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Research Article

Protein Programmed Death-Ligand 1 Expression in Non-Small Cell Lung Cancer (NSCLC) and Its Correlation to Smoking Status in North Sumatera Population

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ABSTRACT

Background: Tobacco smoking is associated to the increase risk of lung cancer, and smoking could also trigger the tumour proportion score from programmed death ligand (PD-L1). **Objective:** This study aims to identify the correlation of non-small cell lung cancer (NSCLC) with the PD-L1 expression and smoking profile on the North Sumatra Population. **Methods:** This research implemented a descriptive study with cross-sectional design. **Results:** This study was carried out from August 2019 to September 2020. Results: Characteristics of patients with NSCLC to the PD-L1 expression were found more in male patients with percentage of 88.6%, whereas the most common type of cancer is adenocarcinoma, accounting for 97.14% of cases with mild degree smoking index for 45.7% (Brinkman index) and IV-stage of clinical status for 68.6%. The tumour proportion score with 1-49% was 51.4% with high expression of PD-L1 (positive) for 74.28%, while lower expression of PD-L1 accounted for 45%. **Conclusion:** There is a correlation between PD-L1 expression and smoking status in NSCLC patients, with p-value of 0.037 (<0.05).

Keywords: non-small cell lung cancer (nsclc), programmed death ligand (pd-l1), smoking status, tumour proportion score

1. Introduction

Cigarette smoking is the main risk factor to cause lung cancer with 80-90% of estimated number. In a cigarette, around 4000 chemical substances, and some of them are carcinogenic matters, including polycyclic aromatic hydrocarbon, aromatic amines, nitrosamines, and organic/inorganic compounds such as benzene, vinyl chloride, arsenic and chromium. These carcinogenic matters have been reported to have relations to DNA mutations [1], and one of which is lung cancer that is triggered by the declining of immune system due to the blocking via smoking [2].

To date, lung cancer is the most common cancer globally as well as the main cause for cell malignancy [3]. Based on histopathological view, lungs tumour is divided into two main types i.e., Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), and the NSCLS is divided into several sub-types which

are adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and unclassified lung carcinoma [4]. Among these types, adenocarcinoma is a type of cancer with the highest prevalence in Indonesia. Adenocarcinoma and squamous cell carcinoma account for 60% of all lung cancers. Several recent studies in Indonesia and Western countries show a shift in the distribution of lung cancer from squamous cell carcinoma to adenocarcinoma [5-8].

Advanced type of NSCLC appears to have high expression of Programmed Death Ligand 1 (PD-L1) with estimated percentage of 23-28%, which notably implies 50% of membranous expression of PD-L1 from the tumor cells [9,10]. Most of studies have reported that there was a correlation between smoking status and tumor proportion score of the PD-L1. This process is due to the higher mutation on the cells which is related to the resulting effect of smoking, thus; higher mutational burden shifts the score on the tumor proportion [11].

As the commonest type of lung cancer worldwide and particularly in Indonesia, the authors interest in assessing the PDL-1 expressions in NSCLC populations. Indonesia annually consumes 215 billion cigarettes and is ranked fifth in the world's largest cigarette-consuming country after China, the United States, Japan, and Russia. WHO data states that 59% of Indonesian men and 3.7% of women are smokers. Overall, in 2001, around 31.5% of the Indonesian population smoked, meaning there were around 60 million smokers in Indonesia. NSCLC also has higher expressions of PDL-1 compare to SCLC. So, according to NCCN guidelines for lung cancer 2021, further diagnostics for evaluated the expressions of PDL-1 was recommended in NSCLC type, while systemic therapy was administered as soon as the diagnostics of SCLC was carried out in both limited and advance stage [12,13]. Further, in the recent studies explained that there was a decrease expressions of common oncogene molecular driver mutations in NSCLC patients in North Sumatera Populations [14], so the alternative treatment with the use of anti PDL-1 is needed. However, there is no data about the prevalence of PDL-1 expressions in Indonesia, particularly in North Sumatera. This study is carried out to understand the correlation of PD-L1 expression and smoking which has been determined before in North Sumatera.

2. Methods

This study implemented cross-sectional designs with correlation design via the comparison of two categories. Data collection was carried out in Adam Malik General Hospital Medan from 2019 to 2020. The inclusion criteria in this study were subjects with diagnosed of NSCLC and confirmed by histopathology and cytology preparations, age > 40 years old, with complete medical records for age, gender, smoking status, staging, and site of metastases. Smoking status then defined as smoker and never smoker based on NIHSS [15]. For the smoker criteria, the degree of smoking consumption further categorized according to Brinkman Indexes (BI). BI was the multiplication results of average cigarettes that have been smoked daily and smoking duration in a year. There are three categories of the indexes i.e., mild with score 0-199, moderate with score 200-599, and severe with score 600 [16]. The exclusion criteria of this study were insufficient cell tumor and sample damage.

Total of 52 tissue samples that have been examined via histopathological tests were delivered to Pathological Anatomy Laboratory of Dharmais Hospital Jakarta. Afterward, from these 52 samples, only 35 samples satisfied the inclusion criteria that are assessed by pathologists, and then; immunohistochemical staining was performed on Ventana 22C3 platform. The staining results then were assessed by 2 pathologists under light microscope, and tumour preposition score (TPS) based on PD-L1 was performed to determine three categories of TPS, moreover; >50% is considered positively strong, 1-49% is considered positively weak, and <1% shows negative [14]. Statistical analysis was carried out to determine the correlation of expression level of PD-L1 to smoking status via chi square test.

3. Results

The following Fig. 1 is the flowchart of this study. Based on Fig. 1, from 100 population, only 52 samples satisfied the inclusion criteria, and among these 52 samples, only 17 samples were excluded due to insufficient tumour cells. As a result, 35 samples were the final samples to be assess on the TPS.

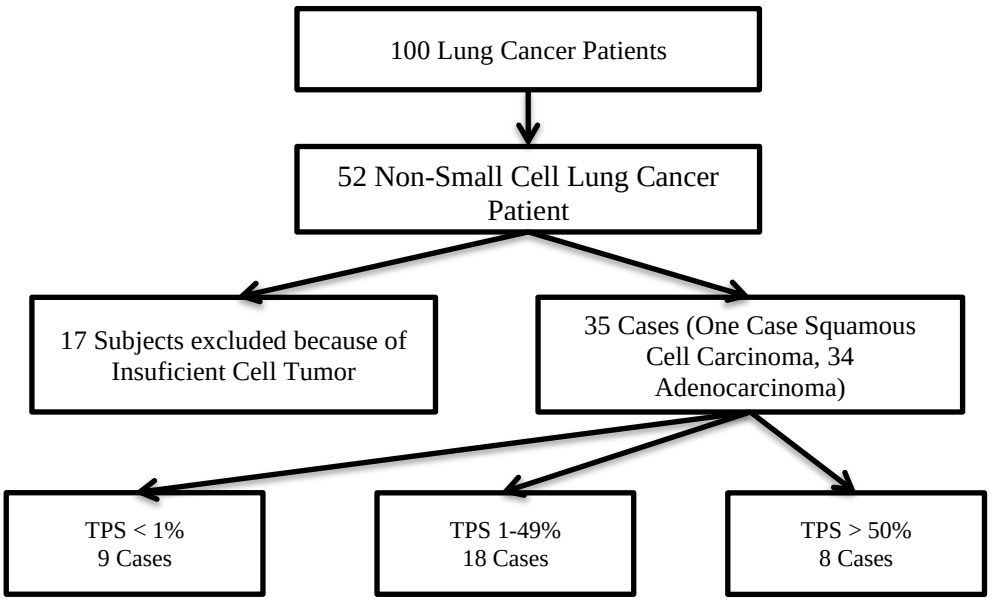
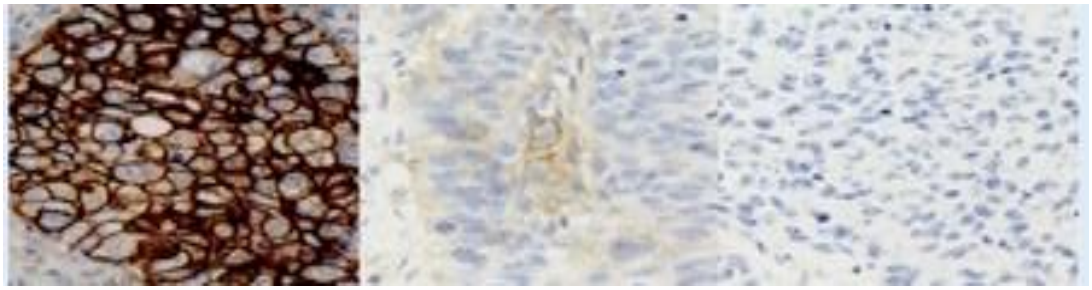


Figure 1. Expression Levels of PD-L1 Based on Tumour Proportion Score

Table 1. Demographical Characteristics of 35 Samples

Characteristic	n=35	%
Gender		
Male	31	88.6
Female	4	11.4
Age		
40-60 years	20	57.1
>60 years	15	42.9
Histopathology Results		
Adenocarcinoma	34	97.14
Squamous Cell Lung Carcinoma	1	2.85
Stage		
IIIA	2	5.7
IIIB	5	14.3
IIIC	2	5.7
IVA	24	68.6
IVB	2	5.7
Metastasis		
Pleura	22	62.9
Cervical lymph node	2	5.7
Bone and liver	1	2.9
Brain and bone	1	2.9
Smoking status		
Never Smoker	7	20
Smoker	28	80
Index Brinkman (IB)		
Mild IB	16	45.7
Moderate IB	0	0
Severe IB	12	34.3
Tumor proportion score (TPS)		
<1%	9	25,7
1-49%	18	51.4
≥50%	8	22.9
Expression PD-L1		
Positive	26	74.28
Negative	9	25.71

According Table 1 above, more than a half of the samples were in 40-60 years of age with 20 cases (57.1%), which is dominated by male patients with 31 cases (88.6%). The most common histopathological characteristics were in adenocarcinoma sub-type accounted for 34 cases (97.14%), and among these 34 samples, advanced stage IVA was the highest for 24 cases (68.8%), followed by stage IVB for 2 cases (5.7%). Smoking status conditions were highly dominated with smoking status (80%), in which almost a half (45.6%) of the smoker cases were mild IB. The Tumour Proportion Score (TPS) showed that 18 cases were in 1-49% TPS, while 8 cases (TPS ≥50%) were confirmed to have high expression levels of PD-L1 (positive).



2a **2b** **2c**

Figure 2. The Staining Photographs on Ventana 22C3 with The Expression Levels of PD-L1 (a) Expression Level with >50%, (b) Expression Level with 1-49%, and (c) Expression Level <1%

Table 2. The Correlation of Programmed Death Ligand-1 (PD-L1) on Lungs Cancer and Smoking Status

Smoking Status	PD-L1		*p-value*
	Negative	Positive	
	n	n	
Never smoker	2	5	0.037
Smoker	7	21	

Based on Table 2, statistical analysis on the correlation of PD-L1 and smoking status was determined via chi-square test to correlate two categorical variables. From the analysis, the p value was <0.05 that indicates to the presence of correlation between these two variables.

4. Discussion

Based on our findings, patients with lung adenocarcinoma were dominated by males. Lung cancer is the second most common cancer among males (13.4%), with nasopharynx cancer being the most common (13.63%), also; these two are most common caused for mortality in males (28.94%). A study by Tarigan et al. found that lung cancer most often occurs in men who are active smokers in the age group over 50 years. Cigarette smoke produces polycyclic aromatic hydrocarbons (PAH) and tobacco-specific N-nitrosamines (TSNA), which can affect the histopathological appearance of cancer cells. PAH is a carcinogen that can induce squamous cell carcinoma-type lung cancer, while TSNA can induce adenocarcinoma-type lung cancer. Based on few studies in North Sumatera Province, particularly in Medan, adenocarcinoma in lungs appear to be most populous types of cancers, in which this type eventually grew into advanced stages [5-8], therefore; it metastasised in several parts of the organs [17].

In this study, there was a high percentage of smokers. Indonesia is the top three countries with the highest prevalence of smoker after China and India, and most of them smoke in their houses [18]. In a study involved to North Sumatera population, severe index level of IB was found in those who smoke clove cigarettes [19].

Rizvi et al., employed a binary classification that has been validated to identify the molecular markers of smoking [20,21]. This classification distinguishes tumours with higher level of transversion such as tumours related to smoking, and tumours with lower transversion which have no related to smoking [21]. This classification is based on the nucleotides transversion of cytosine to adenine (C-A) within the individual and genomic genes, which can be found whether in ex-smokers or smokers [22].

Moreover, nucleotides transversion of C-A has been proven to have inverse correlation with cytosine into

thymidine within transition frequencies [23,24]. Based on previous literature, it may have been argued that tumours-related-smoking must be determined by certain genetical markers given that the basic determinants are only smoking status.

On the other hand, a study has revealed there was correlation between the number of cigarettes and the genetical shifting that have been occurred [24]. All these studies considered the number of cigarettes was not the only factors that significant correlated with the incidence pf tumours-related-smoking. The degree of smoking status described by brinkman index cannot be the significant factors determine the higher risk for lung cancer, because genetic alterations also play important role in developing lung cancer.

Further, recent studies has been stated the difference molecular process in lung cancer between smoker and never smoker, including the type of mutations and the outcome. Yet, it is not described completely if there was difference according to the severity of smoking status.

In contrast to the results of this study, previous studies found that the relationship between smoking and PD-L1 expression was still inconsistent [20,25,26]; however, recently, Kerdidani et al., [27] have conducted an observational study that involved from the early stages of smoking to the emergence of emphysema and lung cancer. The research has reported that the dendritic cells that have been exposed by surrounding microbial tumours within emphysema conditions would increase the regulation of PD-L1/IDO expression via mechanisms that depend on oxidative stress; therefore, the responses were mediating immune tolerance and tumours releasing. Zhao et al., [28] have demonstrated that melanoma generates cells immunity increasing the oxidation process of fatty acids of dendritic cells via Wnt5a-b-catenin-PPAR-γ signalling pathway, which eventually induce the IDO enzyme activities. The same study has also shown that the inhibition within this pathway may reduce immune tolerance from the dendritic cells; as a result, increase the effectivity of anti-PD-1 in transgenic melanoma models. Within hypoxia conditions, Marti et al., [27] has discovered that vascular endothelial growth factor (VEGF) would increase the IDO expression and activity levels in dendritic cells, which have suppressive effects on the specific lymphocyte proliferation of Ag and mitogen. The strong correlations among immune system, angiogenesis, cancer growth and metastasis as well as the involvement of nodus lymph is currently being explored further [30].

Based on tobacco toxicology, Wang et al., [31] have reported that the cigarettes smoke and benzopyrene carcinogen (BaP) induced the PD-L1 expression on the lung epithelial cells via in vitro and in vivo, mediated by aryl hydrocarbon receptor (AhR). The antibody of anti-PD-L1 or AhR deficiency would significantly force the lung cancer that has been induced by the BaP. Furthermore, via multivariate analysis, Ng et al., [32] have suggested that with 1% percent of PD-L1, smoking status is the only significant predictor, nonetheless; they confirmed that smoking status may be a sole predictor as a more crucial and acceptable indicator for the efficacy of anti-PD-1/PD-L1 therapies compared to those in any clinical and relevant characteristics of patients with NSCLC with oncogene control mutation. On the other hand, the associations between smoking and efficacy of anti-PD-1/PD-L1 may also relate to the tumor-infiltrating lymphocytes (TILs) status [27], and any immune-modulator such as B7-H3 (CD276) [33].

In this conceptual thinking, the cytokines concept, microenvironment cells, and precursor could be slightly explained. Several important knowledges about the role of microenvironment of tumor cells in mediating the cancer growth is certainly essential to be consider whether it is solid tumors or hematological malignancy. In this concept, hematological malignancy may be more representative as it has been reported by Leone et al., [34,35] that found the accumulated of dendritic cells of patients with myeloma bone marrow would protect the tumor plasm cells from the destruction by CD8+ T-Cells. Besides, this phenomenon would also mediate the endothelial bone marrow cells to preserve subsets specific tumors by restricting the functions of the T-cells CD8+ in myeloma patients. This significant finding, have implied that interactions among endothelial and tumor cells with CD8+ T-cells may create microenvironmental immunity that perhaps has not disturbance on cancer proliferation. In this study, the limitations are number of samples and the distribution of between smokers and non-smokers which are higher in smokers. Then, rough collection of data, in which several data may be inaccurate also becomes another limitation in this study, thus; it is recommended to conduct further study with detail data.

5. Conclusion

Characteristics of lung cancer patients with adenocarcinoma in Medan city to the expression level of PD-L1 appear to be found more in male patients with smoking status of mild IB, and clinical stages of IV. These finding have demonstrated that there is a significant positive corelation between smoking status and the expression level of PD-L1 with p value < 0.05.

6. Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations but are available from the corresponding author upon reasonable request.

7. Ethical Statement

This study has been approved by the Ethical Committee of Universitas Sumatera Utara. Besides this Sumatera Medical Journal (SUMEJ) is a peer-reviewed electronic internationaljournal. This statement clarifies ethical behavior of all parties involved in the act of publishing an article in Sumatera Medical Journal (SUMEJ), including the authors, the chief editor, the Editorial Board, the peer-reviewer and the publisher (TALENTA Publisher UniversitasSumatera Utara). This statement is based on COPE's Best Practice Guidelines for Journal Editors.

8. Author Contributions

All authors contributed to the design and implementation of this research, data analysis, and finalizing the manuscript.

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11. Conflict of Interest

Authors declares no conflict of interest.

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