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# MORPHOLOGY PROFILE AND PD-L1 EXPRESSION IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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**ABSTRACT**

Lung cancer cases in Indonesia became the second highest with the highest mortality rate in 2022. Various advanced examinations such as histopathology and immunohistochemistry are performed to identify the morphological types of lung cancer. Histopathologically, lung cancer classified into two types are Non-Small Cell Lung Cancer (NSCLC) and Small Cell Lung Cancer (SCLC). After histopathological examination, further immunohistochemical testing is required to help classify the subtype and identify therapeutic markers. One of the markers is the expression of Programmed Death Ligand 1 (PD-L1). Patients with this marker can receive anti-PD-L1 immunotherapy according to the specified criteria. This study determined the morphological profile and PD-L1 expression in patients with Non-Small Cell Lung Cancer (NSCLC) at Siloam MRCCC Semanggi Hospital between 2020 and 2022. The method used was descriptive with a retrospective approach by collecting data from the archives of the Anatomical Pathology Laboratory at Siloam MRCCC Semanggi Hospital. The population in this study comprised all patients diagnosed with NSCLC who underwent PD-L1 IHC testing at Siloam MRCCC Semanggi Hospital between 2020 and 2022. Data collection was conducted using a total sampling method, including all individuals who met the predefined inclusion and exclusion criteria. The final sample consisted of 91 patients diagnosed with NSCLC who had undergone PD-L1 IHC examination during the 2020–2022 period. A total of 91 patients including the inclusion and exclusion criteria were included in the data and analyzed. The analysis revealed that the age group 60-69 years accounted for 39.5% of cases, 54.9% of cases were male, 73.6% of cases had an adenocarcinoma morphology, and 54.9% of cases had a negative PD-L1. The incidence of NSCLC patients who underwent PD-L1 IHK examination based on age was dominated by the 60-69 year age group, and most of them were male with the most common diagnosis being adenocarcinoma morphology type and PD-L1 expression with negative values.

Keywords: immunohistochemistry; lung cancer; NSCLC; PD-L1

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## INTRODUCTION

In physiological conditions, human cells grow and reproduce through the process of proliferation. When human cells become old or damaged, the cells die (apoptosis) and are then replaced with new cells. However, sometimes this process can be disrupted so that abnormal cells can grow uncontrollably. These abnormal cells form lumps of tissue called tumors. Based on their nature, tumors are divided into two, which are cancerous (malignant) and non-cancerous (benign) (Mathew et al., 2023). Currently, lung cancer is recognized as one of the most common cancers. In 2020, around 12.5% of all patients with cancer in the world had lung cancer with an estimated 1.8 million deaths (Bhattarai et al., 2023; Czerw et al., 2024). Based on data from GLOBOCAN (Global Burden of Cancer Study) in 2022, lung

cancer cases in Indonesia reached 13.4% with the highest mortality rate compared to other cancer sufferers, an estimated 11.9% (Ferlay et al., 2021).

Smoking is the main cause of lung cancer. However, there are several other risk factors such as prolonged exposure to air pollution, exposure to carcinogens in the workplace, genetics, and poor diet (de Jong et al., 2023). Based on histopathology, lung cancer can be classified into two categories, which are Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC). Non-Small Cell Lung Cancer has three subtypes which are Adenocarcinoma, Squamous Cell Carcinoma, and Large Cell Carcinoma (Putri et al., 2023). Adenocarcinoma is defined as carcinoma with an acinar/tubular structure or mucin production, while Squamous Cell Carcinoma is defined as carcinoma with keratinization or bridges between cells. However, in cases of poorly differentiated carcinoma, it can allow for misdiagnosis and type of management, so patients who are declared positive for NSCLC after histopathological examination are advised to undergo immunohistochemistry (IHC) examination to help classify lung cancer into certain subtypes and assess biomarkers that are relevant to molecular targeted therapy (Inamura, 2018; Yatabe et al., 2019).

IHC examination utilizes the specific binding between antibodies and antigens to detect specific antigens in cells and tissues (Magaki et al., 2019)With IHC examination, analysis of Programmed Cell Death Ligand 1 (PD-L1) expression, which is a trans-membrane protein expressed by tumor cells, can be evaluated. PD-L1 is a co-inhibitory factor of the immune response. PD-L1 can combine with PD-1 to reduce the proliferation of PD-1 positive cells, inhibit cytokine secretion, and induce apoptosis. PD-L1 also plays a role in various malignancies where it can weaken the host immune response to tumor cells (Han et al., 2020). Now, this expression is applied as a companion diagnostic for anti-PD-1 and anti-PD-L1 agents to identify NSCLC patients who are more likely to benefit from immunotherapy. (Yatabe et al., 2019)(Lantuejoul et al., 2020). Based on this background and the still limited research on morphological profiles and PD-L1 in Indonesia, the author aims to conduct a study entitled Morphological Profile and PD-L1 in Non-Small Cell Lung Cancer (NSCLC) patients at Siloam MRCCC Semanggi Hospital in 2020-2022. This study aims to describe the morphological profile and PD-L1 expression in Non-Small Cell Lung Cancer (NSCLC) patients at Siloam MRCCC Semanggi Hospital in 2020-2022.

## METHOD

This type of research uses a descriptive method with a retrospective approach. Patient data collection was carried out in the Anatomical Pathology Room of Siloam Hospital MRCCC Semanggi in January-April 2024. The population of this study was all patients diagnosed with NSCLC who underwent PD-L1 IHK examination in 2020-2022 at Siloam MRCCC Semanggi Hospital. Patient data collection as a sample used the total sampling method with all subjects who met the inclusion and exclusion criteria. The study sample was patients with a diagnosis of NSCLC accompanied by PD-L1 IHK examination in 2020-2022 as many as 91 patients data.

Inclusion Criteria

1. All patients diagnosed with lung cancer at Siloam MRCCC Semanggi Hospital in 2020-2022.
2. All lung cancer patients who underwent PD-L1 IHK examination at Siloam MRCCC Semanggi Hospital in 2020-2022.

Exclusion Criteria

1. Patients who have incomplete Pathology Anatomy examination data at Siloam MRCCC Semanggi Hospital in 2020-2022.
2. Patients with SCLC category at Siloam MRCCC Semanggi Hospital in 2020-2022.

The processing of data that has been obtained using descriptive statistical analysis techniques using frequency analysis. The results of the analysis will be presented in the form of tables or graphs along with their explanations. This study applies research ethics guidelines that aim to protect patient rights at Siloam MRCCC Semanggi Hospital in 2020-2022.

**RESULT**

Based on all the archive data of the PA laboratory of Siloam MRCCC Semanggi Hospital in 2020-2022, 118 data of lung cancer patients who underwent IHK examination were obtained. From this data, 91 data that met the inclusion and exclusion criteria were entered into SPSS using descriptive statistics frequencies and crosstabs to provide an overview in the form of tables and discussions.

Table 1.
Frequency Distribution of NSCLC Patients with PD-L1 Values by Age

| Age | f | % |
|---|---|---|
| < 20 year | 0 | 0 |
| 30 - 39 year | 1 | 1.1 |
| 40 - 49 year | 9 | 9.9 |
| 50 - 59 year | 23 | 25.3 |
| 60 - 69 year | 36 | 39.5 |
| 70 - 79 year | 20 | 22 |
| ≥ 80 year | 2 | 2.2 |

Based on the results in the table, the frequency of NSCLC patients can be described based on certain age groups. As age increases, more and more cases of NSCLC patients are recorded, so in the age group of NSCLC patients
with the highest cases from 2020 to 2022, there were 36 cases (39.5%) in the 60-69 year age range. However, it began to decline in the 70-79 year age group to 20 cases and decreased further in the ≥80 year age group to 2 cases (2.2%).

Table 2.
Frequency Distribution of NSCLC Patients with PD-L1 Values by Gender

| Gender | f | % |
|---|---|---|
| Male | 50 | 54.9 |
| Female | 41 | 45.1 |

The results of the table in the distribution show that NSCLC patients at Siloam MRCCC Semanggi Hospital in 2020-2022 with male gender had the highest number of cases with 50 cases (54.9%). While female gender was recorded as having 41 cases (45.1).

Table 3.
Frequency Distribution of Patients Based on NSCLC Morphology Who Have PD-L1 Values

| Morphology of NSCLC | Frequency (n) | Percentage (%) |
|---|---|---|
| Adenocarcinoma | 67 | 73.6 |
| Squamous Cell Carcinoma | 20 | 22 |
| Large Cell Carcinoma | 2 | 2.2 |
| Adenosquamous Carcinoma | 1 | 1.1 |
| Pleomorphic Carcinoma | 1 | 1.1 |
| Spindle Cell Carcinoma | 0 | 0 |
| Giant Cell Carcinoma | 0 | 0 |

Based on table 3. it is described that the morphology of NSCLC adenocarcinoma in 2020-2022 had the highest cases, reaching 67 cases (73.6%). Then the second highest case was in squamous cell carcinoma with 20 cases (22%). In the morphology of NSCLC, large cell carcinoma was recorded as having 2 cases. Then, adenosquamous carcinoma and pleomorphic carcinoma had the same number of cases with 1 case. Both spindle cell carcinoma and giant cell carcinoma had no cases in 2020-2022.

Table 4.
Frequency Distribution of NSCLC Patients Based on PD-L1 Expression

| PD-L1 expression | f | % |
|---|---|---|
| Negatives | 50 | 54.9 |
| 1 - < 5% | 19 | 20.9 |
| 5 - 50% | 10 | 11 |
| ≥ 50% | 12 | 13.2 |

The table 4 shows that PD-L1 expression of NSCLC patients at Siloam MRCCC Semanggi Hospital in 2020-2022 had 50 cases (54.9%) that were declared negative. Meanwhile, 19 cases had PD-L1 expression of 1 - <5%. The case with the lowest PD-L1 expression was PD-L1 expression of 5 - 50% with 10 cases (11%). Finally, PD-L1 expression ≥ 50% was recorded as having 12 cases.

Table 5.
Distribution of Morphological Characteristics of NSCLC Having PD-L1 by Age

| Morphology of NSCLC | 30 - 39 year | 40 - 49 year | 50 - 59 year | 60 - 69 year | 70 - 79 year | ≥ 80 year |
|---|---|---|---|---|---|---|
| Adeno-carcinoma | 1 | 7 | 20 | 23 | 14 | 2 |
| Carcinoma | 0 | 2 | 3 | 11 | 4 | 0 |
| Squamous Cell | 0 | 0 | 0 | 1 | 1 | 0 |
| Carcinoma | 0 | 0 | 0 | 1 | 0 | 0 |
| Large Cell | 0 | 0 | 0 | 0 | 1 | 0 |

Based on the results in the table, the most dominant results are the 60-69 and 50-59 year age groups. Cases in the 60-69 and 50-59 year age groups mostly have NSCLC adenocarcinoma morphology with a total of 23 cases and 20 cases.

Table 6.
Distribution of Morphological Characteristics of NSCLC Having PD-L1 by Gender

| Morphology of NSCLC | Male | Female |
|---|---|---|
| Adenocarcinoma | 30 | 37 |
| Squamous Cell Carcinoma | 18 | 2 |
| Large Cell Carcinoma | 1 | 1 |
| Adenosquamous Carcinoma | 0 | 1 |
| Pleomorphic Carcinoma | 1 | 0 |

Table 6. shows that although the total number of male cases is greater than female cases, the number of cases in female gender with adenocarcinoma NSCLC morphology is greater than male cases, which is 37 cases. The morphology of squamous cell carcinoma NSCLC is dominant in the male gender, which is 18 cases, while in females there are 2 cases.

Table 7.
Distribution of NSCLC Morphological Characteristics based on PD-L1

| Morphology of NSCLC | Negatives | 1 - < 5% | 5 - 50% | ≥ 50% |
|---|---|---|---|---|
| Adenocarcinoma | 34 | 16 | 8 | 9 |
| Squamous Cell Carcinoma | 14 | 3 | 2 | 1 |
| Large Cell Carcinoma | 2 | 0 | 2 | 0 |
| Adenosquamous Carcinoma | 0 | 0 | 0 | 1 |
| Pleomorphic Carcinoma | 0 | 0 | 0 | 1 |

Based on the results in the table, the morphology of NSCLC can be described based on PD-L1. The morphology of NSCLC adenocarcinoma with negative PD-L1 has a dominant value of 34 cases, followed by PD-L1 1 - <5% with 16 cases, PD-L1 5 - 50% with a total of 8 cases and PD-L1 ≥ 50% with 9 cases. The morphology of NSCLC squamous cell carcinoma has a total of 14 cases with negative PD-L1 results, PD-L1 1 - <5% has 3 cases, then at 5 - 50% has 2 cases, and at PD-L1 ≥ 50% has 1 case.

**DISCUSSION**

Based on the data, the 60-69 age group has the most cases of lung cancer, especially in the NSCLC category. These results are under the American Cancer Society Journal that lung cancer predominantly occurs in the elderly group and only a few are diagnosed under the age of 45 (Wilder et al., 2024) In addition, analysis from the Cipto Mangunkusumo National General Hospital (RSCM) found that lung cancer has the highest incidence in the 50-70 age group, this can occur because currently there is no government-mandated lung cancer screening program in Indonesia. Although recommended by national guidelines, lung cancer screening programs are carried out voluntarily and at the patient's own expense in private hospitals. The Indonesian Lung Cancer Management Guidelines recommend low-dose chest CT examinations for high-risk patients. Patients who are considered high-risk are those aged <40 years with a smoking history of at least 30 years, or patients aged ≥50 years with a smoking history of at least 20 years and have at least one other risk factor. Former smokers can also undergo the examination if they have quit smoking in the last 15 years before the examination (Asmara et al., 2023).

Data at Siloam MRCCC Semanggi Hospital in 2020-2022 showed the highest cases of NSCLC in men compared to women. This can occur due to the habit of smoking in men being more common than in women and causing the highest incidence of lung cancer in men. Cigarettes can cause combustion residues to enter the trachea so many types of squamous cell carcinoma are found. In addition, cigarettes that use filters cause gene mutations from the low nicotine content of cigarettes, causing carcinogenic particles to form lesions in the peripheral part of the lungs which is the most common place for adenocarcinoma to be found (Hamdani et al., 2023).

Although NSCLC cases in men are higher than in women, it turns out that the difference is not too significant. This insignificant difference may occur because, in recent decades, the smoking rate in women has increased (Park et al., 2023) This is to the data in Table 3.5 which shows that women have dominant cases of NSCLC adenocarcinoma compared to men. A study conducted by Gee and Yendamuri (2024) found that the development of cancer in women, both smokers and non-smokers, is twice as likely as in men. In women who smoke, airway obstruction occurs earlier and with greater thickening of the bronchial walls compared to men who smoke. Meanwhile, women who do not smoke can experience lung cancer because it was found that 69% of women were exposed to environmental tobacco smoke compared to only 17% of men (Gee & Yendamuri, 2024).

The results of this study indicate that the number of NSCLC adenocarcinoma patients has the highest cases (73.6%) followed by squamous cell carcinoma (22%). These results are also the same as the study conducted at Dr. Soedarso Hospital, as many as 76.5% of patients were included in the adenocarcinoma category and followed by squamous cell carcinoma as much as 16.1%. 6 The transition from non-filter cigarettes to filter cigarettes that occurred in the 1960s in Japan and the 1950s in the United States caused a change in incidence based on the most common type of NSCLC morphology, namely from squamous cell carcinoma to

adenocarcinoma. This can occur because smoke from filtered cigarettes that is inhaled deeper than smoke from unfiltered cigarettes carries tobacco carcinogens further to the bronchioles-alveolar, where adenocarcinoma appears. Changing cigarette consumption from non-filter to filter also reduces the production of Polycyclic Aromatic Hydrocarbons (PAHs) which are carcinogenic and trigger squamous cell carcinoma, but simultaneously increases the production of tobacco-specific N-nitrosamines which are carcinogenic and trigger adenocarcinoma (Ito et al., 2011).

If the morphology of NSCLC is based on the percentage of PD-L1, the PD-L1 negative category with adenocarcinoma type NSCLC has the highest cases, then the second highest is adenocarcinoma with a PD-L1 value of 1 - <5% (García et al., 2020)Research conducted by García, et al. also obtained the same results, estimated 50% of adenocarcinoma patients with PD-L1 SP263 values <1% and 24% with PD-L1 SP263 1 - <5%. 23 Under physiological conditions, PD-1 and PD-L1 binding can prevent excessive tissue inflammation. However, the occurrence of tumors can cause negative effects. PD-1 which is widely expressed on active T cells, and its ligand, PD-L1, which is expressed on several types of tumor cells and antigen-presenting cells (APC) if bound will inhibit T cell signaling and function, lymphocyte proliferation, and cytokine secretion. As a result, it can cause tumor cells to avoid immune surveillance from T cells (Jiang et al., 2019).

PD-L1 can be negative due to several things, such as genetic processes, which are the occurrence of JAK1 and JAK2 truncation mutations which are signaling for the interferon-γ (IFN-γ) receptor so that they are unable to express PD-L1, and the absence of T cell infiltration due to the absence of T cells in the tumor so that they cannot express PD-L1 (Ribas & Hu-Lieskovan, 2016) In addition, the tumor may only have PD-L2 expression without PD-L1. Research from Yearley, et al found that out of 94 NSCLC cases, many had PD-L2 values with a few cases being declared negative (Yearley et al., 2017).

PD-L1 examination is certainly inseparable from the purpose of immunotherapy treatment. Immunotherapy targeting PD-1/PD-L1 has been assessed in clinical trials as monotherapy or in combination with chemotherapy (Yatabe et al., 2019). Currently, several PD-L1 IHK tests have been approved by the FDA for the clinical treatment of advanced NSCLC including SP263, 22C3, 28–8, and SP142. 27 NSCLC patients with PD-L1 SP263 values ≥ 1% can be treated using atezolizumab while patients with PD-L1 SP263 values ≥ 50% can be treated with cemiplimab-rwlc (Newswire, 2025)However, mutations in oncogenic drivers such as EGFR and ALK can increase anti-PD1/PD-L1 resistance and inhibit the efficacy of anti-PD1/PD-L1 so that in PD-L1 examination, it is necessary to examine these oncogenic drivers to maximize the effectiveness of therapy (Dantoing et al., 2021).

## CONCLUSION

Based on the results of research that has been conducted on NSCLC patients at Siloam MRCCC Semanggi Hospital in 2020-2022, it can be concluded that: 1) The incidence of NSCLC patients who underwent PD-L1 IHK examination based on age was dominated by the 60-69 year age group with 36 cases; 2) The incidence of NSCLC patients who underwent PD-L1 IHK examination based on gender was mostly male with 50 cases; 3) The incidence of NSCLC patients who were diagnosed with the most adenocarcinoma morphology type was 67 cases; 4) The incidence of NSCLC patients based on PD-L1 expression was mostly negative.

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# MORPHOLOGY PROFILE AND PD-L1 EXPRESSION IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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