Neutrophil–Lymphocyte and Platelet–Lymphocyte Ratios as Prognostic Factors after Stereotactic Radiation Therapy for Early-Stage Non–Small-Cell Lung Cancer

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Introduction: The hematologic indices of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are correlated with clinical outcomes after stereotactic radiation.

Methods: We retrospectively evaluated the pretreatment NLR and PLR in patients treated with stereotactic radiation for early stage non–small-cell lung cancer at our institution. A total of 149 patients treated for non–small-cell lung cancer were identified, and 59 had stage I disease with neutrophil, platelet, and lymphocyte levels within a 3-month period before treatment. Receiver operating characteristic (ROC) analysis was performed to examine cutoff values for survival and nonlocal failure followed by Kaplan–Meier analysis for survival.

Results: With a median follow-up of 17 months, 28 deaths were observed, and the median overall survival for all patients was 43 months. Based on the ROC analysis, NLR and PLR cutoff values for further survival analysis were determined based on the ROC analysis to be 2.98 and 146. The median overall survival was not reached for patients with low NLR or PLR but the survival was 23 months for patients with high NLR or PLR. There was no correlation between NLR and nonlocal failure, but on multivariate analysis PLR was found to be associated with freedom from nonlocal failure. Nonlocal failure rates were 11% for patients with PLR less than 250 and 58% for PLR greater than 250 ($p < 0.001$).

Conclusion: The pretreatment NLR and PLR represented significant prognostic indicators of survival in patients treated for early-stage non–small-cell lung carcinoma with stereotactic radiation. The PLR may be used as a prognostic indicator for nonlocal failure after stereotactic radiation for early-stage lung cancer.

Key Words: Non–small-cell lung cancer, Stereotactic radiation, Early stage, Inflammation.

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An estimated 15% of patients with lung cancer are diagnosed with clinically localized carcinoma of the lung.[1] The primary treatment for early-stage cancer is lobectomy. In those patients where lobectomy is not an option, such as for medically inoperable patients or for those unwilling to undergo surgery, stereotactic body radiation therapy, also known as stereotactic ablative radiotherapy (SABR), has shown efficacy with improved local control and survival outcomes relative to traditional radiation therapy.[2]

The cellular components of the host hematologic system, including cells involved in hemostasis, inflammation, and immunity, may influence survival outcomes in patients with cancer.[3] The neutrophil-to-lymphocyte ratio (NLR) is an easily derived marker of global inflammation with prognostic value for survival in patients with various solid tumors, with higher values associated with more aggressive cancers with poor prognosis.[4–13] Thrombocytosis has also been negatively correlated with overall survival in patients with cancer, and investigators have also shown prognostic value in the platelet-to-lymphocyte ratio (PLR) for various malignancies.[14–17] Both the NLR and PLR have also been shown to demonstrate prognostic utility for a variety of nonmalignant chronic medical conditions as well.[18,19] Although neutrophil, lymphocyte, and platelet counts and ratios may simply be paraneoplastic surrogate markers for tumor-permissive or tumor-rejecting host states each of these cell types has also been shown to interact with and influence developing tumors in preclinical models. Thus, simple inexpensive-independent prognostic factors derived from readily available laboratory values would have a practical impact on clinical oncology.

If the NLR and PLR showed prognostic value for patients undergoing radiation therapy for early-state lung cancer, this information may prove useful in selecting patients for adjuvant systemic therapy as a significant minority of patients with disease seemingly localized on initial staging will develop distant metastases or regional failure. Use of adjuvant therapy in patients with early stage lung cancer, including those treated with SABR, is controversial, and the availability of simple biomarkers for disease dissemination would provide criteria for selecting patients for further treatment with systemic agents. Therefore, we evaluated the association between the NLR and PLRT with survival and other outcomes in patients treated with stereotactic radiation for early stage non–small-cell lung cancer (NSCLC).

PATIENTS AND METHODS

Patients treated at the University of Texas Southwestern (UTSW) for stage I NSCLC of the lung with SABR between January 1, 2006 and August 31, 2012 with recorded whole

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blood counts within 3 months before radiation with biopsy-proven stage I NSCLC were selected for study. Patients treated with stereotactic radiation were either not a candidate for lobectomy or elected not to have surgery. The retrospective study was approved by the UTSW Institutional Review Board at the sponsoring institution.

For radiation treatments, patients were immobilized with a large vacuum pillow inside either a commercially available Elekta Stereotactic Body Frame (Elekta, Stockholm, Sweden) or a larger carbon fiber body frame. Tumor motion was assessed with fluoroscopy. If tumor motion was greater than 1 cm in any direction, respiratory coaching with abdominal compression was used to decrease tumor motion. Maximum intensity projection images from a four-dimensional computed tomography (CT) were registered with the simulation CT scan. The internal target volume was defined using maximum intensity projection images or a Boolean union of inspiration and expiration phases. The planning target volume was generated through a 0.5 cm expansion of the internal target volume in all directions. A treatment plan was generated using 7 to 13 noncoplanar, nonopposing beams using the Pinnacle planning software (Phillips, Amsterdam, The Netherlands). Dosimetry required that 95% of the planning target volume received the prescription dose. Fractionation was based on tumor location, adjacent organ dose limits, and patient involvement in institutional and Radiation Therapy Oncology Group (RTOG) trial protocols.

Follow-up consisted of physical examination and CT scan every 3 months for the first year followed by continued exams with CT scans every 6 months. If there were suspicious findings including increase in consolidation near the treated site or the development of a new lung nodule or enlarging lymph node, a positron emission tomography–CT was performed. Fluorodeoxyglucose (FDG) avidity similar to the avidity at staging was considered evidence for recurrent disease. If there was still doubt, a biopsy was performed. Local failure was any recurrence within the same lobe of the lung that was treated. Nonlocal failure was a recurrence in any distant site or the regional lymph nodes including the hilum and mediastinum.

Patient characteristics were descriptively summarized using means and standard deviations for continuous data and using frequencies for categorical data. Categorical data analyses were performed using a two-sided Fisher's exact test. Multiple linear regression analyses were used to determine factors associated with NLR and PLR. Receiver operated characteristics (ROC) curves were constructed to determine cutoff values of NLR and PLR that yield the joint maximum sensitivity and specificity. Overall survival and nonlocal failure-free survival were calculated using the Kaplan–Meier method measured from the first day of treatment. Comparisons of survival between groups were made using the log-rank test. Results were considered significant if the p value was less than 0.05. Cox regression analyses were used for univariate analyses. Stepwise Cox regression analyses were conducted to identify significant-independent factors associated with overall survival and freedom from nonlocal failure. SPSS version 21 was used for all statistical analyses (SPSS Inc.; Chicago, IL).

RESULTS

One hundred forty-nine patients were treated with SABR for lung cancer in the study period. Ninety-one of these patients had neutrophil, lymphocyte, and platelet counts in our records within 3 months before the initiation of radiation therapy, but only 59 had biopsy-proven stage IA or IB NSCLC. Thirty-four patients had adenocarcinoma, 19 had squamous cell carcinoma, and six were not specified further than NSCLC. Patient characteristics and hematologic data are shown in Table 1. Tumors ranged in size from 1 to 5 cm, with a median value of 2.1 cm. Treatment was delivered in 1 to 8 fractions over 1 to 22 days. Prescribed doses ranged from 34 to 60 Gy (Table 2). Median follow-up for all patients was 17 months. The 1- and 2-year overall survival was 80% and 74%, respectively.

Multiple linear regression analysis showed that age, gender, location of the tumor and stage (IA or IB) were not significantly associated with pretreatment NLR. However, larger tumor size ($p = 0.010$) was negatively associated with NLR. Multiple linear regression analysis showed that PLR was significantly associated with gender ($p = 0.030$) and tumor size ($p = 0.021$). When PLR and NLR were compared with linear regression, there was a strong correlation ($r = 0.772$, $p < 0.001$) between NLR and PLR.

ROC plots were generated to evaluate the relationship between overall survival and both NLR (area under the curve [AUC] = 0.678) and PLR (AUC = 0.681) (Fig. 1). The ROC cutoff values for maximum joint sensitivity and specificity for predicting survival were 2.98 for NLR and 146 for PLR (Table 3). Patients were stratified based on these values, and survival was analyzed using the Kaplan–Meier method. Median overall survival for patients with a NLR less than 2.98 was not reached and for those with NLR greater than or equal to 2.98 was 23 months ($p = 0.007$ by log-rank test, 95% confidence interval [CI], 6–38 months; Fig. 2*A*). Median overall survival for patients with PLR less than 146 was not reached, but for patients with values greater than or equal to 146 was 23 months ($p = 0.003$ by log-rank test, CI, 10–35 months; Fig. 2*B*).

Univariate Cox regression analyses were performed using total dose, age, gender, NLR, PLR, histology, and tumor

TABLE 1. Patient Characteristics

Demographics	Median (Range)
Patients	59
Men:Women	31:28
Age (years)	70 (48–89)
Central tumor location	14
Neutrophil (10^6 per ml)	4.8 (0.8–13.2)
Neutrophilia (>7.5×10^6 per ml)	5
Platelet (10^6 per ml)	230 (21–531)
Thrombocytosis (>400×10^6 per ml)	12
Lymphocyte (10^6 per ml)	1.5 (0.3–5.7)
Lymphocytopenia (<1×10^6 per ml)	12
NLR	2.8 (0.5–33.0)
PLR	151 (25–839)

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

TABLE 2. Treatment Characteristics Including Number of Fractions, Total Dose, and the Number of Patients Treated with Each Number of Fractions

Fractions	Median Dose	Range	Patients
1	34	34	3
3	54	52.5–60	33
4	48		1
5	60	45–60	22
Stage			
IA	54	34–64	43
IB	54	34–60	16

Distribution of patients by stage with median dose and dose range.

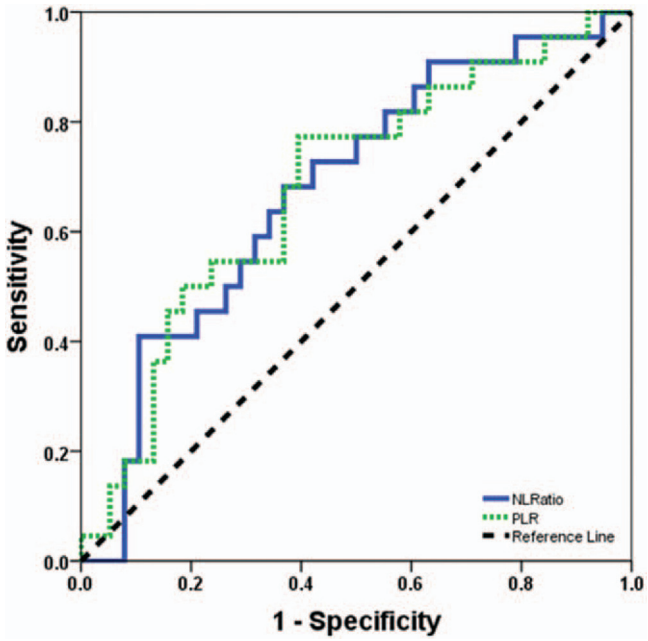

FIGURE 1. ROC curve for NLR and PLR based on overall survival. ROC, receiver operating characteristics; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

TABLE 3. Distribution of Cases Based on ROC Cutoffs

	NLR		PLR			
	<2.98	>2.98	<146	>146	<250	>250
Alive	24	13	23	14	33	4
Deceased	7	15	5	17	14	8
No failure	25	20	23	22	40	5
Local failure	2	0	2	0	2	0
Nonlocal failure	4	8	3	9	5	7

ROC, receiver operating characteristics.

size as possible variables. When NLR and PLR were analyzed as continuous variables, overall survival was not significantly associated with either NLR or PLR. When NLR and PLR were coded as categorical variables with cutoffs of 2.98 and 146, respectively, both NLR ($p = 0.005$) and PLR ($p = 0.003$)

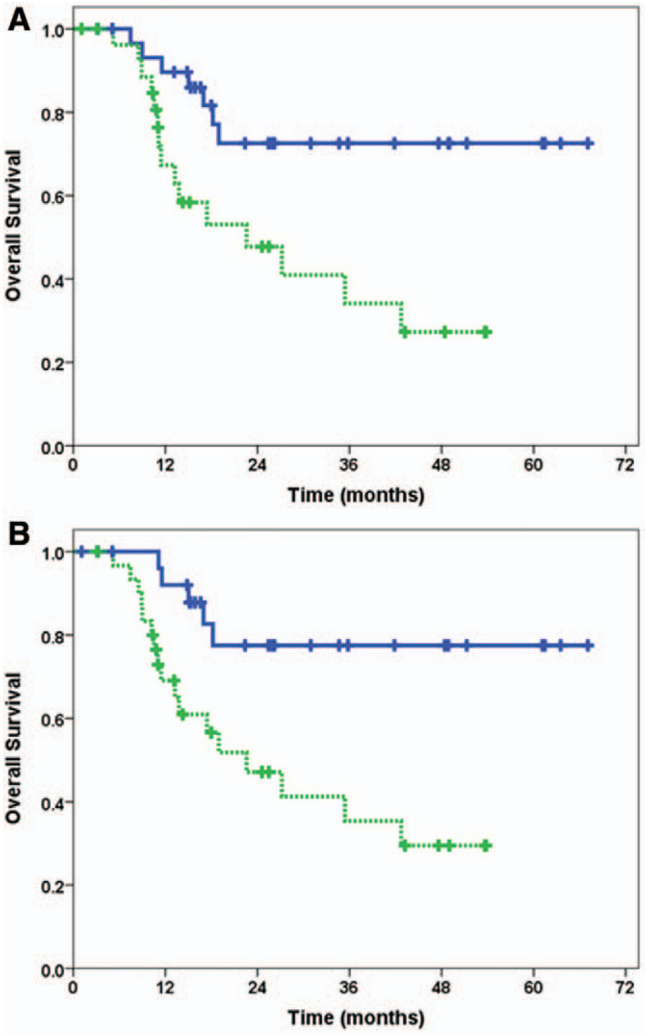

FIGURE 2. Survival in early stage patients. *A*, Survival based on NLR. Solid blue: NLR less than 2.98; dashed green: NLR greater than 2.98. *B*, Survival based on PLR. Solid blue: PLR less than 146; dashed green: PLR greater than or equal to 146. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

were significantly associated with overall survival. On stepwise Cox regression analysis, only PLR coded as a categorical variable (hazard ratio [HR], 4.0; CI, 1.5–11.0; $p = 0.006$) was significantly associated with overall survival likely because PLR and NLR were previously found to be correlated. When examining the results based on the Charleston comorbidity index (CCI), the CCI was not associated with overall survival on univariate or multivariate analysis.

Patterns of tumor failure in the patients were also assessed. Two patients had a local failure, along with 12 nonlocal failures. Both of the patients with local failures had NLR and PLR below the cutoff threshold used in survival analysis. Further analysis of local failure was not undertaken as a result of the low frequency of this event. A separate ROC analysis was performed to assess the best cutoff points for nonlocal failure for both NLR and PLR (Fig. 3*A*). The 1- and

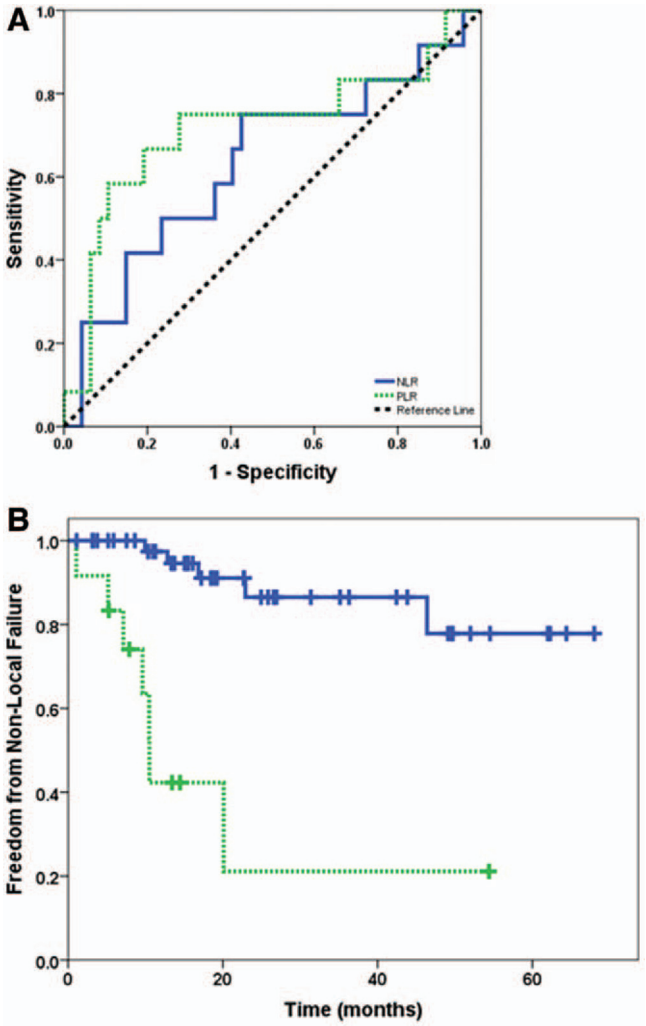

FIGURE 3. ROC curve for NLR and PLR based on development of nonlocal failure. *A,* ROC curve for nonlocal failure. Solid blue: NLR; dashed green: PLR. *B,* Kaplan–Meier survival of patients with or without PLR greater than or equal to 250. Solid blue: PLR less than 250; dashed green: PLR greater than or equal to 250. ROC, receiver operating characteristics; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

2-year rates of freedom from development of nonlocal failure were 86 and 74%, respectively. There was no significant cutoff point observed for NLR (AUC = 0.635; $p = 0.15$), but a PLR cutoff of 250 was found to maximize the sensitivity and specificity (AUC = 0.720; $p = 0.02$) (Table 3). When the patients were divided based on the 250 cutoff for PLR, there were 47 patients with PLR less than 250 with five nonlocal failures and 12 patients with PLR greater than or equal to 250 with seven nonlocal failures. In patients with PLR less than 250, three failures were in different lobes of the lung and three were in the hilum or mediastinum. In patients with PLR greater than 250, two failures were in different lobes of the lung, four were in the hilum or mediastinum, and one was in the brain (Table 4).

Patients were stratified for Kaplan–Meier analysis based on PLR greater than or less than 250 (Fig. 3*B*). Median nonlocal failure-free survival for patients with PLR greater than or equal to 250 was 10.5 months (CI, 9.2–11.8 months, $p < 0.001$). The median nonlocal failure-free survival for those with PLR less than 250 was not reached. Univariate Cox regression analyses for development of nonlocal failure were performed using dose, age, gender, NLR, PLR, and tumor size as possible variables. When NLR and PLR were analyzed as continuous variables, freedom from nonlocal failure was not significantly associated with PLR ($p = 0.133$) or NLR ($p = 0.937$), but it was associated with increasing tumor size (HR, 1.73; CI, 1.02–2.96; $p = 0.044$). When coded as a binary variable with cutoff of 250, PLR ($p < 0.001$) was significantly associated with development of nonlocal failure along with tumor size ($p = 0.003$). On stepwise Cox regression analyses, PLR as a binary variable (HR, 99.7; CI, 10.3–962; $p < 0.001$), tumor size (HR, 2.45; CI, 1.42–4.25; $p = 0.001$), and age (HR, 0.92; CI, 0.85–0.99; $p = 0.020$) were significantly associated with freedom from nonlocal failure. When examining the results based on the CCI, the CCI was not associated with nonlocal failure-free survival on univariate or multivariate analysis.

TABLE 4. Patterns of Failure

	Lung	Hilum or Mediastinum	Brain
<250 (N = 47)	3	2	0
>250 (N = 12)	2	4	1

The location of distant failure based on platelet-to-lymphocyte ratio.

DISCUSSION

The link between inflammation, particularly chronic inflammation, and cancer progression has been known for over a century.[3] Chronic inflammation has been shown to be associated with the induction of lung cancer and cancer in other organs.[20] Chronic inflammation is associated with suppression of anti-tumor immune responses and a proangiogenic "wound healing" environment that favors tumor progression. Cytokines are a key component of the inflammatory process, and their expression can lead to alterations in the levels of lymphocytes, neutrophils, and platelets.[21] Moreover, lymphocytes, neutrophils, and platelets have all individually been implicated in modulation of tumor growth, in both negative and positive associations. Circulating T lymphocytes with specificity for tumor-associated antigens lead to tumor rejection, whereas other populations of lymphocytes such as regulatory T cells may suppress antitumor cytotoxic lymphocytes.[22]

Neutrophils have also been shown to have both tumor-promoting and tumor-suppressing abilities. In a preclinical model, Fridlender et al.[23] showed that neutrophils exhibit plasticity in their anti- and pro-tumor effects under the control of transforming growth factor-β. Other investigators have shown that inhibiting neutrophil infiltration of tumors slowed tumor growth.[24] Neutrophils can inhibit the immune response in lung cancer by tumor-induced secretion of arginase.[25]

Platelets facilitate circulation of tumor cells and may play a role in homing of circulating tumor cells to distant organs.[26]

Previous studies demonstrated that depletion of platelets inhibited metastatic potential, and the reconstitution of platelet levels restored metastatic potential.[27,28] Platelet interactions with tumor cells lead to rolling and tethering of tumor cell aggregates, leading to extravasation through the endothelial wall and immune protection.[26,29] Platelets have been shown to promote the spread of tumors through multiple mechanisms including selectin and integrin interactions with tumor cells.[30]

An outstanding dilemma in the treatment of early-stage lung cancer is selection of patients for the use of adjuvant systemic therapy. In a recently published RTOG phase II evaluation of SABR for treatment of early stage lung cancer in medically inoperable patients, despite excellent local tumor control rates approximately 20% of patients developed distant metastatic disease by 3 years.[2] A simple prognostic biomarker derived from the complete blood count such as the PLR may find use in selecting which subset of patients with clinically staged localized disease would benefit from adjuvant systemic treatment. As SABR is associated with a rapid treatment course typically without significant acute toxicities, chemotherapy can likely be seamlessly integrated into sequential treatment plans for these patients. In our analysis, we did not pursue biomarkers for local treatment failure as the rate of local recurrence was low.

Sarraf et al.[9] recently reported on the NLR as a prognostic biomarker in patients with early stage NSCLC undergoing surgery. As tumor-ablating treatments, surgery and SABR differ in many respects and thus may interact with and influence the host inflammatory state in different ways; as a result, it could not be clear before our study if the NLR would have the same prognostic status as it does in surgical patients. Interestingly, although increased NLR was associated with poor overall survival in our analysis, only the PLR was associated with an increased risk of developing nonlocal failure. This finding may be related to the fact that patients treated in our study typically had significant medical comorbidities (precluding surgical intervention). Elevated NLR has previously been associated with worse outcomes in patients with serious chronic but nonmalignant medical conditions such as renal and cardiac disease.[18,19] Many of the patient deaths in our study were related to these comorbidities as opposed to cancer-related death, but the Charleston comorbidity index was not related to either overall survival or nonlocal failure.

Our study is limited by its relatively small size and our findings need confirmation in larger series before their broad applicability in clinical decision-making for patients. Other studies examining trends in complete blood count (CBC) markers and response to therapy have been done in surgical and chemotherapy series. These modalities require a CBC within 1 week to 1 month before treatment. Because this is not always done routinely before SABR, the CBC in this study was up to 3 months before the initiation of treatment, which makes it more difficult to compare the results of this study to those of other studies. Because the PLR was predictive of development of metastases as a dichotomous variable, it could be examined in future prospective studies for its prognostic value, and these prospective studies should have CBCs closer to the time of treatment initiation. Further study of acute and chronic effects of SABR on hematologic parameters is also needed. High-dose radiation may also modulate neutrophil phenotype, altering the balance of pro- and antitumor neutrophils.[31] Because NLR was associated with OS but not nonlocal failure, further study may find that PLR is the dominant factor relating SABR with nonlocal failure or overall survival.

Overall, this is, to the best of our knowledge, the first study examining the association among stereotactic radiation, hematologic variables, and survival and metastasis outcomes in patients with stage I NSCLC and NLR or PLR. We observed worse outcomes in patients with an elevated NLR or PLR in early stage patients. An elevated PLR was also associated with an increased risk of nonlocal failure. The NLR and PLR can be used as a prognostic tool for patients with early stage disease. Further research should be done to examine the correlation between radiation treatments and the inflammatory response both pretherapy and posttherapy to further optimize treatment strategies.

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