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Research Article

Neutrophil-Lymphocyte Ratio, Platelet Lymphocyte Ratio, And Carcinoembryonic Antigen Relationship With Survival In Non-Small Cell Lung Cancer Patients

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ABSTRACT

Inflammation is crucial to cancer development. A complete blood count is standard patient testing. Thus, inflammatory biomarkers like neutrophil-lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) may predict lung cancer prognosis. Serum carcinoembryonic antigen (CEA) is the main predictive marker of most studies. Elevated NLR, PLR, and CEA levels are frequently associated with poorer overall survival in NSCLC patients. A retrospective cross-sectional study included 50 NSCLC medical records patients from Ulin Regional South Kalimantan Hospital. NLR, PLR, and CEA baseline peripheral blood individuals were investigated for NSCLC overall survival (OS). Patients are separated by OS mean into two groups. Mann-Whitney compared variables. The ROC curve and AUC were used to evaluate the above indicators' prognostic value. The mean of OS was 6 months. NLR, PLR, and CEA patients in ≤ 6 months had higher median values compared to > 6 months groups (8.73 vs. 4.3; 301.23 vs. 217.81; and 106 vs. 27.87). Survival was significantly associated with NLR and CEA (p-values 0.010 and 0.011). NLR >5.90 with AUC 0.725 (sensitivity 63.6%, specificity 29.4%) and CEA >41.39 ng/mL with AUC 0.722 (sensitivity 72.7%, specificity 29.4%). Parallel tests of NLR and CEA testing increased sensitivity and specificity (75.8%, 70.6%). This study revealed that elevated NLR and CEA are associated with patient survival, and monitoring both markers enhances survival prediction accuracy. It can improve insight into disease progression and adjust the therapeutic approach for NSCLC patients.

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INTRODUCTION

According to the Global Burden of Cancer (GLOBOCAN), there were an estimated 2.2 million new cancer diagnoses and 1.8 million cancer-related deaths. In 2020, lung cancer ranked second in terms of frequency of diagnosis and was responsible for the highest number of cancer-related deaths. It accounted for around 11.4% of total cancer cases and 18.0% of all cancer-related fatalities. In men, lung cancer is the primary cause of both the occurrence and death rates of cancer. However, in women, it is the third most prevalent cancer after breast and colorectal cancer in terms of occurrence and the second most deadly after breast cancer. In Indonesia, the incidence of lung cancer is the third highest (8.8%) among all types of cancer, following breast cancer and cervical cancer. In countries such as Indonesia, where smoking rates have recently reached their highest point or are still on the rise, it is expected that the incidence of lung cancer will continue to increase for several decades to come (Sung et al., 2021). Lung carcinoma is categorized into small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Approximately 80% to 85% of all lung malignancies fall within the NSCLC classification (Travis, 2020).

Inflammation has a pivotal role in the advancement of cancer. Inflammatory cells secrete chemicals into the tumor microenvironment, such as growth factors promoting cell division and survival factors restricting programmed cell death. Furthermore, these molecules contain proangiogenic factors and extracellular matrix-modifying enzymes that stimulate the growth of new blood vessels, the invasion of surrounding tissues, and the spread of cancer to other body parts (Jabłońska et al., 2022). Recent evidence has shown that multiple inflammation-related factors can be influential prognostic predictors of lung cancer. These markers indicate the body's reaction to a tumor and offer significant insight into disease progression and outcome. In an enormous register-based cohort of lung cancer patients, inflammation markers such as platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) are suggested as prognostic markers of overall survival (OS) in lung cancer (Winther-Larsen et al., 2022). Another research by Song et al. reported that the PLR and the NLR, indices of the systemic inflammatory response, have been crucial in determining the advancement and prognosis of individuals diagnosed with lung cancer (M. Song et al., 2022). These biomarkers were simple, ubiquitously available, and inexpensive examination through a routine blood test.

An elevated NLR in lung cancer suggests a reduced immune response to tumors caused by T-cell lymphocytes and inflammatory cytokines generated by neutrophils. These neutrophils stimulate the tumor's microenvironment and promote metastasis development (X. Song et al., 2018). Additional study indicates that a higher NLR value before the therapy of NSCLC is associated with a worse overall survival rate (Wang et al., 2019; Yin et al., 2015).

The production of growth factors, such as Vascular Endothelial Development Factor (VEGF), Transforming Growth Factor (TGF)-β, and Platelet Derived Growth Factor (PDGF), by thrombocytes can accelerate tumor development and angiogenesis (Anderson et al., 2023). The research carried out by Lim et al., and Ding et al. demonstrated a strong relationship between PLR (platelet-to-lymphocyte ratio) and the overall survival of patients with NSCLC. Specifically, individuals with greater PLR values tend to have poorer overall survival rates than patients with lower PLR values (Ding et al., 2016; Lim et al., 2019).

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Serum carcinoembryonic antigen (CEA) level is the most widely used tumor marker for lung cancer. It is linked to a heightened risk of relapse and unfavorable patient outcomes (Zhao et al., 2017). Cheng et al. found that elevated CEA was related to advanced TNM stage, worse differentiation, and distant metastasis (Cheng et al., 2019). Another research by Zhang et al. concluded that serum CEA can be a prognostic factor in NSCLC (Zhang et al., 2015). The role of NLR and PLR in prognosis remains uncertain. There is variation in different research studies, and a clear definition of the optimal cut-off value of CEA has not been established, particularly in developing countries such as Indonesia. This study examines the association of NLR, PLR, and CEA levels and the survival rates of patients with NSCLC. Our objective is to utilize the values of NLR, PLR, and CEA to make predictions about the overall survival of patients. Understanding factors that predict prognosis is crucial as it can offer valuable insights to develop personalized treatment options for improved outcomes.

METHODS

This retrospective research was conducted on patients with NSCLC at Ulin Regional South Kalimantan Hospital from January 2017 to December 2019. The subsequent selection criteria were employed: The individual is over 40 years old and has been diagnosed with stage III and stage IV cancer, as per the 7th edition of the American Joint Committee on Cancer (AJCC) TNM Classification of Malignant Tumors, the patient who had complete medical records data for baseline complete blood count (CBC), CEA before treatment and date of death or had a valid phone number (if none date of death data in medical records the family members can be contacted). The study group excluded patients who had been diagnosed with a secondary malignant tumor, an ongoing autoimmune disease, a hematologic malignancy, an infectious condition or were taking chronic steroids. The NLR and PLR were derived from the CBC data. The NLR was calculated by dividing the absolute neutrophil count (ANC) by the absolute lymphocyte count (ALC) derived from a CBC. PLR is determined by dividing the absolute platelet count (APC) by the ALC. Variables are typically presented in statistical analyses using the mean ± standard deviation or the median value with the interquartile range. We categorize the two groups based on the mean of overall survival. The disparities among the groups were evaluated utilizing the Mann–Whitney test. The receiver operating characteristic (ROC) curve analyzes the cut-off values of NLR, PLR, and CEA to predict the efficacy of the poor outcome of NSCLC patients. An elevated Area Under the Curve (AUC) signifies enhanced accuracy of the markers. The statistical analysis was conducted using SPSS 26 software. A p-value < 0.05 was deemed to be statistically significant. The study has received approval from the Ulin Regional South Kalimantan Committee of Ethics (No. 127/XII-RegRiset/RSUDU/20).

RESULTS

Table 1 presents data indicating that out of the 50 patients diagnosed with NSCLC, the average age is 56.72 years, with a majority of 76% being male, with normal mean body mass index (BMI) 19.01 kg/m^2, stage 4a (76%), had metastasis (96%), smoker (58%) and no history of pollutant exposure (56%). The mean of overall survival (OS) is six months.

Table 2 indicates that the group of patients diagnosed with NSCLC who had a life expectancy of fewer than six months had the following characteristics: the majority were under the age of 65 (81.8%), male (69.7%), had a BMI more than 18.5 kg/m^2 (57.78%), diagnosed at stage 4 (4a of 78.79% and

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Table 1. Characteristics of non-small cell lung cancer (NSCLC) patients

Variables	Patients Characteristics (n=50)
Age (years)	
Mean ± SD	56.72 ± 7.77
Median (IQR)	57 (52-62.2)
Sex	
Man (n, %)	38 (76%)
Woman (n, %)	12 (24%)
Body Mass Index (BMI) (kg/m^2)	
Mean ± SD	19.01 ± 3.23
Median (IQR)	18.85 (16.75-20.3)
Stage	
3a	2 (4%)
3b	1 (2%)
3c	1 (2%)
4a	38 (76%)
4b	8 (16%)
Metastasis	
No Metastasis	4 (8%)
Single Metastasis	29 (58%)
Multiple Metastasis	17 (34%)
Smoker	
Yes	29 (58%)
No	21 (42%)
Pollutant exposure risks	
Spraying insecticides on plants	10 (20%)
Cooking with firewood	10 (20%)
Incinerating waste	2 (4%)
No pollutant exposure	28 (56%)
Overall survival (OS) (months)	
Mean ± SD	5.9 ± 7.24
Median (IQR)	3 (1-10)
NLR	
Mean ± SD	8.94 ± 9.12
Median (IQR)	6.12 (3.76-10.69)
PLR	
Mean ± SD	310.08 ± 182.37
Median (IQR)	252.85 (194.97-401.15)
CEA (ng/mL)	
Mean ± SD	208.06 ± 366.30
Median (IQR)	50.11 (7.02-175,25)

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Table 2. Characteristics of NSCLC patients based on average overall survival

Patients Characteristics	≤6 months (n=33)	>6 months (n=17)	p-value
Age (years) (n, %)			
< 65	27 (81.8)	14 (82.4)	1.000 $^{\beta}$
≥65	6 (18.2)	3 (17.6)	
Sex (n, %)			
Man	23 (69.7)	15 (88.2)	0.181$^{\beta}$
Woman	10 (30.3)	2 (11.8)	
BMI (n, %)			
< 18.5	14 (42.42)	7 (41.18)	0.626$^{\alpha}$
≥ 18.5	19 (57.58)	10 (58.82)	
Stage (n, %)			
3a	2 (6.06)	0 (0)	0.480$^{\beta}$
3b	0 (0)	1 (5.89)	
3c	1 (3.03)	0 (0)	
4a	26 (78.79)	12 (70.59)	
4b	4 (12.12)	4 (23.52)	
Metastasis (n, %)			
No Metastasis	3 (9.09)	1 (5.9)	0.500$^{\beta}$
Single Metastasis	21 (63.64)	8 (47.05)	
Multiple Metastasis	9 (27.27)	8 (47.05)	
Smoker (n, %)			
Yes	18 (54.56)	7 (41.18)	0.626$^{\alpha}$
No	15 (45.45)	10 (58.82)	
Pollutant exposure risks			
Spraying insecticides on plants	6 (18.18)	4 (23.53)	0.940$^{\beta}$
Cooking with firewood	7 (21.21)	2 (17.65)	
Incinerating waste	1 (3.03)	1 (5.88)	
No pollutant exposure	19 (57.58)	9 (52.94)	
NLR			
Median (IQR)	8.73 (4.1-14.3)	4.3 (3.43-7.44)	**0.010**$^{\gamma}$
PLR			
Median (IQR)	301.23 (222.45-471.03)	217.81 (169.93-303.93)	0.084$^{\gamma}$
CEA (ng/mL)			
Median (IQR)	106 (26.7-244)	27.87 (2.77-64.6)	**0.011**$^{\gamma}$

IQR=Interquatile range, $^{\beta}$ = *fisher-exact* test; $^{\alpha}$ = *chi* square, $^{\gamma}$ = *mann whitney*

Table 3. Predictive efficacy of the poor outcome of NLR, PLR, and CEA

Variables	AUC	p-value	95% CI	Cut of Value	Sensitivity	Specificity
NLR	0.725	**0.010**	1.586-0.864	5.90	63.6%	29.4%
PLR	0.651	0.084	0.491-0.810	197.50	81.8%	58.8%
CEA	0.722	**0.011**	0.569-0.875	41.39	72.7%	29.4%
Parallel test NLR and CEA	0.788	**0.001**	/	/	75.8%	70.6%

AUC: Area Under the Curve

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4b 12.12%), had metastasis (91%), were smokers (54.56%), and were not exposed history to pollutant exposure (57.57%). There were no associations between survival with demography and clinical variables. NLR, PLR, and CEA values in NSCLC patients with a survival of less than six months exhibited elevated levels than in patients with a survival of > 6 months. The statistical test findings indicated no statistically significant disparity in PLR levels among the groups. Nevertheless, there was a notable disparity in the NLR and CEA values among patients with a survival period of less than six months, with p-values of 0.010 , respectively.

The ROC curve analysis in Figure 1 reveals that this study's variable PLR value of NSCLC patients has an area under the curve (AUC) of 0.651, with a cut-off value of 197.50. The test exhibited a sensitivity rate of 81.8% and a specificity rate of 58.8%. There was no significant correlation between the rise in PLR value and the patient's life expectancy ($p > 0.05$) (Table 3). As shown in Table 3, an NLR cut-off value exceeding 5.90 was substantially correlated with decreased survival, as measured by an AUC of 0.725, sensitivity of 63.6%, and specificity of 29.4% ($p<0.05$). The research findings indicate that having a CEA level higher than 41.39 ng/mL is strongly linked to a reduced chance of survival (AUC = 0.722, sensitivity of 72.7%, specificity of 29.4%; $p < 0.05$). Due to lower sensitivity and specificity, we examined a parallel test of a combination of NLR and CEA. However, when a parallel test was conducted, the sensitivity and specificity were higher, with a sensitivity of 75.8% and a specificity of 70.6%.

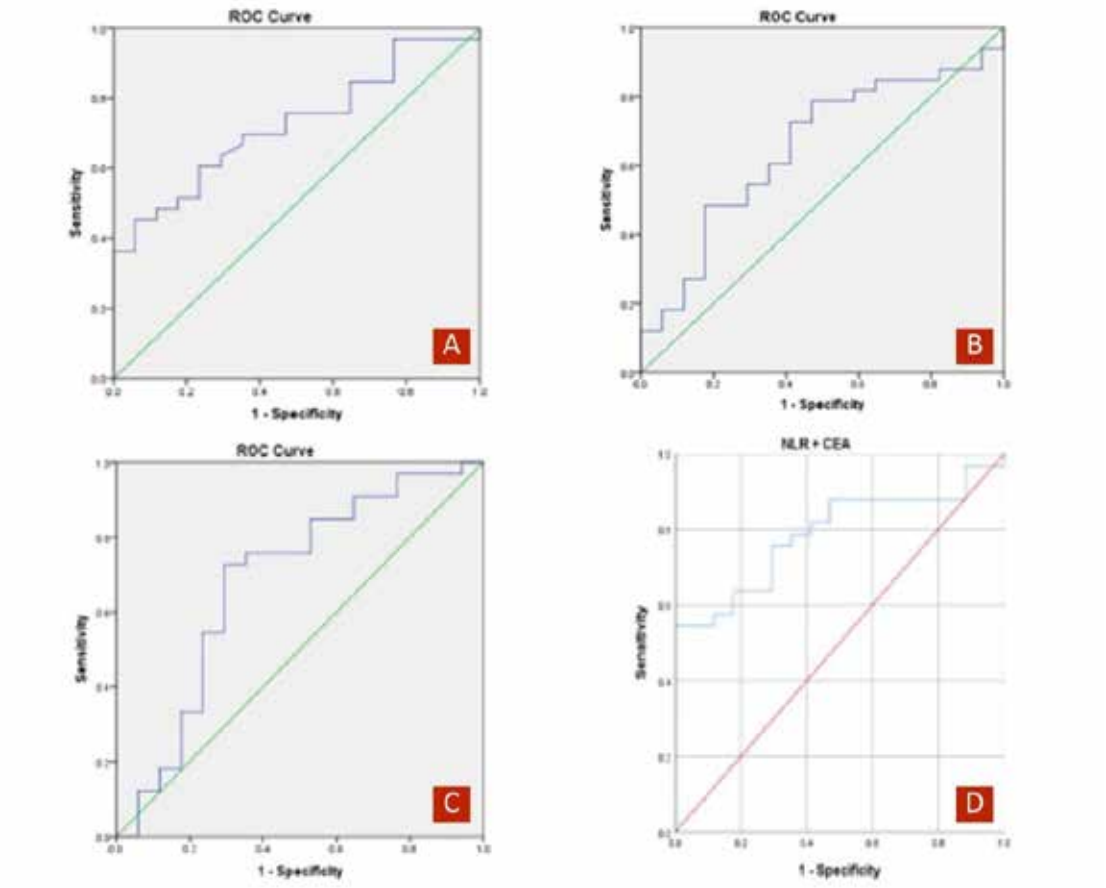

Figure 1. ROC Curve of **(A)** NLR, **(B)** PLR, **(C)** CEA, and **(D)** parallel test of NLR and CEA.

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DISCUSSION

According to the data obtained from this study, it is evident that most patients diagnosed with NSCLC at Ulin Regional South Kalimantan are males, with a male-to-female ratio of 3:1. The mean age was 56.72 years, with many individuals who were smokers and in an advanced stage. It is consistent with several other studies that show similar characteristic results. Faot NE et al.'s research showed that 81.3% of NSCLC patients were male, with an average age of 57 years, and the most stage 4 (Faot & Pradjoko, 2017). The same thing was also shown in a previous study by Haryati et al. from 134 patients diagnosed with primary lung cancer; as many as 76.12% were male, with a ratio between men and women 3:1 (Haryati et al., 2013).

Only a few lung cancer patients can be diagnosed early. It is because of the decline in immunity in old age and the accumulation of carcinogenic causes that most cancer patients only start treatment and show complaints when they are over 40 years old. As for the proportion of men who have lung cancer more than women, this is widely associated with lifestyles related to smoking habits and alcohol consumption, which tend to be higher in men than women. In Indonesia itself, the prevalence of women smokers is low, in contrast to in Western countries where the prevalence of women smoking increases along with the progress of the times and urbanization (Haryati et al., 2013; Putra et al., 2016). Some studies suggest that Environmental Geno toxicants such as polycyclic aromatic hydrocarbon (PAH) compounds derived from smoking and occupational exposure are known to cause deoxyribonucleate acid (DNA) damage that leads to lung cancer. Among these PAH compounds, benzo-α-pyrene is the most widely found in inducing lung cancer (Sanikini et al., 2018).

In addition to cigarettes, the inhalation of chemicals and other factors increase the risk of developing cancer. Cooking with firewood for over 100 hours yearly has an elevated chance of developing lung cancer. Long-term pesticide exposure over 20 years or more poses an additional risk. Particulate matter (PM) 2.5 emitted by mining, factories, municipal waste, transportation, and incineration raises the chance of developing lung cancer (Kangkhetkron & Juntarawijit, 2024; Shankar et al., 2019). This study found that 20% of patients diagnosed with NSCLC had used firewood to cook. Additionally, 20% of the patients had a history of spraying grass with pesticides for over 20 years, primarily due to their farming occupation.

Overall survival is the duration from the moment of diagnosis till the individual's death. Wao H et al. found that untreated NSCLC patients survive an average of 7.15 months (Wao et al., 2013). It was almost similar to this research in the mean of OS results of 6 months (1-24 months), but our study's limitations regarding the treatment were unknown. Another retrospective analysis of 1741 NSCLC patients by Hardstock et al. found a median OS of 351 days and 571 days for positive epidermal growth factor receptor (EGFR) mutation patients from diagnosis (Hardtstock et al., 2020). It differs from our research because of the different total samples and unrecorded molecular tests.

The prognostic significance of NLR and PLR remains unclear. Research studies exhibit variability, and a definitive ideal cut-off number for CEA has yet to be identified, especially in developing countries like Indonesia. This study investigates the association between NLR, PLR, and CEA levels and the survival rates of patients with NSCLC. The NLR, PLR, and CEA values in NSCLC patients exhibited higher levels in individuals with a survival

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period of fewer than six months compared to those with a survival period beyond six months (8.73 vs. 4.3; 301.23 vs. 217.81 and 106 ng/mL vs. 27.87 ng/mL, respectively) in our study. However, statistically, there is no significant difference in the PLR value between patients with an overall survival of 6 months (p value > 0.05). Meanwhile, there is a notable disparity in the NLR and CEA values among patients with a 6-month OS, with a p-value of less than 0.05.

Using the ROC curve and Kappa test, we determined the optimal threshold values for NLR, PLR, and CEA and their corresponding sensitivity and specificity. The research findings indicate that the NLR has a positive diagnostic value greater than 5.90, with a sensitivity of 63.6% and a specificity of 29.4%. Meanwhile, PLR with a cut-off value of 197.50 had a sensitivity of 81.8% and a specificity of 58.8%, which was insignificant. Several studies examining NLR threshold values have reported varying results. For instance, Ozyurek et al. reported that NSCLC patients with NLR values <3 obtained before therapy had a longer life (median 34.76 months vs 19.12 months, p = 0.002) (Ozyurek et al., 2017). In another study by Song et al., a cut-off point value of 3.4 was used for the NLR, resulting in a sensitivity of 54% and a specificity of 73% (X. Song et al., 2018). Yin Yi et al., in their meta-analysis, collected various limits of NLR cut-off point values from various studies ranging from 2.5 to 4.7. The inconsistent thresholds in this research may be attributed to variances in histological composition and clinicopathological factors across different investigations (Yin et al., 2015). Inflammatory studies have shown lymphocytes' role in lung cancer. Inflammation accelerates tumor progression, angiogenesis, and apoptosis, with neutrophils, lymphocytes B and T, playing a role. Neutrophils, the largest leukocyte in the blood, secrete cytokines, growth factors, proteases, and other molecules to stimulate tumor cell growth, while lymphocytes prevent tumor cell proliferation and migration. Increased tumor cell and lymphocyte infiltration improves cytotoxic therapy and patient prognosis. Elevated NLR signifies a greater neutrophil count than lymphocyte, indicating a pro-inflammatory condition and establishing a conducive environment for cancer cells. Several studies have linked elevated NLR values to lower life expectancy and poor prognostics for various cancers, making it a potential prognostic marker for cancer patients (Gupta et al., 2019; M. Song et al., 2022).

A cell adhesion glycoprotein called CEA is expressed in several tissues and found in healthy people with low titers. CEA overexpression is found in several lung cancer cell types, including NSCLC. Tumor cell and blood vessel adhesion may increase lung cancer cell metastatic ability with increased CEA. CEA also promotes cancer cell migration, invasion, proliferation, and angiogenesis. It also interacts with growth factors and signaling pathways, such as the PKA-PGC-1α axis, to enhance tumor cell survival and proliferation (Lei et al., 2024). Serum CEA can predict lung cancer recurrence and mortality (Arrieta et al., 2021). Our study revealed that CEA has a positive diagnostic value greater than 41.39 ng/mL, with a sensitivity of 72.7% and a specificity of 29.4%. Many studies revealed different results of the CEA cut-off value. The Zhao et al. study established a 10 ng/ml threshold for CEA. Patients with CEA levels exceeding this threshold had increased progressive free survival (PFS) and OS. The threshold for CEA levels varied between 2.5 ng/ml and 40 ng/ml across various investigations. The cut-off value of a specific tumor marker may vary in different groups due to age, sex, nationality, or lifestyle (Zhao et al., 2017)

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Given the lower sensitivity and specificity of NLR and CEA, we conducted a parallel test involving both NLR and CEA. Nevertheless, the sensitivity and specificity exhibited an increase, with a sensitivity of 75.8% and a specificity of 70.6%. It indicates the potential role of elevated NLR and CEA combination as prognostic markers in NSCLC.

This study has numerous limitations. Firstly, it is a retrospective single-center study with limited participants. The retrospective design relies on data utilized in the study obtained from secondary sources, notably medical records. This study's secondary data may bias the data-gathering process, reducing the research findings' reliability and generalizability. The medical record may also include incomplete information. The study finding, derived from a limited sample, diminished its statistical power and may not be generalized to a larger population. We also did not analyze the patient's therapy; the presence of comorbidities in individuals may considerably influence the outcome of this investigation. In the future, we recommend undertaking a prospective study to mitigate bias and enhance data quality. Enhancing the sample size and multi-center research can improve the study's statistical power and generalizability with more heterogeneous populations.

CONCLUSION

Inflammatory indicators are essential in the development and advancement of tumors. The NLR and PLR indicate systemic inflammatory responses in the blood. The serum CEA level is the predominant tumor marker utilized for lung cancer and is correlated with unfavorable patient prognoses. Our study found that higher levels of NLR and CEA were associated with a shorter OS than six months. In addition, integrating a combination of NLR and CEA can enhance survival prediction accuracy. It can improve insight into disease progression and adjust the therapeutic approach for NSCLC patients.

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