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Higher aorta dose increased neutrophil-to-lymphocyte ratio resulting in poorer outcomes in stage II-III non-small cell lung cancer

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Abstract

Background: This study focused on the relationship between the neutrophil-to-lymphocyte ratio (NLR) and the dose of organs at risk in patients with stage II–III non-small cell lung cancer (NSCLC) receiving intensity-modulated radiotherapy.

Methods: The clinical characteristics and dosimetric parameters of 372 patients were collected retrospectively. A high NLR was defined as that ≥1.525. Survival analysis was conducted using the Kaplan–Meier and Cox regression analysis. Least absolute shrinkage and selection operator (LASSO) analysis was conducted to select appropriate dosimetric parameters. The risk factors of NLR were evaluated using univariate and multivariate logistic regression analyses.

Results: Patients with a high NLR had poorer progression-free survival (PFS) ($p = 0.011$) and overall survival (OS) ($p = 0.061$). A low NLR (<1.525) predicted better PFS (hazard ratio [HR] 0.676, 95% confidence interval [CI]: 0.508–0.900, $p = 0.007$) and OS (HR 0.664, 95% CI: 0.490–0.901, $p = 0.009$). The aorta dose differed between the low and high NLR groups (all <0.1) in the univariate analysis. An aorta V10 was confirmed as a significant risk factor for a high NLR (odds ratio [OR] 1.029, 95% CI: 1.011–1.048, $p = 0.002$). Receiving chemotherapy before (OR 0.428, 95% CI: 0.225–0.813, $p = 0.010$) and during (OR 0.491, 95% CI: 0.296–0.815, $p = 0.006$) radiotherapy were predictive factors of a low NLR.

Conclusion: The aorta dose was significantly associated with a high NLR. Patients with stage II–III NSCLC with a high NLR had poorer prognosis. Receiving chemotherapy before and/or during radiotherapy predicted a low NLR.

KEYWORDS

aorta dose, intensity-modulated radiotherapy, neutrophil-to-lymphocyte ratio, non-small cell lung cancer, prognosis

INTRODUCTION

Lung cancer is one of the most prevalent malignancies worldwide,[1] with non-small cell lung cancer (NSCLC) being the most common subtype. Although many treatment modalities, such as targeted therapy and immunotherapy, have emerged recently, the lung cancer mortality rate ranks first among cancers.[1] Moreover, radiotherapy (RT) and chemotherapy are standard treatments for stage II-III NSCLC without surgery. In addition, several inflammatory blood indicators (lymphocytes,[2,3] neutrophils,[4] neutrophil-to-lymphocyte ratio [NLR],[5] and platelet-to-lymphocyte ratio[5,6]) have been reported to be prognostic factors[7,8] that partly reflect the status of the body and treatment effects of patients.

Studies have shown that a dose as low as 0.5 Gy for lymphocytes could lead to lymphocyte death,[9] which could decrease immunity. Immune matrices of the lymphocyte subtype have been proven to be connected with the prognosis in the patients receiving immunotherapy.[10] Additionally, the radiosensitivity of different subtype lymphocytes was distinct.[11] Neutrophils are also critical to the immune response and have been demonstrated to drive tumor progression and metastasis.[12] Furthermore, in NSCLC, increased levels of circulating neutrophils are associated with a significantly worsened outcome.[4] Recently, a high NLR has been demonstrated to be associated with low overall survival (OS) in patients with solid tumors.[13,14] Therefore, the NLR is a prognostic indicator in patients with NSCLC,[5,15,16] small cell lung cancer,[17,18] and other cancers.[19–22] Specifically, Nathan et al. revealed that the NLR is a significant prognostic indicator of survival in patients treated for early-stage NSCLC with stereotactic radiation.[5] Moreover, patients with stage IV NSCLC[15] with a high NLR were also significantly associated with poor OS, as were those treated with nivolumab.[16] Additionally, a high NLR was associated with a lower probability of response to immunotherapy in pan-cancer.[23] Since high NLR is correlated with adverse events,[24,25] we should explore measures to avoid a high NLR to prevent a poor prognosis. In intensity-modulated radiotherapy (IMRT), the intrinsic factors between organs at risk (OARs) and the NLR have been rarely investigated. However, Sakaguchi et al. revealed that the spleen V5 and V10 were significantly associated with a high NLR in patients with esophageal cancer.[26] Further, Xia et al. demonstrated that a high 1-month post-RT start NLR was associated with inferior progression-free survival (PFS), and a heart V20, heart V40, and mean body dose were significantly associated with the 1-month post-RT start NLR in patients with lung cancer.[27] However, no studies have investigated the relationship between the NLR during RT and the dose of OARs in a large vessel and hematopoietic tissues in patients with stage II–III NSCLC, which could help predict patient status and identify precise interventions.

Here, we collected data on OARs (vessels and bony structures) for further analysis. This study aimed to identify the independent prognostic role of the NLR in patients with stage II–III NSCLC receiving IMRT. In addition, specific dosimetric factors affecting the NLR in IMRT were further revealed.

METHODS

Patients and ethics statement

We conducted a retrospective study on patients with NSCLC (stages II and III, AJCC eighth edition) who received radical IMRT between April 2014 and December 2019 at our institution. The patients' relevant medical records were reviewed and collected. Eligible patients aged 18–75 years without primary tumor resection were treated with radiation therapy at a dose ≥54 Gy. Moreover, patients with a history of RT or more than one primary tumor were excluded. All included patients were treated with or without concurrent platinum-based chemotherapy.

The institutional review board of our institution approved the procedures, and the requirement for informed consent was waived due to the retrospective nature of this study.

Radiotherapy

Before treatment, the patients underwent computed tomography (CT) simulation in the supine position. Each slice was 5 mm, and the images included the neck, chest, and upper abdomen. The gross tumor volume (GTV) was outlined based on the images. The clinical tumor volume (CTV) expanded by the GTV by 1.2–1.5 cm margins. Similarly, the planning tumor volume (PTV) expanded by the CTV by 0.7 cm margins. Philips Pinnacle[3] treatment planning system (TPS) (version 8.0, Philips) with 6 MV photon coplanar beams was used for the calculations. Cone-beam CT was performed to confirm the tumor location on the first day of RT. At least 95% of the prescribed dose and 99% of the PTV were covered by 95% of the prescribed dose. The representative dose/fractionation for patients receiving IMRT treatment was mainly 60 Gy/30F.

In addition to the conventionally delineated OARs, including the heart, total lungs, and spinal cord, we used the TPS uRT (United Imaging Healthcare) to delineate other OARs, such as the aorta, thoracic spine, sternum, and ribs. Furthermore, we manually checked and modified the delineated structural scope, and two experienced physicians reviewed the completed plans. The dose parameters (mean dose, V5, V10, V15, V20, V30, V35, V40, V45, and V50) of the OARs were derived for further analysis. The Criteria for Delineation of OARs requiring Special Clarification were as follows: (1) aorta: ascending aorta + aortic arch + descending aorta + thoracic aorta; (2) thoracic vertebrae: from the first to the twelfth thoracic vertebra; (3) sternum: sternal manubrium and sternal body; (4) ribs: from the first to the twelfth rib; (5) spinal cord: layers corresponding to the thoracic vertebra; (6) body: all layers within the CT simulation position.

Clinical data collection

Clinical characteristics were exported from medical record systems and manually verified. Patients who received chemotherapy before IMRT or concurrent chemoradiotherapy (CCRT) were reviewed. Additionally, the NLR was calculated by dividing the absolute neutrophil and lymphocyte counts in the peripheral blood. The blood test was conducted at least once a week. The nadir of the NLR during IMRT was collected for further analysis. Patients were followed up regularly to collect survival data, every 3 weeks during the first 2 years, every 6 months during the next

TABLE 1 Clinical characteristics of all patients and two groups

Characteristics	ALL ($N = 372$)	Low NLR ($N = 91$)	High NLR ($N = 281$)	*p*-value
Gender				0.663
Female	58 (15.6%)	16 (17.6%)	42 (14.9%)	
Male	314 (84.4%)	75 (82.4%)	239 (85.1%)	
Age	60.0 (9.47)	59.2 (9.02)	60.2 (9.61)	0.370
Smoking				0.783
No	125 (33.6%)	29 (31.9%)	96 (34.2%)	
Yes	247 (66.4%)	62 (68.1%)	185 (65.8%)	
Tumor laterality				0.738
Left	163 (43.8%)	38 (41.8%)	125 (44.5%)	
Right	209 (56.2%)	53 (58.2%)	156 (55.5%)	
Tumor location				0.275
Upper + middle lobe	295 (79.3%)	68 (74.7%)	227 (80.8%)	
Lower lobe	77 (20.7%)	23 (25.3%)	54 (19.2%)	
Pathology				0.713
ADC	131 (35.2%)	34 (37.4%)	97 (34.5%)	
non-ADC	241 (64.8%)	57 (62.6%)	184 (65.5%)	
ECOG				0.971
0	31 (8.3%)	7 (7.7%)	24 (8.5%)	
1 or 2	341 (91.7%)	84 (92.3%)	257 (91.5%)	
T				0.747
T1-2	201 (54.0%)	51 (56.0%)	150 (53.4%)	
T3-4	171 (46.0%)	40 (44.0%)	131 (46.6%)	
N				0.265
N0-1	61 (16.4%)	11 (12.1%)	50 (17.8%)	
N2-3	311 (83.6%)	80 (87.9%)	231 (82.2%)	
TNM				0.505
II	33 (8.9%)	6 (6.6%)	27 (9.6%)	
III	339 (91.1%)	85 (93.4%)	254 (90.4%)	
Chemotherapy before RT				***0.032***
No	95 (25.5%)	15 (16.5%)	80 (28.5%)	
Yes	277 (74.5%)	76 (83.5%)	201 (71.5%)	
CCRT				**0.019**
No	185 (49.7%)	35 (38.5%)	150 (53.4%)	
Yes	187 (50.3%)	56 (61.5%)	131 (46.6%)	
Dose (Gy)	60.0 (2.09)	59.8 (1.85)	60.1 (2.17)	0.254
Fraction	29.8 (1.70)	30.0 (1.13)	29.7 (1.84)	0.071
Duration (d)	43.4 (5.88)	45.0 (6.00)	42.9 (5.75)	***0.003***
PTV (mm^3)	550 (272)	538 (290)	554 (267)	0.632

Abbreviations: ADC, adenocarcinoma; CCRT, concurrent chemoradiotherapy; d, days; NLR, neutrophil-to-lymphocyte ratio; PTV, planning target volume; RT, radiotherapy.

3 years, and subsequently once a year for further follow-up. Patients without death events were identified using sensors.

Statistical analysis

Receiver operating characteristic (ROC) curves were used to select the cutoff NLR value (based on PFS data). The independent sample *t*-test was used for continuous variables, Wilcoxon rank-sum test was used for ordered categorical variables, and chi-square test was used for binary and unordered categorical variables. The Kaplan–Meier method and log-rank test were also used for survival analyses. Cox regression analysis was performed to confirm risk predictors of survival. Univariate and multivariate logistic regression analyses were performed to identify independent factors associated with a high NLR. For multivariate logistic

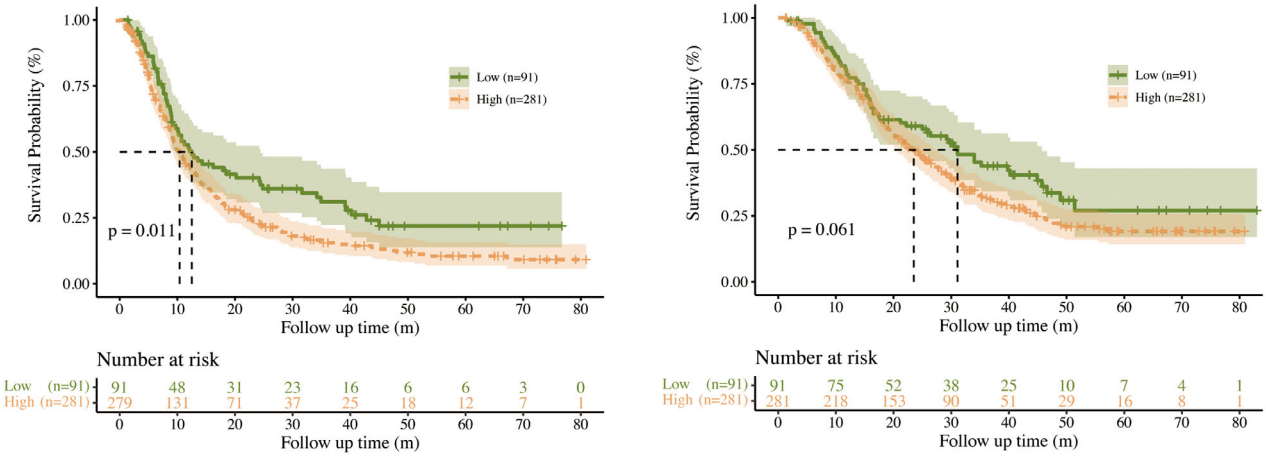

FIGURE 1 Survival analysis of low and high NLR in stage II–III NSCLC. (a) PFS; (b) OS. NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

regression, models were created with backward likelihood ratio elimination, using a $p > 0.1$ for removing variables. LASSO analysis was used to select the appropriate dosimetric variables among the representative dosimetric parameters (Dmean, V5, V10, V15, V20, V25, V30, V35, V40, V45, and V50), subsequently added to the model to analyze which dosimetric parameters were independent risk factors of a high NLR. All analyses were performed using R 4.1.3 (R Foundation for Statistical Computing). Two-tailed $p < 0.05$ were considered statistically significant.

RESULTS

Overall, 372 patients were included in this study. The clinical characteristics of the patients are presented in Table 1. Most patients (79.3%) had tumors located in the upper and middle lobes. The pathological type was mainly nonadenocarcinoma (non-ADC) over ADC (64.8% vs. 35.2%). A total of 339 patients (91.1%) had stage III disease. In addition, most patients received chemotherapy before RT (74.5% vs. 25.5%), and half of the patients were treated with CCRT. For the entire cohort of patients, the median OS and PFS were 23.2 and 10.5 months, respectively.

ROC analysis identified 1.525 as the threshold of the NLR. After classifying the NLR as high or low, 271 patients were found to have a high NLR. Patients in the low NLR group had a higher frequency of chemotherapy before RT (83.5% vs. 71.5%) and CCRT (61.5% vs. 46.6%) than those in the high NLR group. Moreover, patients in the low NLR group had a longer RT duration. A high NLR was associated with poorer PFS (10.4 vs. 12.5 months, p = 0.011) but shared no significant trend with OS (23.5 vs. 33.1 months, $p = 0.061$) (Figure 1). Subsequently, we performed Cox regression analysis (Table 2) and found that a low NLR (<1.525) was a predictor for both better PFS (HR 0.676, 95% CI: 0.508–0.900, $p = 0.007$) and OS (HR 0.664, 95% CI: 0.490–0.901, $p = 0.009$). In addition, a larger PTV was a predictor of worse PFS (HR 1.001, 95% CI: 1.000–1.001, $p = 0.013$) and OS (HR 1.001, 95% CI: 1.000–1.001, $p = 0.010$).

Furthermore, the relationship between NLR and OARs was evaluated. The difference between a high and low NLR was primarily reflected in the aorta dose (Figure 2 and Supplementary Table S1). No significant difference was observed in the other OARs (Supplementary Figure S1). In addition, univariate analysis revealed a statistically significant difference in the aorta dose volume according to the NLR (approximately $p < 0.05$). Aorta V5 and V10 were associated with a high NLR (Supplementary Table S2 and Supplementary Figure S2) according to LASSO analysis. Subsequently, we formed a logistic regression model to predict high NLR (Table 3). An increasing aorta V10 significantly predicted a high NLR (OR, 1.101, 95% CI: 1.003–1.208, $p = 0.042$). In addition, receiving chemotherapy before (OR 0.428, 95% CI: 0.225–0.813, $p = 0.010$) or during (OR 0.491, 95% CI: 0.296–0.815, $p = 0.006$) RT was predictive for a low NLR. The c-statistic value was 0.694 (Supplementary Figure S2).

DISCUSSION

In this study, we demonstrated that the aorta dose is an independent prognostic factor affecting the NLR in RT. Therefore, limiting the aorta dose might be an effective method to reduce the NLR.

Many previous studies have demonstrated that a high NLR is associated with poorer prognosis in pan-cancer.[13] In patients with early-stage[5] and stage IV NSCLC,[15] as well as those treated with nivolumab,[16] a high NLR was found to be significantly associated with poor OS, which is consistent with our results. In this study, we focused on the NLR at the nadir during IMRT to aid in detecting NLR tendency and intervening earlier, which differed from the previous studies. In our study, a high NLR (≥1.525) in patients with stage II–

TABLE 2 Univariate and multivariate Cox regression analysis for PFS and OS

Cox regression analysis for PFS Characteristics		Univariate analysis		Multivariate analysis	
		HR (95.0% CI)	*p*-value	HR (95.0% CI)	*p*-value
Gender	Female vs. Male	1.101 (0.796–1.523)	0.561		
Age	Continuous	0.987 (0.976–0.999)	***0.034***	0.989 (0.977–1.001)	***0.08***
Smoking	No vs. Yes	1.154 (0.902–1.476)	0.256		
Tumor laterality	Left vs. Right	0.793 (0.629–1.000)	**0.050**		
Pathology	ADC vs. non-ADC	1.022 (0.803–1.302)	0.858		
ECOG	0 vs. 1–2	1.170 (0.764–1.793)	0.471		
T	T1-2 vs. T3-4	1.118 (0.885–1.411)	0.350		
N	N0-1 vs. N2-3	1.396 (1.008–1.933)	**0.044**		
TNM	II vs. III	1.471 (0.967–2.238)	**0.071**		
NLR at nadir during RT	High vs. Low	0.696 (0.524–0.924)	**0.012**	0.676 (0.508–0.900)	***0.007***
Chemotherapy before RT	No vs. Yes	0.974 (0.748–1.268)	0.846		
CCRT	No vs. Yes	0.843 (0.668–1.063)	0.149		
Tumor location	Upper + middle lobe vs. lower lobe	0.967 (0.726–1.289)	0.821		
Dose (Gy)	Continuous	0.968 (0.914–1.026)	0.276		
Fraction	Continuous	0.970 (0.908–1.035)	0.357		
Duration (d)	Continuous	1.000 (0.981–1.020)	0.960		
PTV (mm^3)	Continuous	1.001 (1.000–1.001)	**0.014**	1.001 (1.000–1.001)	***0.013***
Cox regression analysis for OS Characteristics		**Univariate analysis**		**Multivariate analysis**	
		HR (95.0% CI)	***p*-value**	**HR (95.0% CI)**	***p*-value**
Gender	Female vs. Male	1.363 (0.945–1.965)	***0.098***		
Age	Continuous	1.009 (0.996–1.023)	0.182		
Smoking	No vs. Yes	0.725 (0.554–0.950)	***0.019***		
Tumor laterality	Left vs. right	0.907 (0.708–1.163)	0.442		
Pathology	ADC vs. non-ADC	1.688 (1.287–2.216)	***<0.001***	1.740 (1.311–2.311)	***<0.001***
ECOG	0 vs. 1–2	1.050 (0.775–1.423)	0.751		
T	T1-2 vs. T3-4	1.451 (0.875–2.409)	0.149		
N	N0-1 vs. N2-3	1.335 (1.041–1.710)	***0.023***	1.694 (1.183–2.425)	***0.004***
TNM	II vs. III	1.417 (0.999–2.009)	***0.051***		
NLR at nadir during RT	High vs. Low	0.750 (0.555–1.104)	***0.062***	0.664 (0.490–0.901)	***0.009***
Chemotherapy before RT	No vs. Yes	1.654 (1.023–2.673)	***0.040***		
CCRT	No vs. Yes	0.948 (0.714–1.257)	0.709		
Tumor location	Upper + middle lobe vs. lower lobe	0.991 (0.773–1.271)	0.945		
Dose (Gy)	Continuous	1.001 (0.940–1.066)	0.975		
Fraction	Continuous	0.992 (0.929–1.060)	0.818		
Duration (d)	Continuous	1.003 (0.983–1.023)	0.804		
PTV (mm^3)	Continuous	1.001 (1.000–1.001)	***0.003***	1.001 (1.000–1.001)	***0.010***

Abbreviations: ADC, adenocarcinoma; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; d, days; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; PTV, planning target volume; RT, radiotherapy.

III NSCLC receiving RT with or without chemotherapy was strongly correlated with poorer PFS. Although OS was not significantly correlated with the NLR, the results implied a poorer prognosis with a high NLR. Furthermore, Cox analysis paralleled the survival analysis and showed that a high NLR was a predictor of PFS and OS. It suggested that physicians can regularly monitor the NLR of patients in clinical treatment.

Few studies have discussed the association between the dosimetric parameters of OARs and the NLR. Xia et al. focused on locally advanced NSCLC and revealed that heart and body doses were significantly associated with the 1-month post-RT NLR.[27] Another study also discussed the relationship between dosimetric parameters and the NLR in esophageal cancer. It demonstrated that the spleen dose was closely related to the NLR in

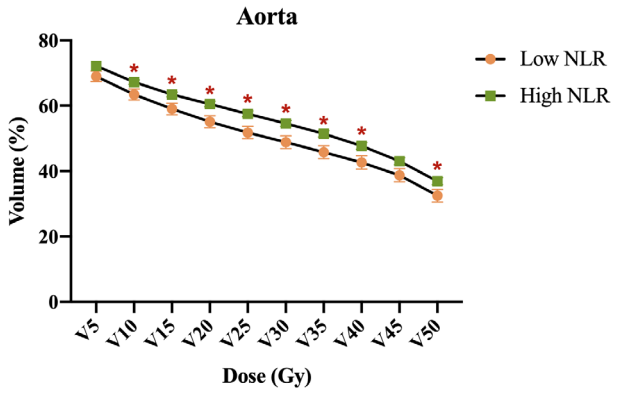

FIGURE 2 The aorta dose volume of low and high NLR. NLR, neutrophil-to-lymphocyte ratio.

patients,[26] which is similar to pancreatic cancer.[28] In this study, we included more OARs that might be related to the NLR, such as the vessels (aorta, heart) and bony structures (sternum, ribs, and thoracic vertebrae). We compared the differences in OARs between the high and low NLR groups to determine the predictive dosimetric parameters of NLR in patients with stage II–III NSCLC without primary tumor resection. We revealed that decreasing the aorta dose might effectively reduce the NLR to obtain superior outcomes. In addition, the modality of radiotherapy was also an important factor that influenced the dose volume of OARs. Proton and heavy ion therapy demonstrated the potential to reduce exposure to target volumes, such as the bone marrow,[29] which might be a strategy to avoid reducing the NLR.

CCRT is the standard treatment for stage II–III NSCLC without surgery. However, in the real world, patients might be unable to adapt to induction chemotherapy or concurrent chemotherapy due to their physical status or other reasons. The relationship between chemotherapy and NLR in stage II–III NSCLC without surgery receiving IMRT has rarely been discussed in the literature. Wang et al. revealed that the absence of CCRT was an independent risk factor of OS rather than PFS.[30] Moreover, Mariusz et al. showed that CCRT was an independent risk factor of OS >2 years rather than >5 years.[31] However, our results suggest that CCRT was not an independent factor of PFS or OS, which was consistent with the results of Contreras et al.[32] Furthermore, we discussed the effect of chemotherapy on the NLR and found that without chemotherapy before or during RT was a significant risk factor of a high NLR. Therefore, it suggested that chemotherapy should be performed as far as possible to gain long-term benefits for patients. Moreover, Contreras et al. revealed that RT alone and CCRT with adjuvant chemotherapy are independent predictors of 4-month post-RT NLR.[32] In addition to chemotherapy, immunotherapy has also been reported as an emerging treatment modality.[33] For example, Xu et al. demonstrated that the survival of patients with an NLR <3 with advanced or metabolic esophageal squamous cell carcinoma at 6 weeks after treatment was significantly better than that of those with an NLR ≥3.

TABLE 3 Univariate and multivariate logistic regression analysis for high NLR

Characteristics		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p* -value
Gender	Female vs. Male	1.214 (0.646–2.283)	0.547		
Age (years)	Continuous	1.011 (0.986–1.036)	0.384		
Smoking	No vs. Yes	0.901 (0.544–1.494)	0.687		
Tumor laterality	Left vs. right	0.895 (0.555–1.444)	0.649		
Pathology	ADC vs. non-ADC	1.131 (0.693–1.848)	0.622		
ECOG	0 vs. 1–2	0.892 (0.371–2.145)	0.799		
T	T1-2 vs. T3-4	1.114 (0.692–1.792)	0.658		
N	N0-1 vs. N2-3	0.635 (0.315–1.280)	0.204		
TNM	II vs. III	0.664 (0.265–1.663)	0.382		
Chemotherapy before RT	No vs. Yes	0.496 (0.269–0.914)	***0.025***	0.428 (0.225–0.813)	***0.010***
CCRT	No vs. Yes	0.546 (0.337–0.885)	***0.014***	0.491 (0.296–0.815)	***0.006***
Tumor location	Upper + middle lobe vs. Lower lobe	1.422 (0.814–2.485)	0.217		
Dose (Gy)	Continuous	1.065 (0.947–1.199)	0.292		
Fraction	Continuous	0.887 (0.751–1.047)	0.156		
Duration (d)	Continuous	0.942 (0.904–0.981)	***0.004***	0.937 (0.898–0.978)	***0.003***
PTV (mm^3)	Continuous	1.000 (0.999–1.001)	0.616		
Aorta V5 (%)	Continuous	1.020 (1.001–1.039)	***0.037***		
Aorta V10 (%)	Continuous	1.021 (1.004–1.039)	***0.018***	1.029 (1.011–1.048)	***0.002***

Abbreviations: ADC, adenocarcinoma; CCRT, concurrent chemoradiotherapy; CT, chemotherapy; d, days; NLR, neutrophil-to-lymphocyte ratio; PTV, planning target volume; RT, radiotherapy.

Additionally, sintilimab was found to be better than conventional second-line chemotherapy.[34] The effect of immunotherapy was not discussed in this study due to the small number of patients receiving immunotherapy after standard chemoradiotherapy.

However, this study has some limitations. First, although data were rarely missing, the risk of patient selection bias was inevitable. Second, this study was conducted at a single center, and the model was not verified by other centers. Third, we found that chemotherapy could influence the NLR; however, each drug might have different effects on lymphocytes and neutrophils, which could lead to different clinical outcomes. Therefore, further investigations should be conducted by expanding the cohort size.

In conclusion, in this study we revealed that increasing the aorta dose was significantly associated with a high NLR in patients with stage II–III NSCLC without surgery treated with IMRT, and a high NLR was associated with poorer prognosis. In addition, receiving chemotherapy before and/or during radiotherapy was a predictor of a low NLR.

AUTHOR CONTRIBUTIONS

Yaqi Li: Conceptualization, Data Curation; Formal Analysis, Investigation, Methodology, Supervision, Writing – Original Draft Preparation. **Xingwen Fan**: Data Curation, Investigation. **Qi Yu**: Data Curation, Investigation. **Haoyang Zhai**: Data Curation, Methodology. **Jing Mi**: Data Curation. **Renquan Lu**: Project Administration. **Guoliang Jiang**: Conceptualization, Writing – Review & Editing. **Kailiang Wu**: Conceptualization, Supervision, Writing – Review and Editing.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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