms were not only due to the amount of fluid but also affected by the patient's height, weight, and the shape of the thoracic cavity. The measurement was made using the formula for the depth of the median (A) point multiplied by the height of the upper and lower limits of fluid (L), then the results were compared with the estimated fluid in the thorax CT scan image. The correlation value between the estimated fluid on ultrasound and the actual amount of fluid after the evacuation was about 0.84. This measurement method had some weaknesses. The first was the difference in fluid volume that can appear when the probe is placed in the different intercostal regions. The next problem was that this formula was difficult to calculate the volume of fluid in massive pleural effusion due to the scapula shadow, which would cause not all of the fluid to be seen on the monitor.[18]

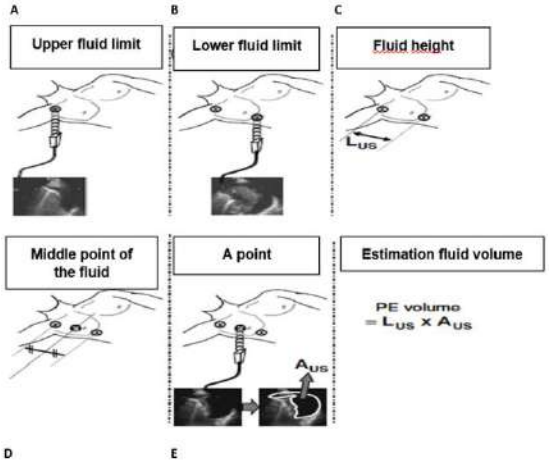


Image 6. Calculating fluid with the Remerand method. (A) and (B) the upper and lower limits of the liquid, (C) the location of Lus i.e. the distance between A and B. (D) and (E) the midpoint to determine the location of Aus. PE: pleural effusion, Lus: the height of the upper and lower limits of fluid, Aus: the area of the midpoint of the fluid that appears on the screen.[18]

## CONCLUSION

Ultrasound is a valuable tool in detecting pleural effusion. Fluid volume measurement can be performed in an upright sitting position or a supine position. The Goecke calculation formula in upright sitting has the predictive value closest to the actual volume of the fluid. Calculation in the supine position using the

Balik method has the most accurate volume to calculate the pleural fluid volume.

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Literature Review

# The Role of miRNA in Non-Small Cell Lung Carcinoma

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## Abstract

Micro Ribonucleic Acids, or miRNAs, are short non-coding RNAs. Their length, on average, is 22 nucleotides, and they function in post-transcriptional regulation of gene expression. MiRNAs have their own nomenclature, and the same miRNAs can be found across different species. MiRNAs play important roles in many physiological and pathological processes in the human body. Regarding cancer, miRNAs are involved in carcinogenesis. MiRNAs work by binding completely or incompletely with messenger RNAs (mRNAs). Complete binding with mRNA produces mRNA degradation, while incomplete binding produces translational inhibition. Eventually, miRNAs decreased gene expression. In cancer, miRNAs show unique and different expression profiles. Based on their role in activating or deactivating intracellular signaling pathways, miRNAs can be classified as oncomiR or tumor suppressor miRNA. In non-small cell lung cancer (NSCLC), miRNAs are associated with gene mutation status, and they have important roles as diagnostic, prognostic, and predictive biomarkers.

**Keywords:** microRNA, NSCLC, biomarkers

## INTRODUCTION

As shown by Globocan 2018 statistics, the incidence of lung cancer was 2,093,876 cases, or approximately 11.6% of all cases, while the mortality rate was 1,761,007 cases, or 18.4% of all cancer deaths. According to this data, lung cancer has the highest incidence and fatality rates worldwide when compared to other types of cancer.[1,2]

According to data from 2018, the incidence of lung cancer is the third highest (30,023 or 8.6% of total new cancer cases in Indonesia), while lung cancer mortality is the highest, with 26,095 fatalities or 12% of total cancer mortality in Indonesia.[3] Non-small cell lung cancer (NSCLC) is the most frequent histological type detected in the population.[4]

*Micro Ribonucleic Acid* (microRNA/ miRNA) is a small RNA that plays an essential role in various physiological and pathological processes in the human body, including NSCLC.[5–7] MicroRNAs can also be used as biomarkers for diagnosis, prognosis, and prediction. MicroRNAs can also be used as biomarkers for diagnosis, prognosis, and prediction.[8,9] This literature

review will describe the role of miRNAs in lung cancer, especially NSCLC.

## microRNA

Based on human genome data, it is known that 2/3 of the human genome is non-coding ribonucleic acid (ncRNA) genes or RNAs that do not contain a code that plays a role in transcription and translation processes. These non-coding RNAs are divided into two major groups based on their function. The first group is housekeeping ncRNAs, which are consistently produced and play a role in regulating intracellular physiological processes. Ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), and small nucleolar RNA (snoRNA) are examples of housekeeping ncRNAs.[10]

The first two housekeeping RNAs mentioned are involved in gene expression processes, especially in translating messenger RNA (mRNA) sequences on the ribosomes to produce proteins. The second group of ncRNAs is the regulatory ncRNAs. This group of ncRNAs regulates gene expression at the post-transcriptional stage. This second group is further subdivided according to the length of the RNA strand. Regulatory ncRNAs with less than 200 nucleotides in length are referred to as short ncRNAs (short or small ncRNAs), whereas those with more than 200 nucleotides in length are referred to as long ncRNAs.[10]

MiRNAs belong to the group of short ncRNAs with an average length of 22 nucleotides and play an essential role in regulating gene expression. Besides miRNAs, other short ncRNAs include small interfering RNA (siRNA) and PIWI-interacting RNA (piRNA). Both types of short ncRNAs also play a role in influencing the translation process of messenger RNA into a protein, as is the case with miRNAs, but this literature review will not discuss their position further. A more concise classification of the division of non-coding RNA can be seen in Figure 1.[10]

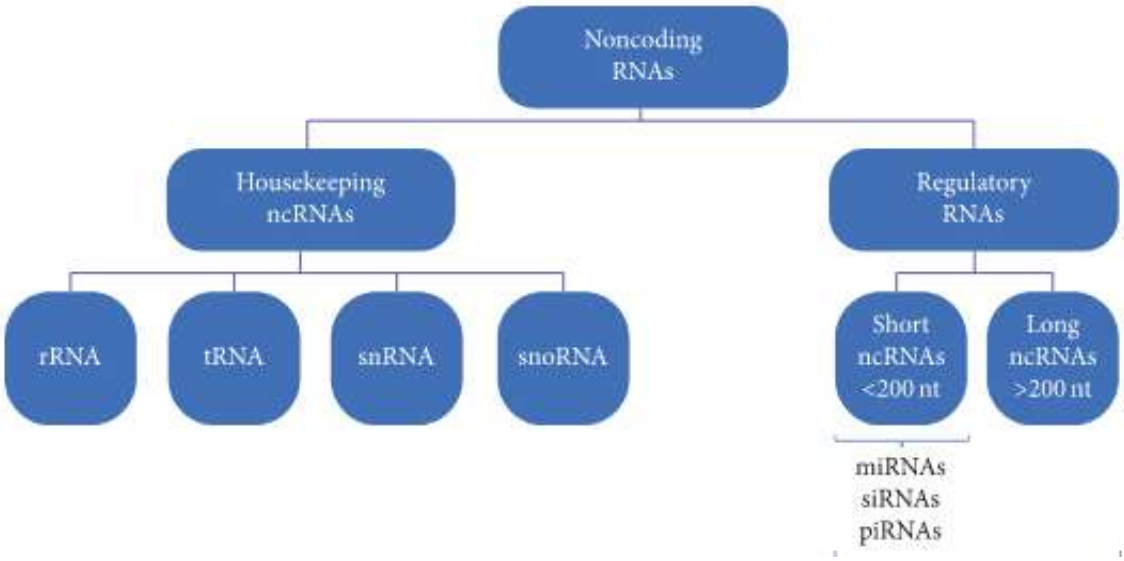


Figure 1. Types of non-coding RNA[10]

In 1993, Lee et al. discovered the first miRNA, lin-4, in Caenorhabditis elegans, a transparent soil-living nematode species, and subsequently, many other miRNAs with homologous sequences were found in different species.[7,11] Most miRNAs are located intracellularly. However, it can also be found in extracellular compartments such as breast milk, saliva, serum, or plasma.[12–15] This extracellular microRNA is stable and resistant to RNAse activity in the blood through several mechanisms, for example, being encased in membrane-bound vesicles (exosomes, apoptotic bodies, and microparticles) bound to proteins.[13,14,16,17]

## microRNA NOMENCLATURE

The name miRNA consists of the species abbreviation and a number. A miRNA naming formula can be seen at the bottom of this paragraph. On the part of the organism are the 3-letter initials of the Latin name of a species from which the miRNA in question was obtained. For example, humans are written as hsa (from *Homo sapiens*), the mouse is written as mmu (from *Mus musculus*), and rice is written as osa (from *Oryza sativa*). The inscription "miR" indicates that this is a mature miRNA. The part after the words "miR" is a number that indicates the family or family of the miRNA. There are only 2 precursor arms, namely 3' or 5' arms.[18]

For example, hsa-miR-99a-5p shows that this mature miRNA is found in humans, belongs to the miR 99a family, and originates from the 5p component. Another example of osa-miR-169-3p shows that this mature miRNA is from Oryza sativa, of the 3p component 169 miRNA family. Below is the miRNA naming formula.[18]

Organism - miRnx - precursor arm and/or y

n = sequential number representing the miR family
x = letter describing a member of the miRNA family
y = number indicating the occurrence of more than 1 mature sequence of the same precursor.

## POSITION miRNA BIOSYNTHESIS AND MECHANISM OF ACTION

The process of miRNA biosynthesis begins in the cell nucleus and ends in the cytoplasm. First, the RNA polymerase II enzyme transcribed the primary miRNA (pri-miRNA) gene. Then, the pri-miRNA formed will be processed by Drosha, an RNAse III enzyme in the cell nucleus, and the cofactor of DiGeorge syndrome critical region 8 (DGCR 8). Through the action of these enzymes and cofactors, pri-miRNAs are transformed into pre-miRNAs, which are 70 nucleotides long.[7,19]

Furthermore, the Exportin-5 protein will transport the pre-miRNA from the cell nucleus to the cytoplasm. Finally, in the cytoplasm, a circular strand (stem-loop) at one end of the pre-miRNA is cut by the Dicer enzyme (RNAase III enzyme) to form a miRNA/MIRNA* duplex with a length of about 22 nucleotides. Ultimately, one strand of the duplex, or the so-called

mature miRNA, is loaded onto the Argonaute protein complex (AGO) to form an RNA-induced silencing complex (RISC). In contrast, the partner RNA strand is degraded.[7,19]

This RISC complex will bind to the target messenger RNA in the seed sequence area, which is the area with the nucleotide sequence paired with the nucleotide sequence of the miRNA.[7] Perfect binding between RISC and messenger RNA will cause the messenger RNA to unravel, while the nearly perfect bond inhibits the translation process.[7,11,19] The action of miRNA in influencing this translation process causes the expression of a gene to be reduced. Another term for that miRNA action is gene silencing, although it does not entirely halt total expression of a gene.[20] An overview of miRNA biosynthesis can be seen in Figure 2.

## THE ROLE OF miRNA IN PHYSIOLOGICAL PROCESSES

Animal and human studies have shown that miRNAs play a role in the homeostasis of physiological processes in the body. Especially in the lungs, miRNAs play an essential role in the immune control process.[6] For example, miR-155 plays a role in differentiating naive T cells into Th1 and Th2 cells in the lung. MicroRNA 26a is highly expressed in alveolar and bronchial epithelial cells and is essential in vascular remodeling and lung development.[21] let-7, miR-29, miR-15, and miR-16 act as tumor suppressor miRNAs in lung cells. MicroRNA 146a/b plays an essential role in the regulation of negative feedback IL-1β-induced inflammation.[6]

## THE ROLE OF miRNA IN LUNG CANCER

Several reports indicated that there was abnormal miRNA expression in cancer, and there were differences in miRNA expression patterns between one cancer and another. The exact cause is unknown but may be due to chromosomal abnormalities, gene mutations, epigenetic changes, or other reasons. In addition, several miRNA genes are often found in cancer-associated gene areas, so that changes in miRNA expression are directly related to changes in genes or chromosomes that occur due to cancer by the previously described mechanism.[22]

Regarding the cancer phenotype, miRNAs can be classified as "oncomyR" or "*tumor-suppressor* miRNAs". This classification was based on its increased or decreased expression in certain malignancies, as well as its impact on intracellular signaling pathways.[22] In lung cancer, let-7 is a tumor suppressor miRNA and the first miRNA known to be dysregulated in lung cancer.[23,24]

Other tumor suppressor miRNAs besides let-7 are miR-34 and miR-200, all of which have decreased expression *(*down-regulation*)* in lung cancer. Oncogenic miRNAs that had increased expression in lung cancer were miR-21, miR-17-92, and miR-221/222. These two types of miRNAs are involved in cell proliferation, apoptosis, and cell migration.[23]

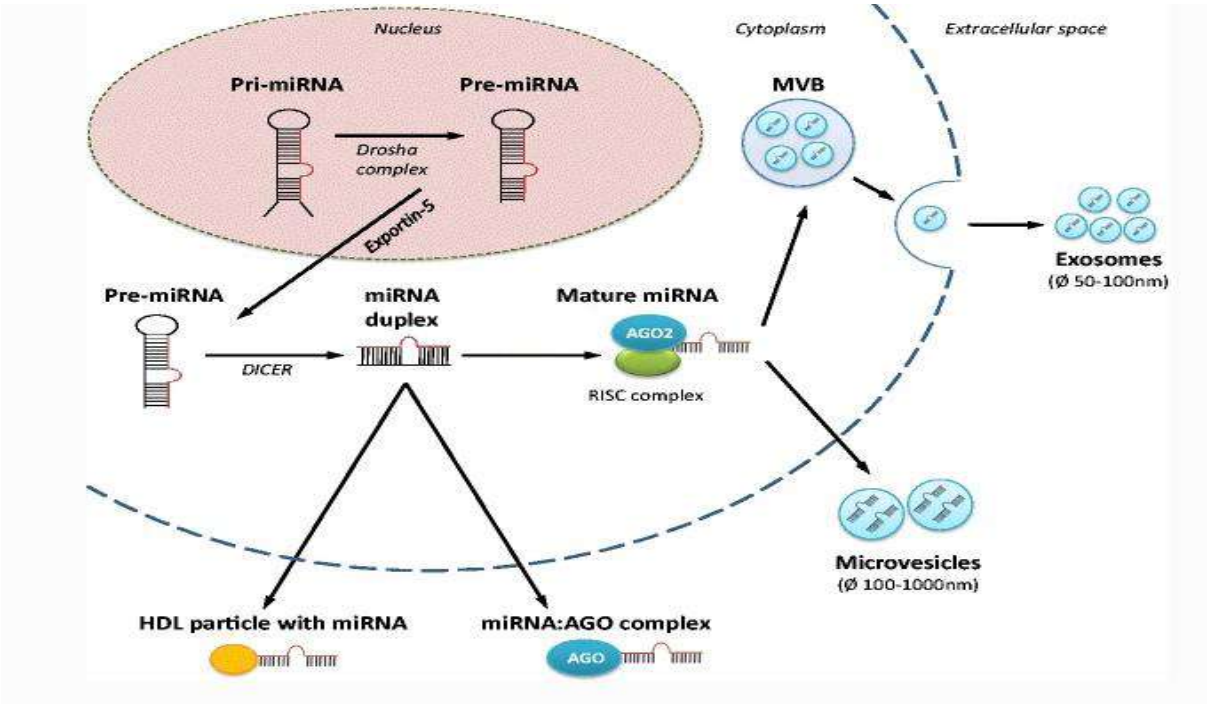


Figure 2. Biosynthesis of miRNA[25]

Table 1. MicroRNA in Physiological Processes in the Lung[6]

| miRNA | Function |
|---|---|
| miR-155 | T cell differentiation in the lung |
| miR-26a | It is highly expressed on alveolar and bronchial epithelial cells. Essential for lung development. |
| Let-7 | Widely expressed in normal lung tissue. As tumor suppressor miRNA in lung cells |
| miR-29 | As tumor suppressor miRNA in lung cells |
| miR-15, miR-16 | As tumor suppressor miRNA in lung cells |
| miR-146a/b | Negative feedback regulation of IL-1β -induced inflammation |

Table 2. OncomiR and tumor suppressor miRNA in lung cancer[23]

| Micro RNA | Gene Target | Biological Process |
|---|---|---|
| *Tumor suppressor* miRNAs are reduced in expression in lung cancer | | |
| Family Let-7 | RAS, HMGA 2, CDK6, MYC, DICER1 | Cell proliferation (RAS, MYC, HMGA2) Cell cycle regulation (CDK6) MiRNA maturation (DICER1) |
| Family miR-34 | MET, BCL2, PDGFRA, PDGFRB, ZEB1, ZEB2, E- Cadherin, vimentin (VIM) | Ligand-induced cell proliferation and apoptosis TNF |
| Family miR-200 | | Promotion of epithelial-mesenchymal transition and metastasis |
| OncomiR whose expression is increased in lung cancer | | |
| miR-21 | PTEN, PDCD4, TPM1 | Apoptosis, proliferation and migration of cells |
| miR-17-92 Cluster | E2F1, PTEN, HIF1A | Cell proliferation and carcinogenesis |
| miR-221/222 | PTEN, TIMP3 | Apoptosis and migration cell |

Table 2 describes in more detail some of the oncomiRs and tumor suppressor miRNAs in lung cancer. Due to the role of miRNAs in carcinogenesis and their varying levels of expression, miRNAs have the potential to act as biomarkers related to diagnosis, prognosis, and predictive response to cancer therapy.[8,9]

## miRNA AND GENE MUTATIONS IN NSCLC

Several studies have shown that miRNA profiles in NSCLC are associated with common gene mutation status in NSCLC. Pak et al. studied 103 lung adenocarcinoma cancer tissue samples and divided them into 3 groups based on EGFR mutations in exon-19, exon-21, and wild type. MicroRNA profiles were obtained using a microarray platform, and 3 significant miRNAs were accepted and validated by qRT-PCR. The three miRNAs were miR-34c, miR-183, and miR-210. They found decreased expression of miR-34c and increased expression of miR-183 and miR-210 in cancer tissues with positive EGFR mutations. MiR-183 expression was significantly increased in cancer tissue with exon-19 EGFR mutation.[26]

Kim et al. examined lung adenocarcinoma tissue specimens with different mutation profiles, namely positive EGFR mutations, positive KRAS mutations, positive ALK mutations, and those that did not contain the three mutations (triple-negative/TN). They found different miRNA expressions in each type of gene mutation studied. The let-7e and miR-342-3p microRNAs were increased in the EGFR and KRAS groups and decreased in the ALK and TN groups.[20]

Analysis of miRNA expression in samples between different groups of mutations showed different results. For example, in the ALK group, the expression of miR-1343-3p was more increased, and miR-671-3p, miR-103a-3p, let-7e, and miR-342-3p were more decreased than in the EGFR/KRAS group. Meanwhile, in the EGFR group, miR-647, miR-200b-5p, miR-361-5p, miR-23b-3p, and miR-27b-3p increased more, and miR-23a-3p decreased more than the expression of these miRNAs in the KRAS group.[20]

## miRNA AS DIAGNOSTIC BIOMARKER

Some miRNAs can be diagnostic markers of certain cancers. Zhao et al. compared the expression levels of miR-21 in the serum of NSCLC patients and healthy people. They discovered that miR-21 expression levels in the serum of NSCLC patients were considerably higher.[27]

Hamamoto et al. investigated miRNA profiles in lung cancer tissue samples from NSCLC patients. They discovered a significant increase in miR-205 expression in tissue samples from squamous cell carcinoma (SCC) lung cancer, which can be employed as a diagnostic marker for SCC.[21,28] Another study found that a panel of 4 miRNAs in plasma (miR-21, miR-126, miR-210, and miR-486-5p) can be used to identify stage I NSCLC with a sensitivity of 73% and a specificity of 97%.[23,29]

## miRNA AS PROGNOSTIC BIOMARKER

Another role of miRNA in cancer-related research is as a prognostic biomarker, that is, a biomarker associated with the outcome of a disease. MiRNA-21 is an oncomiR that acts as a diagnostic and prognostic biomarker. MiR-21 expression was significantly increased in the serum of patients with advanced-stage NSCLC with low survival rates.[24,27,30]

The effect of miRNA-21 on lung cancer may be explained by a study in mice showing that overexpression of miR-21 activates the Raf-MAPK signaling pathway and *phosphatidylinositol 3-kinase* (PI3K) in cells and modulates the number, incidence, and size of lung tumors induced by the K-Ras oncogene in mice.[30]

In Indonesia, Hanafi et al. examined serum miRNA profiles in 52 NSCLC patients using a Real-Time quantitative PCR (qRT-PCR) platform. They found that the expression levels of miR-34 (tumor suppressor miRNA) and miR-148 were low and the expression of 2 oncomiRs was low. High miR-222 and miR-155 are associated with a poor prognosis. High expression of miR-222 and miR-155 was associated with poor prognosis in stage IV M1b adenocarcinoma patients with positive EFGR mutations. In contrast, high expression of miR-34 was found in multiple metastatic adenocarcinomas with negative EGFR mutations.[31] The oncogenic nature of miR-155 is related to its role in signaling pathways in cell proliferation and apoptosis.[32]

## miRNA AS A PREDICTIVE BIOMARKER

Predictive biomarkers are biomarkers associated with response to therapy. Several miRNAs with aberrant expression patterns are associated with therapy resistance in NSCLC. For example, the expression of miR-214 was increased in radioresistant NSCLC cells and could protect radiosensitive cells against the effects of radiation.[25,32]

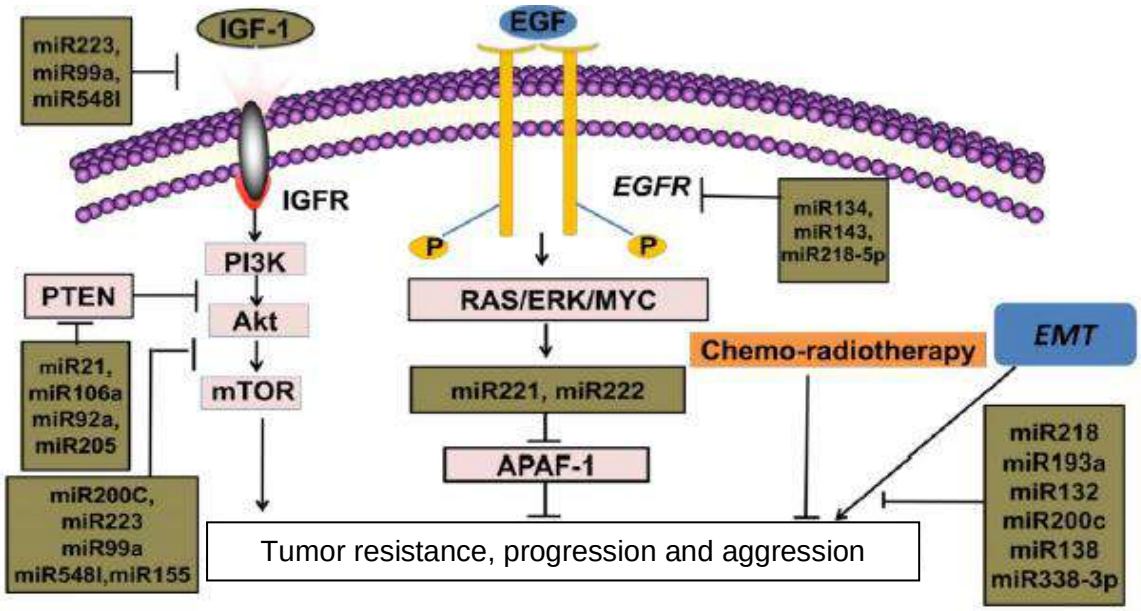


Figure 3. Micro RNA that plays a role in modulating the effects of chemotherapy, radiotherapy, or targeted therapy.[33]

In studies of human lung cancer cell lines, increased expression of miR-9 and let-7g was associated with sensitivity to radiotherapy. In addition, increased expression of these two genes reduces the expression of the NFkB1 gene in cancer cells, and this NFKb1 gene plays a role in repairing DNA damage and increasing cell survival.[24]

There is a relationship between resistance to chemotherapy and miRNA expression. In NSCLC cell lines, miR-135a knockdown increased expression of the *adenomatous polyposis coli* (APC) tumor suppressor gene that regulates mitotic checkpoints during mitosis and plays a role in apoptosis of paclitaxel-resistant cells. Wang et al. found that miR-214 increased its expression in gefitinib-resistant adenocarcinoma cell lines, and *knockdown* of this miRNA led to resensitization of that cell strain to gefitinib.[34] MiR-21 and miR-210 were decreased in the serum of patients with NSCLC who responded well to platinum-based chemotherapy.[24] Cui et al. studied 260 patients with advanced-stage NSCLC and found that high expression of miR-125b in serum was associated with poor treatment response. The results of Cui et al. study showed that miR-125b is a predictive biomarker of cisplatin chemotherapy response.[33] Other miRNAs associated with therapeutic success in NSCLC can be seen in Figure 3.

## CONCLUSION

MicroRNA is a non-coding RNA, which is 22 nucleotides long and plays a role in regulating post-transcriptional gene expression. MiRNA works by binding to messenger RNA and can cause degradation of messenger RNA or inhibition of the translation process. In addition to physiological processes, miRNAs also play an essential role in pathological processes in the human body. MiRNAs play an important role in NSCLC. Some miRNAs serve as oncogenes (oncomiR) or tumor suppressor miRNAs. miRNA expression is associated with gene mutations in NSCLC. MiRNA can serve as a diagnostic, prognostic, and predictive biomarker in NSCLC.

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Literature Review

# Preoperative Assessment Prior to Lung Resection: How to Eliminate the Risk

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## Abstract

Lung resection is part of the treatment of various lung diseases, both malignancy and infection. Although it has great benefits, lung resection can result in a variety of functional disorders that can affect the whole cardiopulmonary system. The mortality of these procedures is 2-4% in segmentectomy and 6-8% in lobectomy, while the mortality of pneumonectomy in the world is 11%. Good preoperative assessment of patients has been reported to have reduced mortality and morbidity after lung resection. Things that need to be considered to assess preoperative eligibility include age, lung function, cardiovascular fitness, nutrition, and performance status. The preoperative pulmonary tolerance assessment is divided into three stages: the first stage is the assessment of lung function and blood gas analysis, the second stage is to assess postoperative prediction of pulmonary function, and the third stage is to assess the maximum oxygen consumption per minute by doing a cardiopulmonary exercise test. Patients who have a good tolerance for lung resection are patients who have predictive postoperative force expiration volume one second (ppo$FEV_1$) values more than 40%, predictive postoperative diffusion capacity of the lung for carbon monoxide (ppoDLCO) more than 50%, and maximum oxygen consumption ($VO_2$ max) more than 15ml/kg/min.

**Keywords:** lung resection, pulmonary tolerance, tolerance assessment

## INTRODUCTION

Lung resection is part of the treatment of various lung diseases, both malignancy and infection. There are several types of lung resection, including wedge resection, segmentectomy, lobectomy, and pneumonectomy. The choice of technique depends on the size of the lesion or the extent of the damage.[1] The lung resection procedure has been carried out since 1933 by Evarts A. Graham, who successfully performed a pneumonectomy in lung cancer patients.[2] In 1940, Blades and Kent reported performing the first lobectomy in a patient with bronchiectasis.[3] The benefits of surgical therapy for various lung diseases are well known. Life expectancy in patients with early-stage non-small-cell

lung carcinoma increased to 48 months. In addition, in cases of bronchiectasis, surgical therapy improves the quality of life and survival.[4]

Despite its great benefits, lung resection can cause a variety of functional disorders that can affect the whole cardiopulmonary system.[5] Patients undergoing lung resection are at high risk for postoperative pulmonary complications. Francois et al reported that the incidence of postoperative pulmonary complications was 49%.[6]

Many factors affect the incidence and types of complications that occur. These include age, the physical status of the patient, such as cardiorespiratory functional status, type, and extent of the procedure, course of the disease, and other therapeutic modalities given.[7] In 2006 in England, it was reported that there were 2400 lobectomies and 500 pneumonectomies performed annually, with the most common indication being lung cancer. In these patients, the mortality is 2–4% for segmentectomy, 6–8% for lobectomy, and 11% for pneumonectomy.[8]

Before lung resection is performed, assessment of tolerance, patient capacity, and postoperative complications is very important. The greatest challenge in conducting a preoperative evaluation is identifying the patient's increased risk of complications and mortality.[9] The British Thoracic Society (BTS) and the Society of Cardiothoracic Surgeons of Great Britain and Ireland (SCTS) have published a guideline for selecting candidates for surgery in malignancy patients. The things that are important factors to assess are age, functional status of the cardiorespiratory system, nutrition, and functional status.[10] Good preoperative assessment of patients has been reported can reduced mortality and morbidity after lung resection.[7]

## PREOPERATIVE ASSESSMENT PRIOR TO LUNG RESECTION

The main causes of postoperative mortality and morbidity in thoracic surgery, especially lung resection, are respiratory complications, including atelectasis, pneumonia, and respiratory failure, which occur in 15-20% of cases.[11] Good preoperative assessment of patients has been reported to have reduced mortality and morbidity after lung resection.[7] The main concerns to assessing preoperative eligibility include age, lung function, cardiovascular fitness, nutrition, and performance status.[10] This assessment is related to the risk that the patient will experience during and after the procedure, such as postoperative cardiac complications, intraoperative death, and postoperative dyspnea.[12]

### Age

Age is a risk factor for postoperative complications, although there is no specific age limit that is a contraindication to lung resection. Based on data collected by the Society of Thoracic Surgeons (STS), it is estimated that around 30 - 35% of patients who are candidates for lung resection in lung cancer cases are over 70 years old.[13]

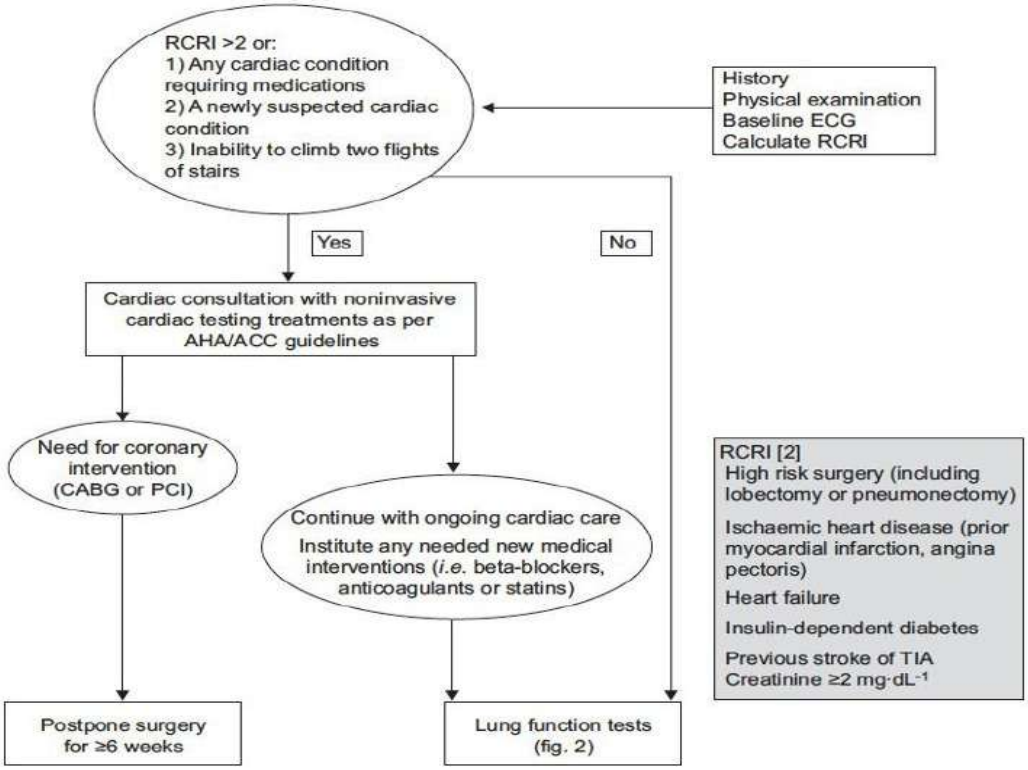


Figure 1. Algorithm for assessing cardiovascular status before lung resection[14]

Fernandes et al stated that patients aged over 65 years were at a 2,6 times greater risk of post-resection pulmonary complications.[4] This is related to physiological changes in the respiratory system caused by aging. In the elderly, there is a decrease in the compliance of the chest cavity, which can reduce vital lung capacity due to degeneration of elastin fibers around the alveolus, and a decrease in the amount of supporting tissue around the alveolus, causing premature closure of the airways, thereby increasing the amount of trapped air and residual volume.[15]

## Cardiovascular Status

Patients who will undergo lung resection have a 2-3% risk of developing cardiovascular complications during and after the procedure. The major risks that may occur include myocardial infarction, pulmonary edema, arrhythmias, and cardiac arrest. Therefore, cardiovascular status assessment is very important to predict the risk of complications that may occur. The American Heart Association (AHA) has a score to assess the risk of cardiovascular complications in patients undergoing lung resection, called the Thoracic Revised Cardiac Risk Index (ThRCRI). The score consists of a history of ischemic heart disease, a history of stroke/transient ischemic attack, and a creatinine level greater than 2mg/dL.[14]

Other tests that need to be done to assess cardiovascular status are electrocardiography, echocardiography, exercise testing, and invasive tests such as primary coronary intervention (PCI) (figure 1).[16]

## Lung Function Test

Spirometry and Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) are the two main modalities of preoperative pulmonary evaluation that should be performed in patients prior to lung resection. These two tests can also be used to estimate ppoFEV$_1$ and ppoDLCO values, which are important indicators for selecting the follow-up tests that need to be performed and can even be used as a basis for excluding patients from surgery.[16]

Spirometry has good sensitivity and specificity in predicting the outcome of patients who will undergo lung resection. Indicators of mechanical function and lung volume showed a correlation with postoperative outcomes, such as FEV1, forced vital capacity (FVC), maximal voluntary ventilation (MVV) and residual volume/total lung capacity ratio (RV/TLC).[17]

The BTS guideline on surgical therapy for lung cancer patients states that the combined examination of spirometry and DLCO is considered more meaningful for predicting postoperative morbidity and mortality.[18] The ppoFEV$_1$ value is obtained by multiplying the preoperative FEV$_1$ value by the number of segments left after surgery divided by 19. Nineteen is the total number of lung segments in normal people.[17]

Many studies state that ppoFEV$_1$ of less than 40% significantly increased the risk of mortality, and ppoFEV$_1$ values of greater than 70% were associated with a lower incidence of postoperative complications. A low-risk patient has a postoperative mortality risk of less than 1% and pulmonary resection is recommended. A moderate-risk patient has a mortality risk of less than 10%, and a high-risk patient has a mortality risk of more than 10% and other treatment strategies are recommended.[19]

## Blood Gas Analysis

Blood gas analysis provides a complete picture of respiratory function, which is influenced by central mechanisms, cardiac function, and metabolism as lung function affects it.[20] Blood gas analysis is used to assess lung function before resection and as an effort to prevent respiratory insufficiency. Hypercapnia and hypoxia have been reported to be risk factors for postoperative complications. One indicator to exclude candidates for lung resection is hypercapnia.[21]

Table 1. Interpretation of ppoFEV1 and ppoDLCO[17]

| ppoFEV1 (% prediction) | Interpretation |
|---|---|
| > 40 | No or minor respiratory complications that need to be anticipated |
| < 40 | Increased risk of perioperative death and cardiopulmonary complications |
| < 30 | Possible need for postoperative ventilation assistance and increased risk of death and complications. Nonsurgical therapy should be considered. |
| >40%, ppoFEV1 >40% and $SpO_2$ room air >90% | Moderate risk, does not require further pulmonary examination |
| <40% | Increased risk of cardiopulmonary complications |
| <40% and ppoFEV1 <30% | High risk, requires cardiopulmonary exercise test |
| <30% | The patient is likely to develop hypoxia without supplemental oxygen |

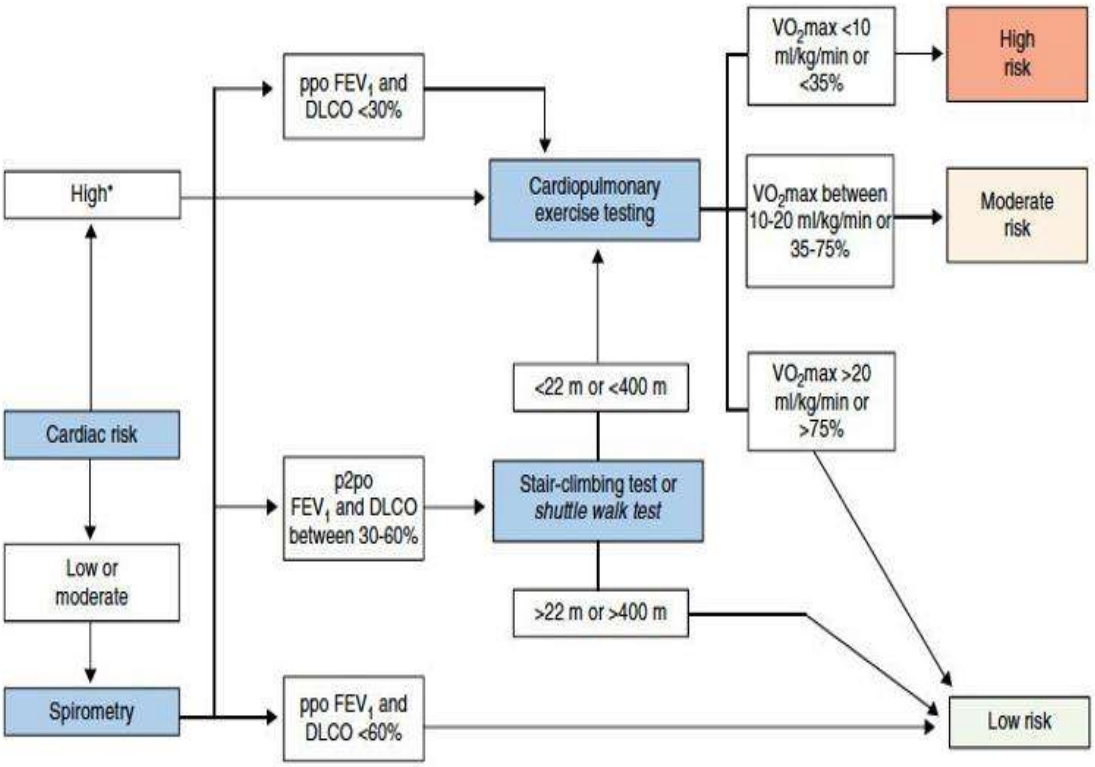


Figure 2. Algorithm for risk assessment of lung resection candidate patients[14]

The results of the study by Saleem et al in 2018 stated that patients with preoperative $CO_2$ partial pressure ($PaCO_2$) more than 45 mmHg were more likely to experience complications when compared to patients who had a preoperative $PaCO_2$ less than 45 mmHg.[22]

## Exercise Test

There are several types of exercise tests that are recommended to assess preoperative tolerance, including the six-minute walking test (6MW), shuttle walk test (SWT), stairs climbing test (SCT), and cardiopulmonary exercise test (CPET). The exercise test is the third stage of pulmonary tolerance assessment before lung resection is performed. This test is indicated for patients with stage I and II assessment results having moderate or doubtful risk. The purpose of this examination is to provide stimulation and pressure to the entire cardiopulmonary system and to estimate postoperative physiological function. During exercise, there is an increase in ventilation, oxygen uptake, carbon dioxide removal, and blood flow in the respiratory system, which correlates with what occurs after surgery.[10,16]

## Six-minute Walking Test (6MW)

The six-minute walking test is a test to assess a person's activity capacity by measuring the distance the patient can walk for six minutes on a flat surface. This test has a good correlation with the values of $FEV_1$ and DLCO.[18] The six-minute walking test is also considered to be able to describe the value of $VO_2$ max. The European Respiratory Society (ERS) recommends this examination as an initial

screening for lung resection candidates even though it is considered less able to describe the risk of postoperative complications. The cut off value recommended by ERS is 400 meters, which can be covered in six minutes, representing a $VO_2$ max 15 ml/kg/minute.[16]

**Shuttle Walk Test (SWT)**

In the shuttle walk test, the patient is asked to walk between two marking funnels that are approximately 10 meters apart. The patient walks according to the given rhythm, which is getting faster and faster. The examination is carried out for 12 minutes or until the patient feels unable to continue the examination. This examination is considered to be significantly correlated with the value of $VO_2$ max. If the distance traveled by the patient is less than 250 meters or there is a decrease in $O_2$ saturation greater than 4%, then the patient is included in the high-risk group.[17] The patient's ability to walk as far as 250 meters is associated with a $VO_2$ max 10 ml/kg/min and 400 meters is associated with $VO_2$ max more than 15 ml/kg/min.[16]

**Stairs Climbing Test**

This examination technique involves asking the patient to climb several levels of stairs at a speed that is adjusted to the patient's ability. Examination is stopped when the patient has reached the maximum level, the patient is tired, short of breath, or chest pain. Parameters observed before and immediately after the examination included blood pressure, pulse, respiration rate, and oxygen saturation. Parameters related to postoperative risk are O2 saturation less than 90% or desaturation occurring more than 4% after exercise. Interpretation of examination results was also correlated with VO2 max (table 2).[17,18] Brunelli et al stated that a decrease in O2 saturation of more than 4% after exercise was associated with postoperative complications, and the incidence of complications in these patients was 36%.[19]

**Cardiopulmonary Exercise Test (CPET)**

Cardiopulmonary exercise test is a high-tech examination carried out using a static bicycle or treadmill. It is carried out in an environment that is regulated in such a way as to ensure good standards and results. The $VO_2$ max is an important parameter that can directly assess exercise capacity.[16] The workload on the examination is set to reach a maximum of 8 - 12 minutes. When symptoms occur, fatigue, an abnormal ECG, or the patient's pulse reach their maximum, the examination is terminated.[11]

Cardiopulmonary exercise test is not performed in all lung resection candidates. This examination is indicated in patients who have a high-risk cardiovascular status, $ppoFEV_1$ and ppoDLCO less than 30%, climbing stairs test less than 22 meters, and shuttle walk test less than 400 meters. The cut-off value for the CPET is $VO_2$ max more than 75% predicted or more than 20 ml/kg/min for pneumonectomy, and a $VO_2$

max value of less than 15 ml/kg/minute indicates a high risk.[10]

## OPTIMIZATION OF PRESURGICAL LUNG FUNCTION

### Smoking Cessation

Various studies have assessed the relationship of smoking status in patients undergoing lung resection with the incidence of complications. Motono et al stated that the incidence of postoperative complications occurred in 33% patients who smoked. This result is greater than the incidence of complications in patients who do not smoke, which is 17%.[21]

Nakagawa et al conducted a study that assessed the relationship between the duration of smoking cessation and the incidence of pulmonary complications after lung resection in 2001. The results of this study indicated that the smoker must have quit more than five weeks before surgery.[23] The European Respiratory Society recommends that patients undergoing lung resection stop smoking at least four weeks before the procedure.[16]

Table 2. Interpretation of stairs climbing test[17]

| Test results | $VO_2$ max conversion | Interpretation |
|---|---|---|
| > 5 levels | > 20 ml/kg/min | Correlated with $FEV_1$ >2 l and low risk of death after pneumonectomy |
| > 3 levels | - | Correlated with $FEV_1$ 1,7 l and low risk of death after lobectomy |
| < 2 levels | - | Correlated with a high risk of death |
| < 1 level | < 10 ml/kg/min | Correlated with a high risk of death |

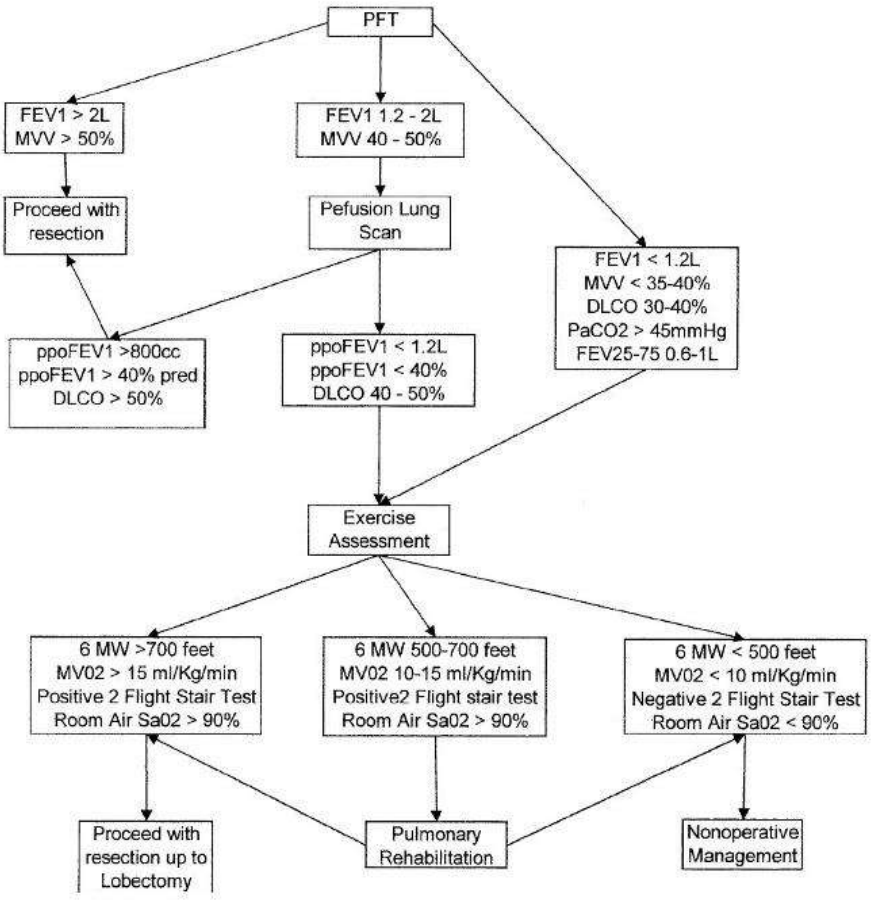


Figure 3. Algorithm for evaluation of pulmonary function for resection[20]

## Pulmonary Rehabilitation

Associated respiratory muscle dysfunction can be caused by the administration of anesthetic drugs from the beginning to the postoperative period. This is considered to increase the risk of postoperative complications, especially pulmonary complications. Optimization of respiratory muscle function can be achieved by performing pulmonary rehabilitation prior to surgery.[24]

Some of the methods that can be used include inspiratory muscle training, chest physiotherapy, and incentive spirometry.[24] Meta-analysis showed 50% of postoperative complications can be reduced by performing incentive spirometry and deep breathing exercises.[25] The ERS guidelines recommend pulmonary rehabilitation before and after surgery because it has benefits in the recovery process and prevents complications.[16]

## Aminophylline Treatment

The function of the respiratory muscles after surgery, especially thoracic surgery, can be caused by direct effects of damage to the muscles or conditions due to the incision or indirectly as a result of mechanical changes in the respiratory system. Research has also shown that lung resection, especially in patients older than 70 years, can reduce the maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) and can cause diaphragmatic paralysis.[26]

The effects of anesthetics on respiratory function are affected by a number of factors, including the agent, dose, the subject's consciousness, and the specific muscle group. Sedation, anesthesia, opioids, and endogenous consciousness impairment all reduce respiratory arousal during the perioperative period. As a result, the total level of stimulation to the respiratory muscles decreases, making the upper airway more susceptible to collapse and respiratory failure.[26]

An effort to reduce the risk is made by giving aminophylline. Aminophylline stimulates the central nervous system, myocardium, and muscles by increasing intracellular cAMP (cyclic adenosine monophosphate) and calcium. Aminophylline is also used to stimulate respiratory muscles and reduce the risk of apnea by blocking adenosine A1 and A2a receptors.[27] Yokoba et al stated that aminophylline can increase inspiratory and expiratory muscle activity. In addition, aminophylline is also considered to increase diaphragmatic muscle strength and slow muscle fatigue in patients with hypoxia and hypercapnia.[28]

## CONCLUSION

Lung resection is a modality of choice in the treatment of various lung diseases, but this action can result in various functional disorders that can affect the whole cardiopulmonary system. Assessment of preoperative tolerance is very important and has been reported to reduce mortality and morbidity after lung resection. The main concerns to preoperative tolerance assessment include

age, lung function, cardiovascular fitness, nutrition, and functional status. Preoperative pulmonary assessment includes pulmonary function tests using spirometry and DLCO, blood gas analysis, and exercise testing. Patients who have good tolerance for lung resection are patients who have low cardiovascular risk, ppo$FEV_1$ values more than 40%, ppoDLCO more than 50% and $VO_2$ max more than 15 ml/kg/min. Preoperative lung function can be optimized by smoking cessation, pulmonary rehabilitation, and intravenous administration of aminophylline.

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**Editor**