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RESEARCH ARTICLE

The clinical value of systemic immune-inflammation index (SII) and prognostic nutritional index (PNI) for predicting the occurrence of metastasis in patients with lung cancer

Verna Biutifasari [1], Ellen Angelique Hardjono [2], Ronald Pratama Adiwinoto [3], Janto Poernomo Hadi [4]

[1]Department of Clinical Pathology, Faculty of Medicine, Hang Tuah University, Surabaya, Indonesia
[2]Faculty of Medicine, Hang Tuah University, Surabaya, Indonesia
[3]Department of Public Health, Faculty of Medicine, Hang Tuah University, Surabaya, Indonesia
[4]Department of Pulmonology, Naval Center Hospital Dr. Ramelan Surabaya, Indonesia

Correspondence:
Verna Biutifasari
Department of Clinical Pathology, Faculty of Medicine Hang Tuah University, Surabaya – 60244, Indonesia

Email: biutifasari.verna@hangtuah.ac.id

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Abstract

Systemic immune-inflammation index (SII) and prognostic nutritional index (PNI) serve as simple and practical tests that help indicate inflammatory and nutritional status to some extent. Lung cancer stands out as the most common contributor to cancer-related mortality globally. It is associated with an unfavorable prognosis. Most patients diagnosed with lung cancer have metastasis at the time of diagnosis. Prognostic heterogeneity of cancer patients causes the need for more prognostic biomarkers. This study aimed to evaluate the clinical value of SII and PNI in predicting metastasis in lung cancer patients. SII and PNI provides a prognostic value in lung cancer. Retrospective cross-sectional research was conducted in this study involving 138 data from medical records at the Inpatient and Outpatient Department of Pulmonology, RSPAL dr. Ramelan Surabaya in April 2019 to July 2023. Kolmogorov-Smirnov test, contingency coefficient test, and ROC analysis were done to analyze the data obtained. Patients with metastatic lung cancer had higher SII than those without metastasis. The group of patients with metastasis had an average SII of 5391.34 and a PNI of 40.11. The group of patients without metastasis had an average SII of 2849.52 and PNI of 43.05. Lung cancer metastasis was correlated significantly with SII but not with PNI. The cut-off value was determined using the ROC curve. The cut-off value for SII was 2198.54 (68.5% sensitivity and 58.7% specificity) and for PNI was 42.2 (62% sensitivity and 54.3% specificity). SII was correlated with lung cancer metastasis and may be a promising indicator predicting of metastasis. PNI showed no significant correlation with lung cancer metastasis.

1. INTRODUCTION

Lung cancer is recognized as the primary cause of cancer-related deaths, holding the highest incidence among cancer fatalities (1). Lung cancer is infrequent before the age of 40, with incidence rates rising steadily until the age of 80. The lifetime risk of developing lung cancer, which is the probability that an individual will develop the disease at some point in their life, is approximately 8% for males and 6% for females (2). In 2018, an estimated 2.1 million new cases of lung cancer were diagnosed, representing 12% of the global cancer burden. Lung cancer remains the most frequently diagnosed cancer among men, with approximately 1.37 million cases that year. The highest incidence rates were reported in regions such as Micronesia (54.1 per 100,000), Polynesia (52.0 per 100,000), Central and Eastern Europe (49.3 per 100,000), and Eastern Asia (47.2 per 100,000). Among women, lung cancer incidence is generally lower, with over 725,000 new diagnoses in 2018. While the incidence rate in men has been declining since the mid-1980s, it only began to decrease

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for women in the mid-2000s, reflecting historical differences in smoking patterns and cessation rates between sexes. Globally, lung cancer is the leading cause of cancer-related death among men and the second leading cause among women (3). In 2018, it accounted for approximately 1.8 million deaths worldwide–1.2 million in men and 576,100 in women—constituting 20% of all cancer-related deaths. Socioeconomic status plays a significant role in lung cancer risk factors, such as tobacco use. Individuals with lower socioeconomic status are more likely to take up smoking and face challenges in quitting. Occupational exposure to carcinogens contributes to an estimated 5–10% of lung cancer cases, with asbestos historically being the most common exposure (1,4,5). Chronic obstructive pulmonary disease (COPD), encompassing conditions like emphysema and chronic bronchitis, is an irreversible inflammatory disorder that narrows small airways and damages alveolar walls. The persistent cycle of injury and repair in the bronchi due to chronic inflammation plays a crucial role in lung cancer development (5). Similarly, asthma has been suspected as a potential risk factor for lung cancer because inflammation is central to the disease's pathogenesis. Tuberculosis, which induces chronic inflammation and pulmonary fibrosis, may also increase lung cancer risk through mechanisms such as genetic alterations and mutations. Indonesia, second only to India, bears one of the highest tuberculosis burdens globally (3,5).

The prevalence of cancer in Indonesia is increasing. Lung cancer remains a significant health challenge in Indonesia. It is among the leading causes of cancer-related deaths, primarily influenced by high smoking rates, which are the highest globally among males. Approximately 70% of lung cancer cases are diagnosed at advanced stages, where treatment options are more limited, leading to poorer outcomes (3). The most recent Globocan data from 2020 shows an increase in new cancer cases to 141.1 per 100,000 people, with cancer-related deaths reaching 85.1 per 100,000 people. Lung cancer is the second most common cause of cancer-related deaths after breast cancer in Indonesia, reaching 15.9% (4). Efforts to address this burden include introducing a national lung cancer screening program for high-risk groups in 2023. This program targets individuals over 45 years old with a smoking history or a family history of lung disease. Despite these initiatives, challenges such as limited access to radiotherapy, a shortage of oncology specialists, and rural-urban disparities in healthcare persist (3).

Non-small cell lung cancer (NSCLC) accounts for approximately 80%–85% of all lung cancer cases. While its incidence has steadily increased over recent decades, the mortality rate has declined, likely due to significant advancements in treatment options. NSCLC treatments include surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy (1). However, the effectiveness of these therapies remains limited, mainly due to the absence of reliable markers to predict disease progression and the prevalence of chemoresistance. Small cell lung cancer (SCLC), a highly aggressive malignancy, represents about 15% of lung cancer cases and is responsible for over 200,000 deaths annually. Strongly linked to smoking, SCLC is characterized by its high metastatic potential and is typically classified into limited-stage (LS-SCLC) and extensive-stage (ES-SCLC) disease (1,6). At diagnosis, around 70% of patients present with ES-SCLC. The prognosis for SCLC remains poor, with 1-year and 2-year overall survival (OS) rates of 58% and 21%, respectively, for LS-SCLC, and 29.4% and 7%, respectively, for ES-SCLC. Standard treatment for LS-SCLC involves a combination of surgery, radiation, and systemic therapy. Surgical resection is recommended for eligible early-stage (I-IIA) patients after confirming the absence of nodal involvement through pathologic mediastinal staging. For patients with stage IIB-IIIC disease, concurrent platinum-based chemotherapy and radiotherapy are the standard approaches. Despite progress over the past decades, survival rates for SCLC have shown minimal improvement. Consequently, identifying novel and reliable biomarkers to predict metastasis in both NSCLC and SCLC remains a critical need (7,8).

In recent years, several indicators reflecting the body's inflammatory state have been shown to correlate with the prognosis of various malignant tumors (9,10). Among these, the systemic immune-inflammation index (SII) has been identified as an objective measure of the balance between inflammatory and immune responses in cancer patients. SII has been recognized as a significant prognostic biomarker for multiple cancers, including hepatocellular carcinoma (HCC), gastric cancer, pancreatic cancer, endometrial cancer, non-small cell lung cancer (NSCLC), and bladder cancer. Additionally, recent studies have explored the prognostic significance of SII in small-cell lung cancer (SCLC); however, the findings remain inconclusive. SII is an inflammatory marker derived from a complete blood count of platelets, neutrophils, and lymphocytes. SII = platelet count ×neutrophils/ lymphocytes. Prior research has confirmed that SII can indicate the balance between immune response and inflammatory response in individuals with cancer (11).

The prognostic nutritional index (PNI), introduced in 1980, evaluates patients' nutritional and immune status by combining serum albumin levels and peripheral blood lymphocyte counts (2,12). Proposed initially to assess prognosis in patients with gastrointestinal cancers, liver cirrhosis, and chronic renal failure, PNI has since been widely used as a marker of nutritional health and a prognostic indicator in various cancers, including esophageal carcinoma, gastric carcinoma, pancreatic cancer, and hepatocellular carcinoma. Inflammatory responses in cancer patients strongly link to albumin and lymphocyte levels, while malnutrition affects 30%–80% of individuals with malignancies (2,10,12–14). Cancer-associated malnutrition often results from dysbiosis, reduced food intake, impaired nutrient metabolism, increased resting energy expenditure, and elevated cytokine levels. Malnutrition in cancer patients results from a complex mechanism involving both the tumor and host response to the tumor. Hypoalbuminemia, commonly observed in advanced cancer patients, is considered a hallmark of malnutrition and cachexia. Hypoalbuminemia can cause downregulation of the immune system, which leads to extensive proliferation of cancer cells. Emerging evidence suggests that sustained inflammation, originating

from the tumor or as a host response, partly drives cancer cachexia. This inflammatory state contributes to malnutrition, poor performance, and increased mortality. The PNI's predictive value for surgical outcomes is well-established in esophageal, colorectal, liver, and pancreatic cancers. However, its utility as a biomarker for lung cancer remains inconclusive. Several mechanisms may explain the association between low PNI and poor prognosis in lung cancer. Serum albumin, a key component of PNI, is an essential indicator of nutritional status. Studies have linked hypoalbuminemia with reduced quality of life, shorter life expectancy, immunosuppression, and loss of muscle mass in cancer patients. Recent studies further demonstrated that hypoproteinemia contributes to malnutrition and weight loss, leading to poorer outcomes and increased cancer-related mortality (8,10,13,15,16).

Additionally, inflammation and the immune system play pivotal roles in cancer development and progression. Peripheral blood lymphocytes reflect systemic inflammation and are critical for cell-mediated immune responses (9,11). A low PNI, indicative of poor nutritional and immune status, underscores the importance of inflammation and immune dynamics in determining cancer prognosis. PNI is an index that combines the albumin levels and total lymphocyte count. It was reported that PNI could reflect cancer patients' immunological and nutritional status (10,16–18).

Inflammation in a variety of tumor types is linked to a poor prognosis. Inflammation is considered a key factor in tumor progression, provides bioactive molecules to the tumor microenvironment, and the product of the inflammatory processes can be considered potential biomarkers. Hematological inflammation parameters (neutrophil, monocyte, lymphocyte, and platelet) hold predictive value for the prognosis of tumors since those reflect the immune status (6,17,19). Metastasis in lung cancer is a multifaceted process. Proinflammatory cytokines and various inflammatory cells are activated at the beginning of tumorigenesis. These mechanisms contribute to the formation of new blood vessels and lymphatic ducts, which are advantageous for the differentiation and growth of tumor cells. The cells must establish a vascular supply to obtain nutrients and oxygen to facilitate tumor growth. Tumor cells must evade lymphocytic attacks to move within the stroma. In addition, they need to adapt to a migratory cell structure to facilitate movement (1,4). Cancer-related inflammation can weaken the immune function at a later stage. Therefore, these markers are expected to serve as valuable prognostic biomarkers in the progression of cancer. Albumin (ALB) reflects the nutrition status correlating with cancer prognosis (2,17).

Tissue sampling is required to confirm a diagnosis in all patients with suspected lung cancer (3). In patients with suspected metastatic disease, a biopsy of a distant disease site is preferred for tissue confirmation. Given the greater emphasis placed on molecular testing for NSCLC patients, a core biopsy is preferred to ensure adequate tissue for analysis. Tumor tissue may be obtained via bronchial or transbronchial biopsy during fiberoptic bronchoscopy, by fine needle aspiration (FNA), percutaneous biopsy using image guidance, or via endobronchial ultrasound (EBUS)-guided biopsy. Indonesia faces significant limitations in medical resources, particularly in the availability of advanced cancer diagnosis and treatment technologies (1,3). Many healthcare facilities lack imaging modalities, molecular diagnostic tools, and targeted therapy options, critical for accurate cancer staging and personalized treatment. Access disparities between urban and rural areas exacerbate the issue, leaving many of the people reliant on basic diagnostic methods. Additionally, the high cost of advanced technologies and limited numbers of trained specialists further hinder the timely and effective management of cancer cases nationwide. SII and PNI are much more minimally invasive, cheap, and fast compared to the biopsy to predict the occurrence of metastases in lung cancer patients, even in places with limited health facilities. The SII and PNI predictive value for cancer prognosis is widely accepted in various cancers (7,8). However, only a few reports have evaluated the significance of SII and PNI in predicting metastasis in lung cancer. Most previous studies did not include patients in the Southeast Asian region, particularly Indonesia. Despite the growing evidence supporting the prognostic utility of the SII and PNI in various malignancies, their role in predicting metastasis in lung cancer remains underexplored compared to other cancer types (7,8,14,18,20). Key research gaps include limited validation of these indices in lung cancer-specific contexts, insufficient mechanistic insights into their association with metastatic progression, and a lack of studies examining their dynamic changes during treatment. Accordingly, the primary purpose of this study was to assess the value of SII and PNI as a predictor of metastasis in lung cancer patients based on medical records.

2. MATERIALS AND METHODS

2.1. Data Collection and Definition

A retrospective observational study was conducted at the Department of Pulmonology and Respiratory in Dr Ramelan Naval Central Hospital Surabaya using data from medical records. A retrospective study design was chosen due to its time and cost efficiency in accessing historical data. The data was collcted by consecutive sampling to minimize selection bias. Consecutively, inpatients and outpatients admitted from April 2019 to July 2023 were enrolled in the study. This study encompassed 138 patients diagnosed with lung cancer. Inclusion criteria comprised individuals aged 18 or older, clinically diagnosed with lung cancer, had complete data written in medical records, had lung cancer with or without metastasis, and had results of complete blood count and albumin level. Both biopsy and CT scan established the diagnosis of lung cancer results from medical records. Exclusion criteria for the patients encompassed those with comorbidities such

as hematopoietic disorders, immune system disorders, acute or chronic infection that could affect routine laboratory examination, and those who were diagnosed with other primary cancer.

2.2. Statistical Analysis

SII and PNI were calculated using the following equation:

$$SII = \frac{\text{neutrophil count} \times \text{platelet count}}{\text{lymphocyte count}} \quad (1)$$

$$PNI = (\text{serum albumin} \times 10) + (0.005 \times \text{lymphocyte count}) \quad (2)$$

Statistical analyses for this study were conducted utilizing the SPSS statistical software, version 25, on the Windows platform. A normality test was performed on the data before performing statistical analyses. The Mann-Whitney U test was applied to evaluate significant differences in platelet counts, neutrophil counts, lymphocyte counts, SII, and PNI between lung cancer patients with and without metastasis. The contingency coefficient was used to estimate the association between parameters and metastasis in lung cancer patients. P-values < 0.05 were considered statistically significant. The optimal cut-off values for SII and PNI were determined through the Receiver Operating Characteristics (ROC) curve analysis. The selected cut-off values were those with the best sensitivity and specificity.

2.3. Ethical Clearance

This study was conducted after receiving approval from Dr. Ramelan Naval Central Hospital Surabaya, Indonesia registered under 63/EC/KEP/2023. Confidentiality of the patients' details was strictly maintained.

3. RESULTS AND DISCUSSION

3.1. Patient Characteristic

One hundred thirty-eight patients diagnosed with lung cancer were included in this study. The study included 95 male patients (68.8%) and 43 female patients (31.2%). Patients were categorized by age as follows: seven patients (5.1%) aged 30–39 years, 17 patients (12.3%) aged 40–49 years, 47 patients (34%) aged 50–59 years, 41 patients (29.7%) aged 60–69 years, 19 patients (13.8%) aged 70–79 years, and seven patients (5.1%) aged ≥80 years. The mean and mode of age were 59 and 52. The most common lung cancer type based on histology was lung adenocarcinoma. The histological types of lung cancer identified in this study were adenocarcinoma in 82 patients (59.4%), squamous cell carcinoma in 19 patients (13.8%), small cell carcinoma in 4 patients (2.9%), poorly differentiated carcinoma in 2 patients (1.5%), and unspecified carcinoma in 31 patients (22.4%). Ninety-two patients were already diagnosed with metastasis (66.7%). Smoking history and BMI were not included in the medical records obtained. The type of therapy the patients received was not fully obtained since most were referred from other hospitals. The baseline characteristics of these patients are detailed in Table 1.

Table 1. Baseline characteristics of the patient

Characteristics		Frequency (138)	Percentage (%)
Sex	Male	95	68.8
	Female	43	31.2
Age (years)	30-39	7	5.1
	40-49	17	12.3
	50-59	47	34
	60-69	41	29.7
	70-79	19	13.8
	≥ 80	7	5.1
Lung Cancer Type (based on histology)	Adenocarcinoma	82	59.4
	Squamous cell carcinoma	19	13.8
	Small cell carcinoma	4	2.9
	Large cell (undifferentiated) carcinoma	2	1.5
	Unknown	31	22.4
Metastasis	Yes	92	66.7
	No	46	33.3

The characteristics recorded were age, platelet count, neutrophil count, lymphocyte count, and albumin level. The mean platelet count in patients with metastases was 360.2 $x10^3/\mu L$, with a minimum count of 64 $x10^3/\mu L$ and a maximum of 727 $x10^3/\mu L$. In patients without metastases, the mean platelet count was 375.11 $x10^3/\mu L$, with a minimum of 76

$x10^3/\mu L$ and a maximum of 654 $x10^3/\mu L$. The mean neutrophil count in patients with metastases was 16.77 $x10^3/\mu L$, ranging from a minimum of 4.05 $x10^3/\mu L$ to a maximum of 110.48 $x10^3/\mu L$. For patients without metastases, the mean neutrophil count was 9.84 $x10^3/\mu L$, with a minimum of 0.48 $x10^3/\mu L$ and a maximum of 33.25 $x10^3/\mu L$. The mean lymphocyte count in patients with metastases was 1.4 $x10^3/\mu L$, with a minimum of 0.18 $x10^3/\mu L$ and a maximum of 4.67 $x10^3/\mu L$. In patients without metastases, the mean lymphocyte count was 1.58 $x10^3/\mu L$, ranging from a minimum of 0.23 $x10^3/\mu L$ to a maximum of 3.19 $x10^3/\mu L$. The mean albumin level in patients with metastases was 3.31 g/dL, with a minimum level of 1.78 g/dL and a maximum of 4.63 g/dL. In patients without metastases, the mean albumin level was 3.51 g/dL, ranging from a minimum of 1.70 g/dL to a maximum of 4.89 g/dL. Calculations were conducted to obtain SII and PNI levels. The mean SII count in patients with metastases was 5391.34, with a minimum of 574.66 and a maximum of 40281.17. In patients without metastases, the mean SII count was 2849.52, ranging from a minimum of 108.32 and a maximum of 12211.47. The mean PNI count in patients with metastases was 40.11, with a minimum of 25.65 and a maximum of 69.65. In patients without metastases, the mean PNI count was 43.05, ranging from a minimum of 20.7 and a maximum of 59.55. Patients with metastasis had higher SII levels and lower PNI levels. Patients' Characteristics based on metastasis are detailed in Table 2.

Table 2. Characteristics of patients based on the occurrence of metastasis

	With Metastasis	Without Metastasis
Age (years)	60 (35-81) ± 11.39	57 (36-80) ± 10.29
Platelet ($x10^3/\mu L$)	360.2 (64-727) ± 140.44	375.11 (76-654) ± 135.38
Neutrophil ($x10^3/\mu L$)	16.77 (4.05-110.48) ± 18.17	9.84 (0.48-33.25) ± 7.24
Lymphocyte ($x10^3/\mu L$)	1.4 (0.18-4.67) ± 0.74	1.58 (0.23-3.19) ± 0.68
Albumin (g/dL)	3.31 (1.78-4.63) ± 0.56	3.51 (1.70-4.89) ± 0.65
SII	5391.34 (574.66-40281.17) ± 6842.66	2849.52 (108.32-12211.47) ± 2941.81
PNI	40.11 (25.65-69.65) ± 7.29	43.05 (20.7-59.55) ± 8.6

^Mean (Maximum-Minimum) ± Standard deviation

There were 101 NSCLC patients, consisting of 82 patients with adenocarcinoma and 19 with squamous cell carcinoma. There were 4 SCLC patients. Others include two patients with large cell (undifferentiated) carcinoma and 31 patients without specified types of lung cancer. The statistical results, including the mean, minimum, maximum, and standard deviation values, are detailed in Table 2.

Table 3. Mann-Whitney U Test of Platelet, Neutrophil, Lymphocyte, SII and PNI

	Platelet	Neutrophil	Lymphocyte	SII	PNI
Significance	0.455	**0.003**	0.428	**0.000**	0.344

Based on the Mann-Whitney U test results in lung cancer patients, significant differences between the metastatic and non-metastatic groups were observed in neutrophil levels and the Systemic Immune-Inflammation Index (SII). However, no significant differences were found in platelet counts, lymphocyte counts, or the Prognostic Nutritional Index (PNI). These findings are consistent with previous research that has reported higher SII values in patients with metastatic disease compared to non-metastatic groups (7–10,21). However, unlike some earlier studies that found significant differences in PNI between metastatic and non-metastatic patients, our results did not show such associations (2,10,12–14).

Table 4. SII and PNI of patients based on cancer type

	NSCLC	SCLC	Others
SII	4723.05 (108.32-40281.17) ± 6405.12	1849.9 (778.69-3251.39) ± 1227.3	4322.85 (851.38-21942) ± 4701.79
PNI	41.15 (20.7-69.65) ± 8.29	43.93 (32.15-49.85) ± 8.27	40.5 (29.45-56.8) ± 6.41

The correlation between SII and the occurrence of metastasis in lung cancer patients was evaluated using a contingency coefficient. There was a significant correlation between SII and the incidence of metastasis in lung cancer patients ($p<0.05$). In contrast, no notable correlation was found between the PNI and the occurrence of metastasis ($p>0.05$). Previous studies investigating the prognostic value of the Systemic Inflammatory Index (SII) and Prognostic Nutritional Index (PNI) in lung cancer patients have reported varied results due to differences in the cut-off values applied. The optimal cut-off values for SII and PNI were calculated using the receiver operating characteristics (ROC) curve analysis. The optimal cut-off values were 2198.54 for SII and 42.20 for PNI. As a result, patients were divided into low or high groups for further analysis based on the optimal cut-off values [SII ≤ 2198.54 (low) and SII > 2198.54 (high); PNI ≤ 42.2 (low) and PNI > 42.2 (high)].

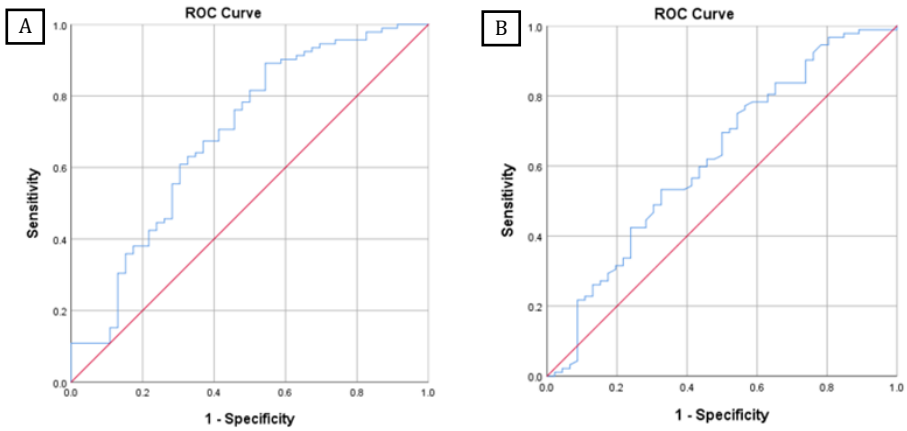

Figure 1. ROC curve to compare the performance of SII (A) and PNI (B)

Table 5. Cut-off value, sensitivity, and specificity of SII and PNI

Variable	Cut-off	Sensitivity	Specificity	AUC
SII	2198.54	68.5%	58.7%	0.692
PNI	42.20	62.0%	54.3%	0.622

Table 6. Contingency coefficient of SII and PNI

	Value	Significance (p)
SII	0.252	0.002
PNI	0.153	0.069

In a study of lung cancer patients, those with metastases and a systemic immune-inflammation index (SII) of less than 2198.54 comprised 29 patients (31.5%). In contrast, 63 patients (68.5%) had an SII of 2198.54 or greater. Among lung cancer patients without metastases, 27 patients (58.7%) had an SII below 2198.54, while 19 patients (41.3%) had an SII of 2198.54 or higher.

Our study on the prognostic nutritional index (PNI) and systemic immune-inflammation index (SII) in lung cancer patients has opened up new avenues for further research. Lung cancer patients with metastases and a PNI ≤42.2 accounted for 57 patients (62%), while those with a PNI >42.2 comprised 35 patients (38%). Among lung cancer patients without metastases, 21 patients (45.7%) had a PNI ≤42.2, while 25 patients (54.3%) had a PNI >42.2. The contingency coefficient test for SII showed a result of $p<\alpha$, indicating a significant correlation between SII and the occurrence of metastasis in lung cancer patients. Conversely, the contingency coefficient test for PNI showed a result of $p>\alpha$, indicating no significant correlation between PNI and the occurrence of metastasis in lung cancer patients. Higher SII and lower PNI are associated with the occurrence of metastasis. Our study suggests that SII is a better biomarker than PNI in predicting metastasis in lung cancer patients, and we encourage further research to explore its potential in patient prognostics due to its higher sensitivity and specificity compared to PNI.

3.2. Relationship Between SII and PNI

Lung cancer is an aggressive neoplasm associated with a significant global mortality rate. It stands as the predominant cause of cancer-related deaths. The majority of the patients that have lung cancer in this study are males. Males are more likely to develop lung cancer because of their smoking habits. The incidence rate peaked in this study's 50-59 age group. The respiratory system degenerates with several structural, physiological, and immunological changes with age.

The most prevalent type of lung cancer identified in this study is adenocarcinoma. Adenocarcinoma is the most common type of lung cancer of smokers or nonsmokers in men and women, regardless of their age. It is noted for having extensive genomic gains and losses, along with a high frequency of somatic mutations. Importantly, driver mutations that initiate tumor cells are predominantly observed in adenocarcinoma, underscoring its role in tumor initiation and maintenance. Among lung cancer subtypes, adenocarcinomas have been the most thoroughly studied in terms of recurrent genomic alterations and somatic mutations. A significant category of these alterations includes "driver mutations," which are genetic changes in signaling protein-encoding genes that play a pivotal role in tumor initiation and maintenance. Lung adenocarcinomas frequently develop due to mutations in the *EGFR* gene (1,3,5).

Furthermore, it's important to note that driver mutations in lung cancer are typically mutually exclusive, a key finding that indicates a single mutation is sufficient to drive tumorigenesis. This understanding is crucial in the context of the identified distinct subsets of lung adenocarcinomas, characterized by specific chromosomal rearrangements that lead

to aberrant activation of tyrosine kinases such as *ALK*, *ROS1*, *NTRK*, and *RET*. Notably, driver mutations are predominantly identified in adenocarcinomas. The majority of the patients included in this study present with metastasis. Lung cancer is usually asymptomatic in its initial stages and typically diagnosed at an advanced stage (3,8,22).

Numerous studies have highlighted the link between inflammation and tumor development, identifying inflammation as a key factor in promoting tumor initiation and progression (9,10,13). Inflammatory processes contribute bioactive molecules to the tumor microenvironment, making their products potential biomarkers for cancer prognosis. Inflammatory cells, including neutrophils, lymphocytes, and platelets, play a crucial role in oncogenesis and cancer development. Neutrophils play a significant role in tumor progression by secreting cytokines and chemokines, such as vascular endothelial growth factor (VEGF), to promote angiogenesis and facilitate distant metastasis. Neutrophils promote cancer cell invasion, proliferation, and metastasis (6,12,17). Conversely, lymphocytes are crucial for cancer immune surveillance, preventing tumor growth and progression. Tumor-infiltrating lymphocytes, as critical components of the tumor microenvironment, mediate antitumor immune responses by inhibiting tumor cell proliferation and metastasis. Consequently, lymphocytes are vital for immune defense against tumors. Lymphocytes are important immune system components that can suppress the proliferation and migration of cancer cells. Platelets contribute to tumor cell growth by releasing vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF- β) (9,10,23).

Tumor-associated platelets contribute to metastasis by releasing ATP into the bloodstream, which relaxes endothelial barrier function. Tumor-associated macrophages modify the tumor microenvironment through collagen turnover, aiding tumor-associated collagen degradation. The pro-metastatic effects of platelets are linked to their adhesion to tumor cells, forming a protective shield against cell death (16). Individuals with elevated levels of neutrophils and platelets, and/or reduced levels of lymphocytes, are at a higher risk of developing cancer (20). SII is an index that combines those three parameters. Higher SII suggests an imbalance in the inflammatory response, potentially resulting in tumor invasion and unfavorable prognosis. An elevated SII suggests an enhanced inflammatory response and a diminished immune response, consistent with findings linking high SII levels to tumor invasion and metastasis. Furthermore, a high SII might reflect a high tumor burden, metastatic disease, or diffuse malignancy, all of which drive tumor progression. High SII, characterized by elevated neutrophils and platelets alongside reduced lymphocyte levels, maybe a reliable biomarker of tumor progression and poor prognosis. The TNM (tumor, node, metastasis) staging system remains the gold standard for predicting cancer prognosis. However, in our study, comparisons of ROC curves revealed that while TNM staging outperformed SII as a prognostic index for lung cancer patients, SII is a valuable complementary marker. It is simple, inexpensive, non-invasive, and easily accessible, making it a practical complementary to TNM staging in clinical practice (3,9).

Albumin, a crucial player in organization of cellular growth, also plays a significant role in stabilizing DNA and acting as a buffer in biochemical reactions. Its contribution to maintaining the balance of sex hormones against cancers is equally noteworthy (13). The onset of malnutrition in cancer patients is a result from a complex mechanism involving both the tumor and the host's response to the tumor (24). Hypoalbuminemia, a condition that can cause downregulation of the immune system, leads to the extensive proliferation of cancer cells. PNI, which combines both albumin and total lymphocyte count, has been found to be a reliable indicator of cancer prognosis. Notably, higher SII and lower PNI were associated with poor prognosis in different types of cancer (2,10,12).

Lung cancer is a heterogeneous disease in its pathogenesis, carcinogenesis, pathological diagnosis, molecular diagnosis, and therapy (3). Various factors, such as stress, liver disorders, hydration status, aging, and inflammation, can affect the albumin level (24). This study has several differences from the previous studies. This study combines NSCLC and SCLC, while some previous studies only analyze one type of lung cancer (14,15,22). Past studies evaluated PNI prospectively, whereas this study used a retrospective design to analyze data. Some previous studies only used samples with the same therapy (6,14,22,23,25). The difference in the therapies used in this study could affect the results. Some of the patients have received albumin therapy, which affects their albumin levels. Other factors that could affect the result of this study are the patient's environmental exposure, socio-economic history, type of therapy used, treatment adherence, and site of metastasis.

The SII and PNI are simple, low-cost, and easily measured parameters that could be incorporated into screening or monitoring the occurrence of metastasis in lung cancer. However, both indices have limitations. While sensitive to systemic inflammation, the IIS is influenced by various conditions, including infections, malignancies, and autoimmune disorders, which can confound its interpretation. Likewise, the PNI is affected by factors such as acute inflammation, liver dysfunction, and fluid status, which may not directly relate to nutritional health. Different studies use varying cut-off values to define high or low SII and PNI levels, limiting their comparability and widespread clinical application (2,9,10,20). Despite these drawbacks, the SII and PNI remain practical and accessible tools, offering significant insights when used with other clinical and laboratory assessments.

It is essential to acknowledge several limitations in this study. First, this study was carried out at a single facility and involved limited samples. More extensive and multi-center studies are needed to obtain a more comprehensive understanding of the clinical application of SII and PNI in diagnosing metastatic lung cancer. Second, there is a lack of

studies that evaluate the correlation of SII or PNI in metastatic lung cancer. Third, the online medical records were only available in 2019, and detailed information on risk factors was lacking. Prospective studies are essential to validate the findings of this study and establish a more substantial evidence base for the prognostic value of the SII and PNI in lung cancer with metastasis. Additionally, combining SII and PNI with other biomarkers could significantly enhance the accuracy of metastasis diagnosis, paving the way for more precise and individualized clinical decision-making.

4. CONCLUSIONS

The study findings indicate a significant association between the SII and the occurrence of metastasis in patients with lung cancer. However, no significant correlation was observed between the PNI and metastasis in lung cancer patients. SII, a simple, easily accessible, low-cost, and non-invasive marker, may serve as a predictor for the occurrence of metastasis in lung cancer patients. SII is a better biomarker than PNI for predicting metastasis because of its higher sensitivity and specificity compared to PNI.

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