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SUMEJ
Sumatera Medical Journal
Journal homepage: https://talenta.usu.ac.id/smj

Research Article

Levels of Squamous Cell Carcinoma Antigen and Interleukin-6 as Biomarkers in NSCLC Patients

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ARTICLE INFO

Article history:
Received 12 June 2024
Revised 27 March 2025
Accepted 29 March 2025
Available online 01 May 2025

E-ISSN: 2622-1357
P-ISSN: 2622-9234

How to cite:
Lydia Arieta, Noni Novisari Soeroso, Setia Putra Tarigan, Putri Chairani Eyanoer, "Levels of Squamous Cell Carcinoma Antigen and Interleukin-6 as Biomarkers in NSCLC Patients", SUMEJ, Vol. 08, No. 02, May 2025.

http://doi.org/10.32734/sumej.v8i2.20027.

ABSTRACT

Background: Squamous Cell Carcinoma Antigen (SCC-Ag) and Interleukin-6 (IL-6) has been widely used for monitoring Non-Small Cell Lung Cancer (NSCLC). **Objective:** This concentration also known to be higher in Non Small Cell Lung Cancer. **Methods:** This research used descriptive study among NSCLC patients. Blood sampling was used with serum. ELISA platform was used to rate SCC-Ag and IL-6 serum. **Results:** From 20 samples NSCLC, we found 20 males (100%), active smokers (80%). From histology type, Adenocarcinoma 12 cases (60%). The most of subjects were in stage IVA (70%). The Squamous Cell Carcinoma Antigen levels of NSCLC patients showed that as many as 20 samples (100%) were within normal limits and did not show an increased. **Conclusion:** Levels of IL-6 increased as many as 15 samples (75%), and IL-6 levels were still within the normal range sample (25%). Tumor marker are not meant to detect marker growth, but only as a marker that found in lung cancer,but IL-6 as the one of the pro-inflammation cytokines that shows an increased in patients NSCLC.

Keywords: biomarker lung cancer, IL-6, NSCLC, prognostic, SCC-Ag

1. Introduction

Lung cancer is the leading cause of malignancy in the world, accounting for up to 13 percent of all cancer diagnoses [1-5]. In the United States, there were an estimated 213,380 new cases in 2007, 160,390 deaths from lung cancer [6-9]. Currently, China has the highest incidence and mortality rate due to lung cancer, with an increasing number of younger patients affected compared to the past 20 years. According to Globocan, in 2020, Indonesia has reported 396,914 new cancer cases with a death rate of 234,5114. The incidence of cancer in Indonesia (136.2/100,000 population) ranks 8th in Southeast Asia, while in Asia, it is 23rd [10].

In recent years, tumor markers with potential utility in the clinical management of various neoplasias have emerged. Serum tumor markers are frequently used for cancer screening and as a measure of the effectiveness of treatment. They are non-invasive diagnostic tools for malignant tumors. NSE and proGRP are useful

indicators of small cell lung carcinoma. CEA, SCC-Ag, CYFRA21-1, SLX, and CA19-9 are frequently used for screening for non-small cell lung cancer (NSCLC), and 77% of patients with NSCLC had at least one positive marker from CEA, SCC, or CYFRA21-1 [11]. Squamous cell carcinoma antigen (SCC-Ag) remains a commonly used tumor marker for monitoring non-small cell lung cancer (NSCLC), although recent publications discourage its routine usage due to its limited sensitivity. Squamous cell carcinoma (SCC) antigen, a subfraction of the TA-4 antigen, is a glycoprotein secreted by various tumours, including those of the lung [13].

Squamous cell carcinoma antigen (SCC-Ag), a novel tumor marker that has been effectively used for cervical squamous cell carcinoma (SCC) diagnosis and recurrence detection, has recently been the subject of research by certain scientists. According to the initial findings, SCC-Ag has a strong specificity for lung SCC and may be helpful in monitoring and managing the disease's course of treatment [2]. Theodoros et al. reported the prognostic significance of the postoperative decrease in the SCC-Ag level. The hazard ratio of 0.144 (95% CI 0.074–0.281) shows that the greater the postoperative decrease in the SCC-Ag level, the greater is the probability of surviving. In fact, a smaller decrease in the SCC-Ag level by 1 ng/ml would approximately decrease seven-fold the probability of surviving, whereas a higher preoperative SCC-Ag level (by 1 ng/ml) would decrease it six-fold [26]. Chronic inflammation is associated with lung cancer carcinogenesis.

Pro-inflammatory cytokines are associated with lung cancer incidence. One such pro-inflammatory cytokine is interleukin 6 (IL-6) which is expressed in pre-malignant epithelial cells, and its expression is associated with poor prognosis in lung cancer patients [4]. IL-6 is one of these cytokines which involves immunological response, inflammation, hematopoiesis, and even the growth and death of certain malignancies [21]. It also plays a significant role in the body's reaction to injury or infection [6]. A substantial decrease in lung cancer survival was linked to serum IL-6 levels (≥4.0 pg/mL) in both Caucasians and African Americans [5]. Poor prognosis in NCSLC patients was significantly correlated with high serum IL-6 concentrations, according to a meta-analysis of nine studies with a total of 1291 patients [15].

2. Methods

This was a study of descriptive design, with total sampling conducted from oncology clinic and inpatient clinic at USU Hospital, Adam Malik Hospital and St. Elisabeth Hospital Medan. This research will be conducted after being approved by the Research Ethics Committee of the Faculty of Medicine, USU/RSUP H. Adam Malik Medan. All the subjects signed a written consent form. The research experimental protocol was carried out in strict accordance with the applicable guidelines. Patients who participated in this study were diagnosed with non-small cell lung cancer confirmed by cytology and histopathology examination from December 2022 - December 2023. Numbers of sample was 20 samples. Data collected included sex, age, smoking status, family history of cancer, type of non-small cell lung carcinoma, terminal staging, status performance, SCCA, IL-6.

Inclusion criteria were patients with cytologically and histopathologically confirmed lung cancer patients aged >35 years, lung cancer patients who have PS1 or ECOG I status performance without any comorbidities and complicating factors such as SVCS and massive pleural effusion, willing to participate in the study and sign the informed consent. Exclusion criteria were patients with comorbidities and complicating factors such as SVCS and massive pleural effusion, samples that have errors or damage during examination, ranging from unrepresentative specimens to errors in staining. Patients who had signed the informed consent were interviewed according to the Global Health Status questionnaire.

Due to its critical significance in the diagnosis and prognosis of SCCs and other disorders, regular clinical SCC-Ag testing has become more necessary. In this study, ELISA platform (semi-quantitative) was used to rate Squamous Cell Carcinoma Antigen and IL-6 serum. ELISA, a test based on antigen–antibody reaction and color change to identify protein levels, used to be the most common method for detecting SCC-Ag.

ELISA is insufficient to satisfy clinical demands because of its drawbacks, which include poor detection efficiency, a restricted linear range, poor reproducibility, and laborious experimental techniques [3]. The normal value of SCC-Ag is 0-2ng/ml, this value is in accordance with research conducted by Jiezhou Li in 2021 which states that serum levels >2ng/ml are markers of Squamous Cell Carcinoma [9]. Measurement of IL-6 levels or concentrations was performed using the ELISA method with cutt of levels 0-5,9pg/ml. Research conducted by Ludkk which states that serum IL-6 levels are higher in lung cancer. This is due to inflammatory stress that produces inflammatory cytokines IL-6 participates in tumourigenesis by acting directly on lung epithelial cells through nuclear factor kappa B-subunit1 (NFKB1) signalling which stimulates proliferation, migration and invasion of cancer cells.

The data collected will be analysed descriptively to see the frequency distribution of the variables studied. It aims to determine the development of a particular physical facility or the frequency of occurrence of a particular aspect of a phenomenon, and to describe a particular phenomenon in detail. All samples with

informed consent from patients were examined after permission was obtained from the Ethics Committee of H.Adam Malik General Hospital, USU Hospital and St. Elisabeth Hospital Medan (Fig. 1).

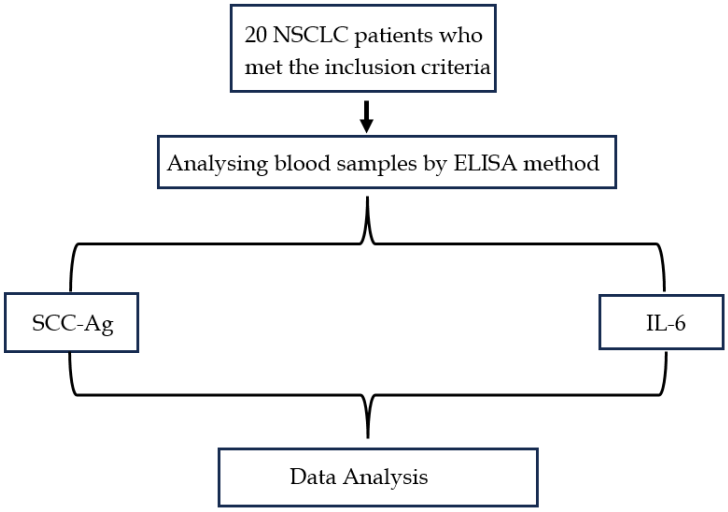

Figure 1. Research Flow

3. Results

The demographic characteristics of the patients are shown in Table 1. Male sex was more frequently found in Non-Small Cell Lung Cancer and no female patients were found. Based on age were mostly 41-60 years old (55%), followed by age above >60 years old (45%). Based on smoking status, it shows that most patients with Non-Small Cell Lung Cancer are active smokers.

Table 1. Patient Characteristic

	Characteristic	n=20	%
Sex	Male	20	100
	Female	0	0
Age Group	<40 years old	0	0
	41-60 years old	11	55
	>60 years old	9	45
Smoking Status	Active Smoker	16	80
	Non Smoker	4	20
Type of Histology	Adenocarcinoma	12	60
	Squamous cell carcinoma	7	35
	Large cell carcinoma	1	5
TNM Staging	IIIA	2	10
	IIIB	2	10
	IIIC	2	10
	IVA	14	70

Based on the type of histology, most patients with Non-Small Cell Lung Cancer (NSCLC) are Adenocarcinoma as many as 12 samples (60%), 7 samples (35%) Squamous Cell Carcinoma and only 1 sample (5%) Large Cell Carcinoma (Tab 1-3). According to the cancer stage distribution data, most of the study subjects were in stage IV as many as 14 samples (70%).

Table 2. Distribution of Research Samples Based on SCC-Ag Levels of NSCLC Patients

	SCC-Ag Values	n=20	%
Normal	0-2ng/ml	20	100
Abnormal	>2ng/ml	0	0
Total		20	100

Based on the results of the study, the SCCA value showed that as many as 20 samples (100%) SCC-Ag levels were within normal limits and did not show an increase, but the IL-6 levels of NSCLC patients showed 15 samples (75%), and IL-6 levels that were still in the normal range were 5 samples (25%).

Table 3. Distribution of Research Samples Based on IL-6 Levels of NSCLC Patients

	IL-6 Values	n=20	%
Normal	0-5.9pg/ml	5	25
Abnormal	>5.9pg/ml	15	75
Total		20	100

4. Discussion

It is known that lung cancer is closely related to age group >40 years old and the results of this study are similar to lung cancer research in the UK where which, between 2007 and 2009, an average of three-quarters of lung cancer cases were diagnosed in people of the same lung cancer cases were diagnosed in people in the same age group, with age-specific age-specific incidence rates rise sharply from the age of 40 years, peaking at 80-84 years [8]. This is likely due to the fact that exposure to carcinogens carcinogenic substances requires a long time to cause an imbalance between oncogene between the function of oncogenes and suppressor genes in the process of cancer cell growth and development. cancer cells [23].

Based on smoking status, it shows that most non-small cell carcinoma lung cancer patients are active smokers, namely 16 samples (80%) and only 4 samples (20%) who have never smoked. In accordance with several previous studies which state that the risk of lung cancer in smokers is 20-40 times higher than that of non-smokers. Of the samples who did not smoke, it may be due to prolonged exposure to carcinogenic substances at a young age and a decrease in the ability of the immune system in old age, which allows carcinogens to cause lung cancer. ability of the immune system in old age, which allows carcinogenesis [20]. Quitting smoking after a diagnosis of NSCLC significantly improves survival rates. A study found that patients who quit smoking had a median survival of 659 days compared to 348 days for those who continued to smoke [6].

Based on the type of histology, patients with Lung Cancer type Non Small Cell Lung Cancer (NSCLC) is the most common type of lung cancer, adenocarcinoma as many as 12 samples (60%), 7 samples (35%) of lung cancer type squamous cell carcinoma and only 1 sample (5%) of lung cancer of the type of large cell carcinoma. The results of this study are the same as the research conducted by Mong and Mong and colleagues found that the most histological type of lung cancer was adenocarcinoma 67,9% [18]. In 2004, the most common histology type at Friendship Hospital was adenocarcinoma. The most common histology type was adenocarcinoma 80% [21]. The increase in the percentage of The increase in the percentage of adenocarcinoma occurred due to a change in the type of cigarette to low tar filter cigarettes where filter cigarettes are less effective at filtering out small particles so that these particles enter the airway so that these particles enter the distal airway [24].

According to the cancer stage distribution data, most of the study subjects were in stage IV. Similar results were also found in SanchezLara's study. This is following the prevalence of advanced lung cancer which is higher than the early stages because in the early stages, the prevalence of lung cancer is higher than the prevalence of early stages. lung cancer because in the early stages, lung cancer often shows no symptoms or lung cancer is often asymptomatic or shows non-specific symptoms, so that the lung cancer is only diagnosed when it is advanced [18].

Based on age group, most lung cancer patients came from age 41-60 years (55%) followed by age >60 years (45%). The normal value of SCC-Ag is 0-2ng/ml, this value is in accordance with research conducted by Jiezhou Li in 2021 which says that serum levels >2ng/ml are markers of Squamous Cell Carcinoma. However, from this study based on the SCC-Ag value, it shows that as many as 20 samples (100%) SCC-Ag levels are within normal limits and do not show an increase. This is in line with Yongchang Yang's study in 2023 that there was no statistically significant difference in serum SCC-Ag levels between the two, lung cancer

group and benign lung disease group, because SCC-Ag has the lowest sensitivity level (8.8%, 11.3%, and 8.6% in SC, AC, and SCC, respectively) and the lowest Youden index (0.01), it may not be a reliable marker for diagnosing lung cancer [30].

Likewise, in the Kagohashi study, SCC-Ag showed a sensitivity of only 13.0% in metastatic patients, which was significantly lower than that of CYFRA21-1, another tumor marker used for NSCLC. in a study involving 400 NSCLC patients, elevated levels of SCC-Ag were found in 29.6% of patients, with a sensitivity of only 13.0% for NSCLC, suggesting limited diagnostic utility [10]. Nonetheless, due to its significantly low sensitivity, it is better to use SCC-Ag together with CYFRA21-1, which is also specific for lung cancer.

Squamous Cell Carcinoma Antigen (SCC-Ag), a tumor-specific antigen, was first isolated by Kato and Torigoe from squamous cell carcinoma tissue (KSS) tissue of the cervix in the 1970s. [11] SCC-Ag consists of two highly homologous isoforms, SCCA1 and SCCA1. Isoforms, SCCA1 and SCCA2, encoded by the SERPINB3 and SERPINB3 genes, respectively. SERPINB3 and SERPINB4 genes, and are located on the long arm of chromosome. SCCA1 and SCCA2, also called SERPINB3 and SERPINB4, belong to the serine protease inhibitor (SERPINBs) family and consist of an ovalbumin-like domain with nine α-helices and three β-sheets sheets, as well as a reactive center loop that is essential for binding and inhibit the target protease [25].

Meanwhile, IL-6 levels of NSCLC patients showed an increase of 15 samples (75%), and IL-6 levels that were still in the normal range were 5 samples (25%). The same results were also obtained by research conducted by Ludkk which stated that IL-6 serum levels were higher in lung cancer. Studies have shown that NSCLC patients with higher baseline IL-6 levels tend to have a poorer response to chemoimmunotherapy. These patients often show progressive disease and shorter progression-free survival (PFS) and overall survival (OS) compared to those with lower IL-6 levels. The predictive value of IL-6 was confirmed with an area under the curve (AUC) of 0.677, demonstrating its potential as a prognostic marker [29].

Elevated IL-6 levels are associated with poorer performance status and increased risk of progressive disease in patients with severe lung cancer. IL-6 is a multifunctional cytokine that influences various biological processes, including immune response, inflammation, and cancer progression. In the context of lung cancer, high levels of IL-6 correlate with malnutrition, poor performance status, and shorter survival, making it a significant prognostic marker of cancer progression. Monitoring IL-6 levels can be critical to improving prognosis and tailoring treatment strategies [1]. This is caused by inflammatory stress that produces inflammatory cytokine IL-6 participating in tumorigenesis by acting directly on lung epithelial cells through nuclear factor kappa B-subunit1 (NFKB1) signaling that stimulates proliferation, migration, and invasion of cancer cells [17].

IL-6 levels may serve as a predictive biomarker for NSCLC treatment outcomes. High IL-6 expression correlates with shorter PFS and OS, and is associated with upregulation of the adenosine pathway, which contributes to immune evasion [19]. IL-6 is identified as a key cytokine that influences the response to immune checkpoint inhibitors (ICIs) in non-small cell lung cancer (NSCLC). Patients with lower baseline levels of IL-6 in plasma or tumor tissue tend to benefit more from ICIs. IL-6 increases PD-L1 expression in tumors through the JAK1/STAT3 pathway, leading to immune evasion. This suggests that high levels of IL-6 may contribute to resistance to ICI [16]. IL-6 contributes to an immunosuppressive tumor microenvironment by promoting the infiltration of myeloid-derived suppressor cells, M2 macrophages, and regulatory T cells, while reducing the presence of CD8+ T cells. This environment favors tumor growth and resistance to immunotherapy [16].

5. Conclusion

In conclusion, SCC-Ag has limited sensitivity for diagnosing NSCLC, while IL-6 shows greater potential as a biomarker for prognosis and therapy management. The combination of biomarkers, such as SCC-Ag, CYFRA21-1, and IL-6, may provide better diagnostic accuracy and therapeutic prediction for lung cancer patients.

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 received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, under approval number 1107/KEPK/USU/2023.

8. Author Contributions

Each author has made substantial contributions to this study, including conceptualization, study design, implementation, data collection, analysis, and interpretation. All authors have participated in drafting, revising, and critically reviewing the manuscript. They have provided final approval of the version to be published and have been involved in the decision regarding the journal for submission. Furthermore, all authors agree to take full responsibility for every aspect of the work.

9. Funding

This research did not receive any external funding.

10. Acknowledgements

The authors would like to thank the USU Hospital, Adam Malik Hospital and St. Elisabeth Hospital Medan for their contributions to this research.

11. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

[1] An J, Gu Q, Cao L, Yang H, Deng P, Hu C, et al. Serum IL-6 as a vital predictor of severe lung cancer. Ann Palliat Med. 2021;10(1):20209. Available from: https://doi.org/10.21037/apm-20-2229.

[2] Body JJ, Sculier JP, Haymakers N, Paesmans M, Ravez P, Libert P, et al. Evaluation of squamous cell carcinoma antigen as a new marker for lung cancer. Cancer. 1990;65:1552–6. Available from: https://doi.org/10.1002/1097-0142(19900401)65:7<1552::aid-cncr2820650717>3.0.co;2-d

[3] Crombach G, Scharl A, Vierbuchen M, Wurz H, Bolte A. Detection of squamous cell carcinoma antigen in normal squamous epithelia and in squamous cell carcinomas of the uterine cervix. Cancer. 1989;63:1337–42. Available from: https://doi.org/10.1002/1097-0142.

[4] Davalos AR, Coppe JP, Campisi J, Desprez PY. Senescent cells as a source of inflammatory factors for tumor progression. Cancer Metastasis Rev. 2010;29(2):273–83. Available from: https://doi.org/10.1007/s10555-010-9220-9

[5] Enewold L, Mechanic LE, Bowman ED, et al. Serum concentrations of cytokines and lung cancer survival in African Americans and Caucasians. Cancer Epidemiol Biomarkers Prev. 2009;18(1):215–22. Available from: https://doi.org/10.1158/1055-9965.EPI-08-0705.

[6] Gemine RE, Davies GR, Lanyon K, Rees SE, Campbell I, Lewis KE, et al. Quitting smoking improves two-year survival after a diagnosis of non-small cell lung cancer. Lung Cancer. 2023;186:107388. Available from: https://doi.org/10.1016/j.lungcan.2023.107388.

[7] Hong DS, Angelo LS, Kurzrock R. Interleukin-6 and its receptor in cancer. Cancer. 2007;110(9):1911–28. Available from: https://doi.org/10.1002/cncr.22999.

[8] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60(5):277–300.

[9] Jiezhou L, Yangqing C, Xiandao W, Chan W, Meifang X. The value of combined detection of CEA, CYFRA21-1, SCC-Ag, and pro-GRP in the differential diagnosis of lung cancer. Original Article. 2021;10. Available from: https://doi.org/10.21037/tcr-21-527.

[10] Kagohashi K, Satoh H, Ishikawa H, Ohtsuka M, Sekizawa K. A re-evaluation of squamous cell carcinoma antigen (SCC) as a serum marker for non-small cell lung cancer. Med Oncol. 2008;25:187–9. Available from: https://doi.org/10.1007/s12032-007-9021-3.

[11] Kato H, Torigoe T. Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. Cancer. 1977;40(4):1621–8. Available from: https://doi.org/10.1002/1097-0142(197710)40:4<1621::aid-cncr2820400435>3.0.co;2-i.

[12] Katsunori K, et al. A re-evaluation of squamous cell carcinoma antigen (SCC) as a serum marker for non-small cell lung cancer. Med Oncol. 2008;25:187–9. Available from: https://doi.org/10.1007/s12032-007-9021-3.

[13] La Vecchia C, Franceschi S, Levi F. Epidemiological research on cancer with a focus on Europe. Eur J Cancer Prev. 2003;12(1):5–14. Available from: https://doi.org/10.1097/00008469-200302000-00003.

[14] Lai RS, Hsu HK, Lu JY, Ger LP, Lai NS. Cyfra 21-1 enzyme-linked immunosorbent assay: Evaluation as a tumour marker in non-small cell lung cancer. Chest. 1996;109:995–1000. Available from: https://doi.org/10.1378/chest.109.4.995.

[15] Liao C, Yu Z, Guo W, et al. Prognostic value of circulating inflammatory factors in non-small cell lung cancer: a systematic review and meta-analysis. Cancer Biomark. 2014;14(6):469–81. Available from:

https://doi.org/10.3233/CBM-140423.
[16] Liu C, Yang L, Xu H, Zheng S, Wang Z, Wang S, et al. Systematic analysis of IL-6 as a predictive biomarker and desensitizer of immunotherapy responses in patients with non-small cell lung cancer. BMC Med. 2022;20(1):187. Available from: https://doi.org/10.1186/s12916-022-02356-7.
[17] Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. Mol Cancer Res. 2006;4(4):221–33. Available from: https://doi.org/10.1158/1541-7786.MCR-05-0261.
[18] Mong C, Garon EB, Fuller C, Mahtabifard A, Mirocha J, Mosenifar Z, et al. High prevalence of lung cancer in a surgical cohort of lung cancer patients a decade after smoking cessation. J Cardiothorac Surg. 2011;6:1–7. Available from: https://doi.org/10.1186/1749-8090-6-19.
[19] Naqash AR, McCallen JD, Mi E, Iivanainen S, Marie MA, Gramenitskaya D, et al. Increased interleukin-6/C-reactive protein levels are associated with the upregulation of the adenosine pathway and serve as potential markers of therapeutic resistance to immune checkpoint inhibitor-based therapies in non-small cell lung cancer. J Immunother Cancer. 2023;11(10). Available from: https://doi.org/10.1136/jitc-2023-007310.
[20] Purnamawati P, Tandrian C, Sumbayak EM, Kertadjaja W. Tinjauan pustaka: analisis kejadian kanker paru primer di Indonesia pada tahun 2014–2019. J Kedokteran Meditek. 2021;27(2):164–72.
[21] Sánchez-Lara K, Turcott JG, Juárez E, Guevara P, Núñez-Valencia C, Oñate-Ocaña LF, et al. Association of nutrition parameters including bioelectrical impedance and systemic inflammatory response with quality of life and prognosis in patients with advanced non-small-cell lung cancer: a prospective study. Nutr Cancer. 2012;64(4):526–34. Available from: https://doi.org/10.1080/01635581.2012.668744.
[22] Seike M, Yanaihara N, Bowman ED, Zanetti KA, Budhu A, Kumamoto K, et al. A cytokine gene signature of the lung adenocarcinoma and its tissue environment predicts prognosis. J Natl Cancer Inst. 2007;99(16):1257–69. Available from: https://doi.org/10.1093/jnci/djm083.
[23] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics. CA Cancer J Clin. 2023;73(1):17–48.
[24] Simonato L, Agudo A, Ahrens W, Benhamou E, Benhamou S, Boffetta P, et al. Lung cancer and cigarette smoking in Europe: an update of risk estimates and an assessment of inter-country heterogeneity. Int J Cancer. 2001;91(6):876–87. Available from: https://doi.org/10.1002/1097-0215
[25] Sun Y, Sheshadri N, Zong WX. SERPINB3 and B4: From biochemistry to biology. Semin Cell Dev Biol. 2017:170–7.
[26] The Ministry of Health of The Republic of Indonesia. Cancer in Indonesia ranks 8th in Southeast Asia and 23rd in Asia (Penyakit Kanker di Indonesia Berada Pada Urutan 8 di Asia Tenggara dan Urutan 23 di Asia). [Internet]. 2020 [cited 2021 Feb 16].
[27] Theodoros V, Theodoros T, Christina S, Panagiotis Z, Paraskevi K, Dimitrios P, et al. Diagnostic and prognostic significance of squamous cell carcinoma antigen in non-small cell lung cancer. Lung Cancer. 2001;32:137–44.
[28] Wingo PA, Ries LAG, Giovino GA, Miller DS, Rosenberg HM, Shopland DR, et al. Annual report to the nation on the status of cancer, 1973–1996, with a special section on lung cancer and tobacco smoking. J Natl Cancer Inst. 1999;91(8):675–90.
[29] Yang Y, Chang S, Wang N, Song P, Wei H, Liu J. Clinical utility of six serum tumor markers for the diagnosis of lung cancer. iLABMED. 2023;1(2):132–41.
[30] Yang L, Liu C, Yang G, Hao X, Zhang S. IL-6 triggers chemoimmunotherapy resistance by creating immunosuppressive tumor microenvironment in non-small cell lung cancer. Ann Oncol. 2023;34(Suppl 1):S831.