Volume 24, No 1 | International Journal of Radiation Research, January 2026

Relationship between peripheral-blood immuno-inflammatory markers, radiotherapy efficacy, and 1-year overall survival rate among patients with stage III non-small cell lung cancer

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► ***Original article***

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Received: May 2025
Final revised: July 2025
Accepted: August2025

Int. J. Radiat. Res., January 2026; 24(1): 151-157

DOI: 10.61186/ijrr.24.1.23

Keywords: *Carcinoma, non-small-cell lung, inflammatory markers, radiotherapy, survival rate, stage III neoplasms.*

ABSTRACT

Background: Locally advanced non-small cell lung cancer (NSCLC) is often associated with unfavorable clinical outcomes. This study aims to examine the association between peripheral immuno-inflammatory biomarkers, the effectiveness of radiotherapy, and 1-year survival rates in stage III NSCLC. ***Materials and Methods:*** This study reviewed 180 stage III NSCLC patients treated with radical radiotherapy from 2020 to 2024. Pretreatment neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), and lymphocyte-to-monocyte ratio (LMR) levels were measured and compared with healthy controls. Biomarker differences were analyzed across clinical subgroups and between radiotherapy response groups. Using median values as cutoffs, one-year survival data were assessed, with Cox regression determining prognostic factors. ***Results:*** Patients with NSCLC had significantly higher NLR, PLR, and SII and lower LMR than the control group ($P<0.05$). The good-response group had lower NLR, PLR, and SII and higher LMR ($P<0.05$). Higher NLR, PLR, and SII were associated with worse 1-year survival, while higher LMR predicted better outcomes ($P<0.05$). Cox analysis confirmed that all four markers were independent prognostic factors ($P<0.05$). ***Conclusion:*** The peripheral blood markers NLR, PLR, SII, and LMR are closely associated with radiotherapy efficacy and 1-year survival in stage III NSCLC.

INTRODUCTION

Lung cancer is a major public health challenge, and in 2020, it accounted for 11.6% of cancer cases and 18.4% of cancer-related mortality worldwide, which makes it the most lethal malignancy [1]. Histopathologically, lung cancer is predominantly categorized as small-cell lung cancer (SCLC) and non-SCLC (NSCLC) [2]. NSCLC accounts for approximately 80–85% of all lung-cancer diagnoses, making it the most prevalent subtype [3]. Early-stage lung cancer typically presents with nonspecific manifestations. Symptoms like chronic cough, chest discomfort, and hemoptysis are hallmarks of advanced disease but are similar to those of benign respiratory conditions, which leads to delays in diagnosis and suboptimal outcomes [4]. Therefore, enhancing the early detection and diagnosis of lung cancer is key to improving patients' long-term prognosis.

Epidemiological research demonstrates that organized screening with low dose computed tomography scans (LDCT) can decrease mortality rates from lung cancer by roughly 20% in populations at elevated risk [5]. However, LDCT alone provides only a preliminary assessment and cannot definitively determine whether most nodules are benign or malignant. Moreover, commonly used laboratory indicators are still limited to tumor markers, and the high costs of detection methods limit their application in some primary hospitals [6]. For decades, the tumor node metastasis (TNM) staging framework has been crucial in determining treatment strategies and estimating survival rates in NSCLC [7]. Nevertheless, pathological TNM staging can only be definitively determined after surgery, which limits its application in preoperative diagnosis. Thus, there is an urgent need to identify biomarker techniques that are inexpensive, convenient, reproducible, and have high specificity and sensitivity to improve the rate of NSCLC diagnosis and effectively predict pathological staging.

In 1863, the German pathologist Rudolf Virchow first observed the infiltration of a large number of leukocytes in tumor tissues and proposed a possible link between tumors and inflammation [8]. Virchow was the first to suggest that tumors originate from sites of chronic inflammation and considered inflammation to be one of the important predisposing factors for tumor development. Contemporary studies demonstrate a significant association between inflammatory mechanisms and various oncogenic processes, including tumor initiation,

[DOI: 10.61186/ijrr.24.1.23]

development, and metastasis, with approximately 15–20% of malignant tumors being associated with chronic inflammation or infection [9]. Inflammation promotes tumor growth, angiogenesis, inhibition of apoptosis, and deoxyribonucleic acid (DNA) damage through various mechanisms, thereby influencing tumor progression, metastasis, and prognosis [10].

Cancer growth and metastasis are heavily influenced by the surrounding tumor microenvironment (TME), in which inflammation plays a significant role [11]. The TME is a dynamic and multifaceted niche that encompasses tumor cells, immune and inflammatory cells, stromal components, and blood and lymphatic vessel networks. Additionally, it features various inflammatory cytokines and chemokines that tumor cells actively secrete through autocrine and paracrine pathways. This specialized microenvironment serves as a foundation through which tumor cells can rapidly proliferate, invade surrounding tissues, and metastasize [12]. Immune-inflammatory components, are important cellular mediators within the TME and include peripheral blood neutrophils, lymphocytes, monocytes, and platelets [13].

Accumulating evidence indicates a positive correlation between circulating neutrophil counts and the extent of neutrophil infiltration in tumor tissues [14]. Tumor-derived granulocyte colony-stimulating factors and chemokines can induce abnormal release and recruitment of neutrophils from the bone marrow to the TME, which leads to an increase of neutrophils in peripheral blood [15]. CD8+ T cells mediate tumor-cell killing through MHC class I molecule-dependent antigen recognition, and a decrease in their number can promote tumor progression [16].

Thrombocytosis is common in patients with tumors, and its mechanism involves tumor-induced activation of megakaryocytes, which leads to a hypercoagulable state and promotes hematogenous tumor metastasis [17]. After chemokines recruit monocytes to tumor tissues, the monocytes differentiate into tumor-associated macrophages, which accelerate cancer development through pro-angiogenic effects and immunosuppression. Furthermore, the density of these macrophages is positively correlated with the density of tumor micro vessels [18]. These common immune-inflammatory cells in peripheral blood are all objective evaluation indicators of inflammatory responses with established links to cancer advancement and disease prognosis. Therefore, inflammatory composite indicators derived from these immune-inflammatory cells have attracted significant attention, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), and lymphocyte-to-monocyte ratio (LMR).

Peripheral blood immuno-inflammatory markers, including NLR, PLR, SII, and LMR, are widely studied owing to their accessibility, cost-effectiveness, high reproducibility, and prognostic value in oncology. While prior research has investigated the predictive significance of these biomarkers across different cancer types, limited research has specifically focused on their association with radiotherapy outcomes and survival. This study endeavors to advance understanding in this area by offering a thorough analysis of how these readily measurable markers can predict treatment response and long-term prognosis. It may provide clinicians with a valuable tool for personalized radiotherapy planning and enhanced patient management.

MATERIALS AND METHODS

Patients

This retrospective analysis enrolled 180 stage III NSCLC patients and received treatment at our institution from March 2020 to March 2024. The following inclusion criteria were applied: diagnosis with stage III NSCLC; age ≥18 years; no prior surgery, radiotherapy, chemotherapy, or other malignancy-related treatments before enrollment; tolerance of radiotherapy; availability of complete clinical and postoperative pathological data; and follow-up for more than 1 year. The exclusion criteria were secondary lung cancer; a history of chest surgery; severe internal medical diseases; comorbid psychiatric disorders or consciousness disturbances; concurrent malignancies at other sites; an abnormal autoimmune system; pre-existing infection before blood-sample collection; pregnancy or lactation; and transfer to another hospital during the study period.

Radiotherapy

Before undergoing radiotherapy, patients with stage III NSCLC underwent routine clinical examinations, including imaging studies, laboratory tests, and cardiopulmonary function assessments. Target-volume delineation was performed using a spiral computed tomography (CT) machine (GE Discovery 690, GE Healthcare, America) with sensitive organs being marked simultaneously. The lesions were reconstructed in three dimensions to determine the tumor volume and planned target volume, and then radiotherapy was administered (Varian TrueBeam, Varian Medical Systems, America). Patients received a cumulative radiotherapy dose of 60–66 Gy.

Efficacy evaluation

At 3 months post-radiotherapy, patient outcomes were assessed using the RECIST 1.1 criteria as follows. Complete response (CR) was considered as total disappearance of the target lesions, no new lesions, and normal tumor markers. Partial response (PR) involved ≥30% reduction in total target lesion

[DOI: 10.61186/ijrr.24.1.23]

diameters with no new lesions or worsening non-target lesions. Stable disease (SD) corresponded to changes in lesion diameters between those indicated for PR and progressive disease (PD) (neither ≥30% shrinkage nor ≥20% growth) with no new lesions. Progressive disease (PD) corresponded to a ≥20% increase in total lesion diameters or emergence of new lesions. Patients were then divided into a good (CR+PR) and poor (SD+PD) response group.

Laboratory data collection

Fasting complete blood data of all stage III NSCLC patients within one week before surgery and all healthy individuals in the control group were collected. Complete blood count tests were performed using an automated hematology analyzer (BC-5000, Mindray, China). The collected data included the white blood cell count, neutrophil count, lymphocyte count, monocyte count, and platelet count. Corresponding values for the NLR, PLR, SII, and LMR were calculated.

Follow-up

Post-chemotherapy surveillance included all patients with tri-monthly clinical follow ups and comprehensive one-year survival documentation. The median NLR, PLR, SII, and LMR were used as stratification thresholds to analyze differential one-year survival outcomes across biomarker-defined subgroups.

Statistical analysis

Using SPSS 25.0, categorical data (*n*, %) were analyzed using chi-squared tests, while continuous variables (mean±standard deviation) were analyzed with *t*-tests or an analysis of variance (ANOVA). Survival distributions were plotted using the Kaplan–Meier estimator, and Cox regression was used to identify prognostic factors for stage III NSCLC ($P<0.05$).

RESULTS

Clinical characteristics data

Table 1 showed that the two groups exhibited no significant differences in fundamental characteristics like age, gender, BMI, and smoking history ($P>0.05$).

Comparison of NLR, PLR, SII and LMR levels

Table 2 showed that the NSCLC group exhibited significantly higher NLR, PLR, SII and, lower LMR ($P<0.05$). This suggests that patients with NSCLC exhibit significant inflammatory responses and abnormalities in immune status.

Comparison of patients with different clinical characteristics before radiotherapy

Table 3 showed that before radiotherapy, NLR, PLR, SII, and LMR did not exhibit statistically significant differences among patients with different ages, sexes, BMIs, pathological classifications, tumor locations, and maximum tumor diameters ($P>0.05$).

Table 1. Clinical characteristics.

Variable	NSCLC group (*n*=180)	Healthy control group (*n*=180)	χ^2/*t*-value	*P*-value
Age (years)	58.83±10.57	59.56±12.33	0.601	0.548
Gender				
Female	80 (44.44)	91 (50.56%)	1.348	0.246
Male	100 (55.56)	89 (49.44%)		
BMI (kg/m²)	23.61±1.63	23.48±2.15	0.685	0.494
Smoking history				
Yes	105 (58.33)	95 (52.78%)	1.125	0.289
No	75 (41.67)	85 (47.22%)		
Histology				
Adenocarcinoma	119 (66.11)			
Squamous carcinoma	57 (31.67)			
Large cell carcinoma	4 (2.22)			
Tumor location				
Left lung	78 (43.33)			
Right lung	70 (38.89)			
Double lungs	32 (17.78)			
Maximum tumor diameter (cm)				
<5	68 (37.78)			
≥5	112 (62.22)			

Abbreviation: NSCLC: non-small cell lung cancer; BMI:body mass index.

Table 2. Comparison of NLR, PLR, SII and LMR levels (Mean±SD).

Variable	NSCLC group (*n*=180)	Healthy control group (*n*=180)	*t*-value	*P*-value
NLR	2.17±0.76	1.63±0.45	8.289	0.000
PLR	147.73±43.67	116.54±34.28	7.538	0.000
SII	459.58±59.78	342.33±65.67	17.714	0.000
LMR	4.10±0.93	5.98±0.64	19.157	0.000

Abbreviation: NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune inflammation index; LMR: lymphocyte-to-monocyte ratio.

Comparison of patients with different radiotherapy outcomes

There were 96 patients (PR) in the good-response group and 84 patients (SD+PD) in the poor-response group. Table 4 showed that NLR, PLR, and SII were lower in the good-response group, LMR was markedly higher ($P<0.05$).

Comparison of one-year survival rates

Table 5 shows that the survival rates of the high NLR group, high PLR group and high SII group are lower than those of the low-level group, while the survival rate of the high LMR group is higher.

One-year survival curves for different levels of NLR, PLR, SII and LMR

The Kaplan–Meier survival analysis indicated that there were significantly better survival periods in the low NLR group ($P=0.001$), low PLR group ($P=0.007$), low SII group ($P=0.000$), and high LMR group ($P=0.005$) (table 6 and figure 1).

Factor analysis of one-year survival

Table 7 showed that NLR, PLR, SII, and LMR were influential factors for 1-year survival of stage III

[DOI: 10.61186/ijrr.24.1.23]

patients with NSCLC after radiotherapy (P<0.05).

Table 3. Comparison of NLR, PLR, SII and LMR levels in stage III NSCLC patients with different clinical characteristics before radiotherapy.

Clinical characteristics	*n*	NLR	PLR	SII	LMR
Age (years)					
<60	76	2.14±0.80	145.58±43.30	452.33±62.81	4.14±1.00
≥60	104	2.19±0.74	149.31±44.08	464.88±57.20	4.07±0.88
t-value		0.409	0.564	1.395	0.517
P-value		0.684	0.574	0.165	0.606
Gender					
Female	80	2.19±0.79	151.09±41.35	462.14±58.59	4.09±0.94
Male	100	2.16±0.75	145.05±45.46	457.53±60.94	4.11±0.93
t-value		0.237	0.922	0.513	0.105
P-value		0.813	0.358	0.609	0.917
BMI (kg/m²)					
<24	86	2.21±0.77	145.06±40.02	465.21±58.34	4.08±0.94
≥24	94	2.14±0.76	150.18±46.84	454.43±60.92	4.12±0.93
t-value		0.602	0.786	1.210	0.242
P-value		0.548	0.433	0.228	0.809
Smoking history					
Yes	105	2.18±0.79	151.68±42.44	462.22±56.64	4.06±0.95
No	75	2.17±0.73	142.22±45.05	455.89±64.13	4.15±0.93
t-value		0.086	1.437	0.699	0.611
P-value		0.932	0.152	0.486	0.542
Histology					
Adenocarcinoma	119	2.21±0.81	147.81±45.70	456.14±61.73	4.10±0.93
Squamous carcinoma	57	2.09±0.67	147.88±39.51	466.42±57.51	4.10±0.97
Large cell carcinoma	4	2.20±0.41	143.53±49.91	464.34±15.13	4.15±0.79
F-value		0.473	0.019	0.579	0.007
P-value		0.624	0.981	0.562	0.993
Tumor location					
Left lung	78	2.28±0.77	149.72±43.36	464.05±58.42	4.08±0.95
Right lung	70	2.13±0.78	145.56±43.49	459.10±58.68	4.13±0.96
Double lungs	32	1.98±0.69	147.66±45.95	449.73±65.93	4.07±0.85
F-value		1.929	0.165	0.652	0.063
P-value		0.148	0.848	0.522	0.939
Maximum tumor diameter (cm)					
<5	68	2.12±0.71	143.28±42.18	461.92±56.93	4.11±0.91
≥5	112	2.20±0.79	150.44±44.52	458.6±61.66	4.09±0.95
t-value		0.687	1.068	0.409	0.114
P-value		0.493	0.287	0.683	0.909

Table 4. Comparison of NLR, PLR, SII and LMR levels in stage III NSCLC patients with different radiotherapy outcomes (Mean±SD).

Variable	Good-response group (*n*=96)	Poor-response group (*n*=84)	*t*-value	*P*-value
NLR	1.85±0.61	2.55±0.74	6.905	0.000
PLR	132.33±34.68	165.33±46.35	5.448	0.000
SII	430.74±52.29	492.55±50.15	8.063	0.000
LMR	4.52±0.88	3.63±0.75	7.254	0.000

Table 5. Comparison of one-year survival rates of stage III NSCLC patients with different NLR, PLR, SII and LMR levels.

	Survival	Death	χ^2-value	*P*-value
High NLR group	41 (45.56)	49 (54.44)	8.144	0.004
Low NLR group	60 (66.67)	30(33.33)		
High PLR group	43 (47.78)	47 (52.22)	5.076	0.024
Low PLR group	58 (64.44)	32 (35.56)		
High SII group	39 (43.33)	51 (56.67)	8.071	0.005
Low SII group	62 (68.88)	28 (31.11)		
High LMR group	59 (65.56)	31 (34.44)	6.520	0.011
Low LMR group	42 (46.67)	48 (53.33)		

Table 6. Analysis of factors affecting the 1-year survival of patients with stage III NSCLC after radiotherapy.

	Median survival (months)	95% CI	log-rank χ^2-value	*P*-value
High NLR group	9.69	10.474-11.215	10.669	0.001
Low NLR group	10.96	10.603-11.308		
High PLR group	9.80	9.221~10.251	0.007	7.342
Low PLR group	10.84	10.474-11.215		
High SII group	9.57	9.055~10.078	0.000	15.663
Low SII group	11.07	10.753~11.403		
High LMR group	10.83	10.435~11.232	7.891	0.005
Low LMR group	9.81	9.326~10.296		

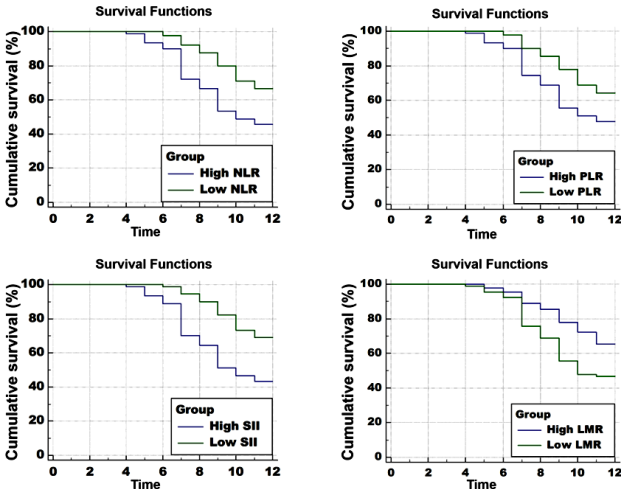

Figure 1. Kaplan-Meier survival curves illustrating the one-year overall survival rates of stage III NSCLC patients based on levels of NLR, PLR, SII and LMR.

Table 7. Analysis of factors affecting the 1-year survival of patients with stage III NSCLC after radiotherapy.

	B	*P*-value	OR	95% CI
NLR	1.292	0.000	3.641	2.659~4.984
PLR	0.019	0.000	1.020	1.015~1.025
SII	0.018	0.000	1.019	1.014~1.023
LMR	-0.294	0.024	0.745	0.577~0.962

[DOI: 10.61186/ijrr.24.1.23]

DISCUSSION

Studies have demonstrated that tumor cells promote systemic immune and inflammatory effects in the body by secreting mediators such as chemokines and cytokines, and peripheral blood immuno-inflammatory markers can dynamically reflect the state of immune balance [19]. Several hematologic indices have emerged as valuable prognostic biomarkers in oncology, including NLR, PLR, SII, and LMR, due to their clinical practicality, excellent reproducibility, and cost-effectiveness [20].

The findings indicated that patients with stage III NSCLC had markedly increased NLR, PLR, and SII compared to the control group, as well as lower LMR. This result aligns with earlier studies suggesting significant abnormalities in the immuno-inflammatory microenvironment of patients with NSCLC [21-23]. Neutrophil counts in the blood increase as tumors promote their release from the bone marrow [24]. Additionally, the TME can suppress lymphocyte function and reduce their numbers, leading to increased NLR [25].

In addition to stimulating tumor angiogenesis, platelets significantly contribute to the progression of cancer through the release of pro-angiogenic factors, as well as by physically shielding tumor cells from immune clearance, which results in increased platelet counts and an elevated PLR [26]. SII is a comprehensive index that integrates information on neutrophils, platelets, and lymphocytes, and its elevation reflects enhanced systemic inflammatory responses and disrupted immune homeostasis in patients with tumors [27]. Lymphocytes are the core of anti-tumor adaptive immunity [28]. In contrast, the TME facilitates the polarization of infiltrating monocytes toward a tumor-associated macrophage phenotype with pro-tumor functions, which promotes immune suppression and tumor progression [29]. A decreased LMR suggests a reduction in lymphocytes and an increase in monocytes, indicating impaired anti-tumor immune function and enhanced immunosuppressive status [30].

The good-response group showed statistically significant reductions in NLR, PLR, and SII, whereas LMR was elevated, which demonstrates a strong correlation between these biomarkers and radiotherapy outcomes. The tumoricidal effect of radiotherapy primarily involves directly damaging tumor-cell DNA through ionizing radiation, which leads to cell apoptosis or necrosis [31]. Additionally, radiotherapy can induce tumor cells to release DAMPs, such as HMGB1 and CRT, which trigger the activation of immune cells and bolster immune reactions against tumors [32]. However, radiotherapy may also trigger immunosuppressive effects in the body, and studies have found that radiotherapy reduces the number of lymphocytes in peripheral blood, leading to impaired immune function [33]. Radiotherapy may also enhance PD-L1 expression within the TME, which triggers the PD-1 inhibitory pathway for T cells and consequently weakens their ability to combat tumors [34]. Radiotherapy also induces local inflammatory responses, which leads to the release of inflammatory factors that may exacerbate immunosuppression.

High levels of NLR, PLR, and SII are generally considered markers of enhanced systemic immunosuppression and inflammatory responses. Changes in these indicators may reflect impaired immune function after radiotherapy, which is unfavorable for the clearance of tumor cells and the recovery of immune function [35]. Conversely, a high LMR indicates a relatively strong anti-tumor immune capacity of the body [36]. Lymphocytes can be activated after radiotherapy, which can enhance their cytotoxic effects on tumor cells, while a lower number of monocytes reduces the influence of immunosuppressive factors. Therefore, patients with a higher LMR tend to have better radiotherapy outcomes.

Individuals in the high NLR, PLR, and SII groups had worse one-year survival outcomes than those in the low-level groups, whereas a higher survival rate occurred in the high LMR group. Cox regression analysis confirmed that the peripheral blood levels of NLR, PLR, SII, and LMR are important influential factors for the one-year survival after radiotherapy. This suggests that the examined markers are not only associated with the efficacy of radiotherapy but also serve as reliable predictors for patients' long-term survival outcomes.

From the perspective of tumor biology, high NLR, PLR, and SII reflect an immunosuppressive and pro-tumor inflammatory state in the TME, which facilitates tumor-cell survival, proliferative capacity, and metastatic potential, leading to lower survival rates. Persistent inflammatory responses can induce the production of anti-apoptotic proteins by tumor cells, which enhances their resistance to radiotherapy and chemotherapy. The suppressed immune condition hinders the body's ability to effectively remove cancerous cells, consequently elevating the chances of tumor reappearance and spread [37, 38]. A high LMR may reflect good tolerance to radiotherapy and favorable immune-activation capacity. After radiotherapy, the body can rapidly recover immune function and continuously exert anti-tumor effects, which improve survival rates.

Dynamic monitoring of changes in the markers examined could have significant clinical importance during radiotherapy for stage III NSCLC. If the levels of NLR, PLR, and SII gradually decrease while LMR increases, it suggests that the radiotherapy is effective, the inflammatory state of the TME is improving, and immune function is being enhanced. Conversely, if these markers show no significant

[DOI: 10.61186/ijrr.24.1.23]

change or if they increase, it may indicate a poor treatment response and necessitate timely adjustments to the therapeutic strategy, such as combining radiotherapy with immunotherapy or optimizing the radiotherapy regimen. Moreover, these markers could be utilized for prognostic stratification to guide intensive follow up and comprehensive interventions for high-risk patients, which could help to optimize individualized treatment decisions and improve both survival rates and quality of life. Therefore, incorporating these markers into evaluation systems for the efficacy of radiotherapy could provide clinicians with objective real-time monitoring indicators that could help to improve treatments.

Research limitations

This study's small sample size may limit the generalizability of the markers across diverse clinical features and treatments. The follow up duration was only one year, which limits the insights that can be obtained about patients' extended survival and fluctuations in immune-inflammatory indicators. Subsequent research should focus on expansive, multi-institutional clinical studies to further explore the connections between these biomarkers, radiotherapy response, and long-term outcomes in stage III NSCLC. In-depth research should also investigate the molecular mechanisms of immune-inflammatory markers in tumor development and radiotherapy response, explore their relationships with other tumor markers, and construct a more comprehensive tumor-prognosis evaluation system. A promising avenue for future investigation is the formulation of tailored therapeutics that act on immune-inflammatory markers to enhance patient outcomes via immune-response modulation.

CONCLUSION

Our findings demonstrate that pretreatment levels of the systemic immuno-inflammatory markers NLR, PLR, SII, and LMR in peripheral blood show significant associations with both the radiotherapy response and 1-year overall survival among patients with stage III NSCLC. These markers not only reflect the state of immune-inflammatory imbalance in tumor patients, but also serve as potential indicators for evaluating radiotherapy efficacy and predicting patient prognosis. They provide important references for the selection of clinical treatment regimens, monitoring therapeutic efficacy, and prognostic assessment. However, current research on peripheral -blood immuno-inflammatory markers is still in the exploratory stage, and additional high-quality research is needed to confirm and refine these findings.

Acknowledgment: None

Consent to publish: The manuscript has neither been previously published nor is under consideration by any other journal. The authors have all approved the content of the paper.

Consent to participate: We secured a signed informed consent form from every participant.

Ethic approval: This study was approved by the Ethics Committee of the General Hospital of Benxi Iron.

Data availability statement: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Funding: None.

Conflicts of interest: The authors declare that they have no financial conflicts of interest.

Author contribution: All authors contributed equally to all parts of this work, prepared, revised and agreed to submit the manuscript for publication.

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[DOI: 10.61186/ijrr.24.1.23]