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NLR, MLR, and PLR are adverse prognostic variables for sleeve lobectomy within non-small cell lung cancer

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Abstract

Background: The goal of the research was to examine the value of peripheral blood indicators in forecasting survival and recurrence among people suffering central-type non-small cell lung cancer (NSCLC) undergoing sleeve lobectomy (SL).

Methods: Clinical information was gathered from 146 individuals suffering from NSCLC who had SL at our facility between January 2014 and May 2023. Peripheral blood neutrophil lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), and platelet lymphocyte ratio (PLR) levels were determined by receiver operating characteristic (ROC) curve to establish the threshold points. Kaplan–Meier survival analysis was employed to evaluate the prognostic value of different groupings, and both univariate and multivariate Cox proportional hazards model (referred to as COX) were performed.

Results: The disease-free survival (DFS) and overall survival (OS) cutoff values were carried out via ROC analysis. Kaplan–Meier survival analysis revealed notable differences in OS for NLR (≥2.196 vs. <2.196, $p = 0.0009$), MLR (≥0.2763 vs. <0.2763, $p = 0.0018$), and PLR (≥126.11 vs. <126.11, $p = 0.0354$). Similarly, significant differences in DFS were observed for NLR (≥3.010 vs. <3.010, $p = 0.0005$), MLR (≥0.2708 vs. <0.2708, $p = 0.0046$), and PLR (≥126.11 vs. <126.11, $p = 0.0028$). Univariate Cox analysis showed that NLR (hazard ratio [HR]: 2.469; 95% confidence interval [CI]: 1.416–4.306, $p < 0.001$), MLR (HR: 2.192, 95% CI: 1.319–3.643, $p = 0.002$) and PLR (HR: 1.696, 95% CI: 1.029–2.795, $p = 0.038$) were correlated alongside OS. Multivariate Cox analysis showed that NLR (HR: 2.036, 95% CI: 1.072–3.864, $p = 0.030$) was a separate OS risk variable. Additionally, the pN stage (HR: 3.163, 95% CI: 1.660–6.027, $p < 0.001$), NLR (HR: 2.530, 95% CI: 1.468–4.360, $p < 0.001$), MLR (HR: 2.229, 95% CI: 1.260–3.944, $p = 0.006$) and PLR (HR: 2.249, 95% CI: 1.300–3.889, $p = 0.004$) were connected to DFS. Multivariate Cox analysis showed that pN stage (HR: 3.098, 95% CI: 1.619–5.928, $p < 0.001$) was a separate DFS risk variable.

Conclusion: The study demonstrates that NLR, MLR, and PLR play a convenient and cost-effective role in predicting survival and recurrence among individuals alongside central-type NSCLC having SL.

KEYWORDS
monocyte lymphocyte ratio, neutrophil lymphocyte ratio, platelet lymphocyte ratio, prognostic factor, sleeve lobectomy

Rui Han and Fan Zhang contributed equally to this work as co-first authors.

INTRODUCTION

According to the American Cancer Society, there will be 125 070 lung and bronchus cancer-related fatalities and 234 580 fresh cases in the USA in 2024. It is the most prevalent type of cancer in terms of incidence among men and second only to breast cancer among women, while it ranks first in terms of mortality for both genders.[1] Pneumonectomy (PN) has long been considered the gold standard for treating central-type non-small cell lung cancer (NSCLC) involving the main bronchus, with this surgical approach being associated with postoperative complications and mortality rates.[2] Increasing evidence suggests that sleeve lobectomy (SL) could provide comparable tumor inhibition to PN while also enhancing the postoperative standard of life.[3–6] Therefore, prognostic indicators that are both affordable and dependable are required for NSCLC patients receiving SL.

Systemic inflammatory reaction serves an essential part within the development and spread of cancer.[7–9] Numerous investigations have shown the significant function of inflammatory indicators within the prognosis of various cancer sufferers. For example, increased platelet lymphocyte ratio (PLR) and neutrophil lymphocyte ratio (NLR) have been linked to shorter overall survival (OS) and progression-free survival (PFS) and worse response rates among individuals alongside metastatic NSCLC receiving nivolumab.[10] A separate predictor of late-stage breast cancer recurrence is elevated NLR.[11] Additionally, the NLR, PLR, and monocyte lymphocyte ratio (MLR) are closely related to the prognosis of NSCLC sufferers[12,13] Prior research has demonstrated that elevated NLR and PLR are connected to poor prognosis within postoperative central-type NSCLC patients,[14] but the prognostic role of NLR, MLR, and PLR within SL has not been reported. NLR, MLR, and PLR hold promise as cost-effective prognostic markers for SL patients, offering new options for predicting postoperative survival and recurrence status.

Therefore, the aim of this study was to report for the initial time the predictive functions of NLR, MLR, and PLR within long-term survival and recurrence of those suffering from NSCLC following SL therapy in a large single-center sample.

METHODS

Study cohort

We carried out a retrospective examination of 146 sufferers diagnosed alongside NSCLC and undergoing bronchial and/or vascular sleeve lobectomy at Cancer Hospital Chinese Academy of Medical Sciences between January 2014 and May 2023. Inclusion criteria were: (1) Diagnosis of primary NSCLC. (2) Underwent SL. (3) No other malignant tumors in other organs. (4) No neoadjuvant therapy before surgery. Patients excluded from our study were: (1) Missing clinical data. (2) Non-R0 resection. (3) Systemic steroids, prior or ongoing autoimmune diseases. All patients underwent chest computed tomography (CT), brain magnetic resonance imaging (MRI)/cranial CT, abdominal ultrasound, bone emission computed tomography (ECT), or whole-body positron emission tomography CT (PET-CT) to rule out distant metastases. In a multidisciplinary team debate, thoracic surgeons and oncologists decided on the surgical approach after receiving informed permission from the sufferers. Prior to the initiation of treatment without intervention, baseline complete blood counts were collected from patients through venous blood samples. Two prominent specialists through the Pathology Department of Cancer Hospital Chinese Academy of Medical Sciences performed the pathological diagnosis. Accurate postoperative staging was gathered based on the eight/ninth edition of the TNM system by the American Joint Committee on Cancer (AJCC).

From each patient's hospital file, we gathered pertinent clinical information, such as demographics and perioperative information. Postoperative complications were categorized in accordance with the Clavien-Dindo classification.[15] Follow-up after surgery was conducted through outpatient visits and telephone follow-ups, with routine check-ups at one, three, six, and 12 months after surgery, subsequently by semi-annual visits until the fifth year. Each follow-up required physical examinations, chest CT, and relevant lung tumor marker tests. The final follow-up date was May 5, 2024. The research has been authorized through the Ethics Committee of Cancer Hospital Chinese Academy of Medical Sciences and carried out based on the Helsinki Declaration (revised in 2013).

Surgical criteria

The SL technique[16] involves resecting a portion of a normal bronchus from a lung lobe and then anastomosing the cut ends of the bronchus. Several circumstances may warrant consideration of a SL: (1) When the tumor is situated near the lobe's bronchial aperture and there is enough space between it and the carina to permit anastomosis. (2) When the clinical stage is below stage IIIA. The thoracic surgeon has the final say on the surgical strategy. In certain cases, an open thoracotomy may replace a thoracoscopic procedure during surgery. The surgical resection involves removing a segment of the affected bronchus and pulmonary artery, sending the upper and lower margins of the bronchus/pulmonary artery for intraoperative frozen pathology to confirm negative margins, followed by circumferential bronchial and pulmonary artery anastomosis using 3–0 proline and systematic or lobe-specific lymph node (LN) dissection. Postoperatively, a chest tube is placed to facilitate lung expansion and fluid drainage.

Statistical analysis

Mean ± standard deviation is used to represent continuous data, whereas *t*-tests or Mann–Whitney U tests are employed to assess continuous parameter. Grouping factors are presented as frequencies (%) and contrasted employing χ^2 or Fisher's exact test. The NLR is determined via separating the absolute neutrophil count through the lymphocyte count measured within peripheral blood before treatment. The PLR is determined via separating the corresponding platelet count through the lymphocyte count. The MLR is determined via separating the monocyte count through the lymphocyte count. OS is characterized as the time from operation to death or last follow-up. DFS is characterized as the time from operation to radiological or clinical progression, or to the last contact with no evidence of progression. Survival analysis was carried out via Kaplan–Meier survival analysis. Unless otherwise specified, statistical evaluations were carried out with SPSS software version 27.0 (IBM-SPSS Inc). All tests were two-tailed. Graphs were generated employed GraphPad Prism version 9.0, unless otherwise specified in the text.

RESULTS

Cohort study

This investigation comprised 146 patients in all. Table 1 shows the clinical and demographic details of each patient. The sufferers who participated had an average age of 59.93 ± 9.97 years. Males accounted for 91.8% of all cases. The percentage of individuals who smoked was greater (82.2%). The majority of sufferers underwent right upper SL and left upper SL (66.4% and 13.7%, respectively). Thoracotomy was the most common surgical approach (77.4%). Squamous cell carcinoma (SCC) was the most typical histological category (78.8%). The average number of LNs dissected was 21.65 ± 9.22. The number of LN stations dissected was 5.81 ± 1.38. The average length of hospital stay (LOS) was 12.95 ± 6.15 days. The total postoperative chest tube drainage was 1887.97 ± 1308.84 mL. The average extubation time was 8.42 ± 5.92 days. The most of sufferers were within stage I–II (78.8% of ninth pTNM stage, 76.0% of eighth pTNM stage) of tumor staging. The disease-free survival was 62.67 ± 38.10 months, and the OS was 66.77 ± 35.53 months. All perioperative complications encountered by the sufferers are detailed within Table 2.

Determination of optimal threshold values for predicting survival using NLR, MLR, and PLR

The median values of NLR, MLR, and PLR within the study population were 2.31, 0.2738, and 123.66, respectively. There was a significant relationship found across NLR and MLR (Spearman's Rho = 0.68, $p < 0.001$), along with across NLR and PLR (Spearman's Rho = 0.49, $p < 0.001$). ROC was performed using NLR, MLR, and PLR as continuous variables to predict survival. The optimal threshold value for NLR was identified to be 2.196 (AUC = 0.654) when NLR = 2.196, yielding a maximum Youden index of 0.246 for predicting patient survival. The same approach was applied to MLR and PLR for predicting survival. The optimal threshold value for MLR was found to be 0.2763 (AUC = 0.623) when MLR = 0.2763, with a maximum Youden index of 0.259. Similarly, for PLR, the optimal threshold value was identified to be 126.11 (AUC = 0.615) when PLR = 126.11, resulting in a maximum Youden index of 0.179. The predictive diagnostic performance of these three variables for survival is illustrated in Figure 1a. Baseline characteristics among the different groups stratified by the cutoff values are presented within Table 3.

Optimal threshold values for predicting recurrence were determined for NLR, MLR, and PLR

According to NLR, MLR, and PLR as continuous variables, ROC were constructed to predict postoperative recurrence in patients. The optimal threshold value for NLR was identified to be 3.010 (AUC = 0.616) when NLR = 3.01, with a Youden index of 0.246, for predicting patient survival based on this cutoff value. The same approach was applied for MLR and PLR in predicting survival. The optimal threshold value for MLR was identified to be 0.2708 (AUC = 0.609) when MLR = 0.2708, with a Youden index of 0.230. The optimal threshold value for PLR was identified to be 161.99 (AUC = 0.587) when PLR = 161.99, with a Youden index of 0.219. The diagnostic performance of these three variables in predicting recurrence is illustrated in Figure 1b in this study. Baseline characteristics among different groups according to the threshold values are shown within Table 4.

Kaplan–Meier analysis for subgroups of NLR, MLR, and PLR

Higher NLR, MLR, and PLR were connected to shorter OS and DFS as shown in Table 2. Following the implementation of threshold values for NLR, MLR, and PLR, we found statistically significant variations in OS across the two categories that were formed from the population, as demonstrated in Figure 2a-c and Table 3. Similarly, significant differences were also observed in DFS, as shown in Figure 2d-f and Table 4.

Cox univariate and multivariate analyses were conducted to evaluate the effect of various elements on OS and DFS. Univariate analysis revealed that NLR (hazard ratio [HR]:2.469; 95% confidence interval [CI]: 1.416–4.306, $p < 0.001$), MLR (HR: 2.192, 95% CI: 1.319–3.643, $p = 0.002$) and PLR (HR: 1.696, 95% CI: 1.029–2.795, $p = 0.038$) were connected to adverse OS within patients. In

TABLE 1 The demographic and clinical characteristics of all patients.

Factors	Total ($N = 146$)
Age, years, mean ± SD	59.93 ± 9.97
Sex, *n* (%)	
Male	134 (91.8)
Female	12 (8.2)
Smoking history, *n* (%)	
Yes	120 (82.2)
No	26 (17.8)
BMI, cm/kg^2	24.53 ± 3.34
Tumor location, *n* (%)	
Right upper lobe	97 (66.4)
Involved the right middle lobe	1 (0.7)
Left upper lobe	20 (13.7)
Right lower lobe	9 (6.2)
Left lower lobe	19 (13.0)
Surgical approach, *n* (%)	
Thoracoscopic surgery	33 (22.6)
Open thoracotomy	113 (77.4)
Conversion from thoracoscopic to thoracotomy, *n* (%)	8 (5.5)
Operation time, min, mean ± SD	191.46 ± 60.38
Number of LN dissection, mean ± SD	21.65 ± 9.22
Number of LN dissection stations, mean ± SD	5.81 ± 1.38
Pathologic TNM stage, ninth	
IA	32 (21.9)
IB	15 (10.3)
IIA	35 (24.0)
IIB	33 (22.6)
IIIA	20 (13.7)
IIIB	11 (7.5)
Pathologic TNM stage, eighth	
IA	32 (21.9)
IB	15 (10.3)
IIA	11 (7.5)
IIB	53 (36.3)
IIIA	26 (17.8)
IIIB	9 (6.2)
Pathologic T stage, eight/ninth	
1a	3 (2.1)
1b	21 (14.4)
1c	37 (25.3)
2a	39 (26.7)
2b	24 (16.4)
3	14 (9.6)
4	8 (5.5)
Pathologic N stage, ninth	
0	60 (41.1)
1	62 (42.5)
2a	16 (11.0)
2b	8 (5.5)
Pathology, *n* (%)	
ADC	12 (8.2)
SCC	115 (78.8)
Others	19 (13.0)
Tumor size, cm, mean ± SD	3.46 ± 1.58
Degree of differentiation, *n* (%)	
High	10 (6.8)
Middle	78 (52.7)
Low	47 (32.2
Unknown	11 (8.2)
LOS, days, mean ± SD	12.95 ± 6.15
Thoracic close drainage, days, mean ± SD	8.42 ± 5.92
Total postoperative thoracic drainage, mL, mean ± SD	1887.97 ± 1308.84
NLR, mean ± SD	2.68 ± 1.37
MLR, mean ± SD	0.2992 ± 0.1345
PLR, mean ± SD	142.94 ± 66.49
OS, months, mean ± SD	66.77 ± 35.93
DFS, months, mean ± SD	62.67 ± 38.10

Note: As the data was generated using statistical software, the percentage may be inaccurate. Counting data were tested by chi-square test. Rank sum test was used for stratified data. Mann–Whitney U test was used for continuous variables.
Abbreviations: ADC, adenocarcinoma; BMI, body mass index; DFS, disease-free survival; LN, lymph node; LOS, length of stay; MLR, monocyte lymphocyte ratio; NLR, neutrophil lymphocyte ratio; OS, overall survival; PLR, platelet lymphocyte ratio; SCC, squamous cell carcinoma; TNM, tumor node metastasis.

TABLE 2 Postoperative complication statistics.

Complications, *n* (%)	Total ($N = 146$)
Clavien–Dindo I	
Fat liquefaction	1 (0.7)
Clavien–Dindo II	
Aerodermectasia	1 (0.7)
Atelectasis needing suction	1 (0.7)
Pulmonary infection	6 (4.1)
Persistent pulmonary leakage (≥7 days)	21 (14.4)
Clavien–Dindo III	
Bronchopleural fistula	3 (2.1)
Progressive hemothorax	1 (0.7)
Chylothorax	2 (1.4)
Clavien–Dindo IV	
Respiratory failure	1 (0.7)
Clavien–Dindo V	
Dead	1 (0.7)

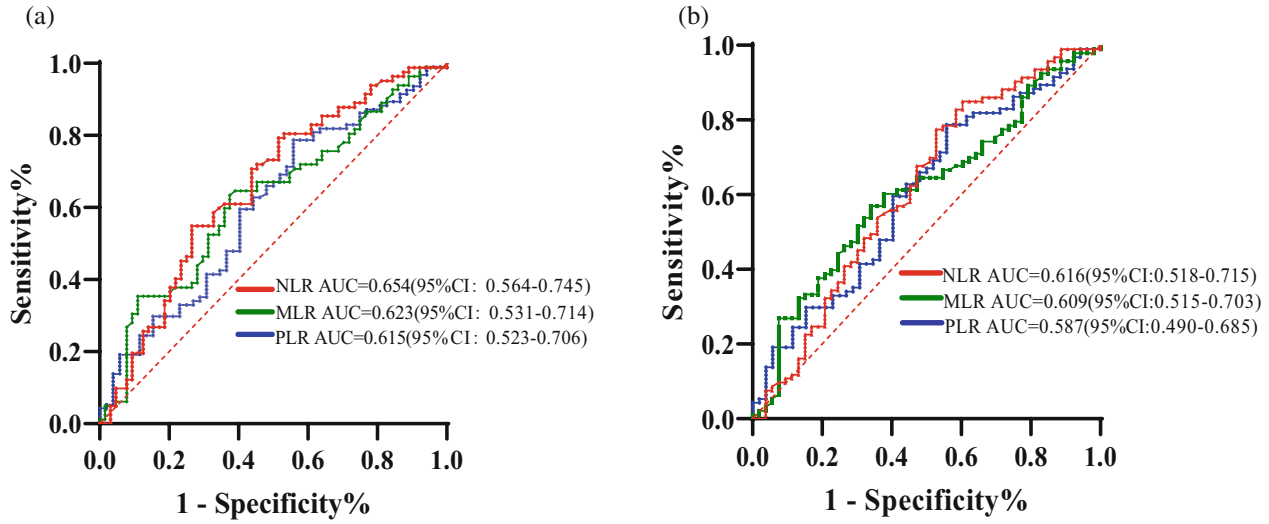

FIGURE 1 (a) Receiver operating characteristic (ROC) of neutrophil lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), and platelet lymphocyte ratio (PLR) diagnosis of overall survival (OS) in sleeve lobectomy. (b) ROC of NLR, MLR, and PLR diagnosis of disease-free survival (DFS) in sleeve lobectomy.

the multivariate study, factors with a univariate analysis $p \leq 0.1$ and clinically relevant factors were considered. NLR (HR: 2.036, 95% CI: 1.072–3.864, $p = 0.030$) was discovered to be an additional risk variable for OS (Table 5). Univariate analysis showed that pN stage (HR: 3.163, 95% CI: 1.660–6.027, $p < 0.001$), NLR (HR: 2.530, 95% CI: 1.468–4.360, $p < 0.001$), MLR (HR: 2.229, 95% CI: 1.260–3.944, $p = 0.006$) and PLR (HR: 2.249, 95% CI: 1.300–3.889, $p = 0.004$) were connected to DFS in sufferers. In the multivariate analysis, factors with a univariate study $p \leq 0.1$ and clinically relevant factors were included. The pN stage (HR: 3.098, 95% CI: 1.619–5.928, $p < 0.001$) was found to be a separate predictive variable for DFS (Table 6).

DISCUSSION

Thoracic surgery has seen a significant increase in the usage and development of SL in the past few years. Numerous investigations have proven this surgical method's security and effectiveness, showing its potential to replace traditional lobectomy in central-type NSCLC.[4] While research has indicated the predictive role of preoperative inflammation in postoperative outcomes of central-type NSCLC,[14] the prognostic value of preoperative inflammatory markers for SL has not been reported. In our study, we carried out a retrospective study of 146 individuals who went through SL for central-type NSCLC, examining the impact of inflammatory indicators NLR, MLR, and PLR on the prognosis of SL. To the best of our understanding, this investigation reflects the first large-scale, single-center research worldwide on the function of NLR, MLR, and PLR within sleeve lobectomy for NSCLC.

Currently, biomarkers remain a major focus in oncology research, used for disease diagnosis, treatment assessment, and patient prognosis. In the last century, Virchow et al.[8] explored the connection among inflammation and cancer. Subsequent research has more and more demonstrated the importance of inflammatory indicators within the diagnosis and prognostic assessment of different cancers. Studies by Mazzella et al.[9] highlighted the significant impact of preoperative inflammatory status upon the long-term prognosis of surgical sufferers alongside NSCLC. Sahin et al.[17] identified PLR and NLR as inflammatory markers for NSCLC. Wang et al.[12] stated that lower NLR, MLR, and PLR were correlated with improved postoperative outcomes within NSCLC. Michihito et al.[18] found that elevated PLR is linked to poor postoperative outcomes in NSCLC, especially in those who did not undergo neoadjuvant treatment. Our study results support the connection of elevated NLR, MLR, and PLR alongside adverse prognosis in central NSCLC, providing preliminary confirmation in NSCLC patients undergoing SL for the first time.

Mantovani et al.[19] reported that systemic inflammation increases tumor cell progression, and changes in the tumor microenvironment leading to increased angiogenesis and metastasis are associated with poor prognosis. Inflammation associated with tumors can lead to gene mutations, genomic instability, and epigenetic changes, which might encourage the growth and angiogenesis of cancer cells.[7] Systemic inflammatory response in cancer sufferers accelerates metabolic states, leading to cachexia. Decreased neutrophils are associated with reduced angiogenesis and decreased secretion of antiapoptotic factors, inhibiting cancer growth and progression.[20] Immune-regulatory cytokines accelerate the course of the illness and raise the possibility of distant metastases by recruiting neutrophils in tumor-related inflammation. The prognostic significance of NLR remains within locally advanced NSCLC and metastatic NSCLC sufferers.[21,22] To encourage tumor growth and proliferation,

TABLE 3 Patients were divided into different groups according to the cutoff value for OS.

Factors	NLR			MLR			PLR		
	Low NLR $N = 62$	High NLR $N = 84$	*p*-value	Low MLR $N = 76$	High MLR $N = 70$	*p*-value	Low PLR $N = 74$	High PLR $N = 72$	*p*-value
Age, years, mean ± SD	58.27 ± 11.65	61.7 ± 78.49	0.143	57.86 ± 11.39	62.84 ± 7.65	0.013	59.85 ± 10.27	60.65 ± 9.90	0.694
Sex, *n* (%)			0.953			0.372			0.016
Male	57 (91.9)	77 (91.7)		68 (89.5)	66 (94.3)		72 (97.3)	62 (86.1)	
Female	5 (8.1)	7 (8.3)		8 (10.5)	4 (5.7)		2 (2.7)	10 (13.9)	
Smoking history, *n* (%)			0.083			0.053			0.071
Yes	47 (75.8)	73 (86.9)		58 (76.3)	8 (11.4)		65 (87.8)	55 (76.4)	
No	15 (24.2)	11 (13.1)		18 (23.7)	62 (88.6)		9 (12.2)	17 (23.6)	
BMI, mean ± SD	25.07 ± 3.31	24.13 ± 3.32	0.108	25.27 ± 3.41	23.74 ± 3.09	0.006	24.93 ± 3.15	24.12 ± 3.49	0.110
Tumor Location, *n* (%)			0.354			0.573			0.399
Right upper lobe	46 (74.2)	51 (61.4)		49 (65.3)	48 (68.6)		51 (68.9)	46 (64.8)	
Involved the right middle lobe									
Left upper lobe	8 (12.9)	12 (14.5)		12 (16.0)	8 (11.4)		7 (9.5)	13 (18.3)	
Right lower lobe	3 (4.8)	6 (7.2)		3 (4.0)	6 (8.6)		6 (8.1)	3 (4.2)	
Left lower lobe	5 (8.1)	14 (16.9)		11 (14.7)	8 (11.4)		10 (13.5)	9 (12.7)	
Surgical approach, *n* (%)			0.693			0.471			0.774
Thoracoscopic surgery	15 (24.2)	18 (21.4)		19 (25.0)	14 (20.0)		16 (21.6)	17 (23.6)	
Open thoracotomy	47 (75.8)	66 (78.6)		57 (75.0)	56 (80.0)		58 (78.4)	55 (76.4)	
Operation time, min, mean ± SD	192.94 ± 70.42	190.37 ± 52.17	0.770	194.68 ± 69.88	187.96 ± 48.26	0.981	188.39 ± 70.33	194.61 ± 48.37	0.077
Number of LN dissection, mean ± SD	20.95 ± 8.86	22.17 ± 9.50	0.649	20.34 ± 9.09	23.07 ± 9.22	0.041	5.85 ± 1.47	5.77 ± 1.33	0.374
Number of LNs dissection stations, mean ± SD	5.58 ± 1.47	5.77 ± 1.32	0.666	5.75 ± 1.49	5.87 ± 1.27	0.584	5.93 ± 1.35	5.68 ± 1.42	0.294
Pathologic TNM stage, ninth			0.016			0.027			0.227
IA	22 (35.4)	10 (11.9)		22 (28.9)	10 (14.4)		19 (25.7)	13 (18.1)	
IB	6 (9.7)	9 (10.7)		10 (13.2)	5 (7.1)		7 (9.5)	8 (11.1)	
IIA	14 (22.6)	21 (25.0)		16 (21.1)	19 (27.1)		16 (21.6)	19 (26.4)	
IIB	8 (12.9)	25 (29.8)		12 (15.8)	21 (30.0)		18 (24.3)	15 (20.8)	
IIIA	8 (12.9)	12 (14.3)		13 (17.1)	7 (10.0)		12 (16.2)	8 (11.1)	
IIIB	4 (6.5)	7 (8.3)		3 (3.9)	8 (11.4)		2 (2.7)	9 (12.5)	
Pathologic TNM stage, eighth			0.034			0.102			0.893
IA	22 (35.4)	10 (11.9)		22 (28.9)	10 (14.4)		19 (25.7)	13 (18.1)	
IB	6 (9.7)	9 (10.7)		10 (13.2)	5 (7.1)		7 (9.5)	8 (11.1)	
IIA	4 (6.5)	7 (8.3)		5 (6.6)	6 (8.6)		5 (6.8)	6 (8.3)	
IIB	17 (27.4)	36 (42.9)		22 (28.9)	31 (44.3)		25 (33.8)	28 (38.9)	

(Continues)

TABLE 3 (Continued)

Factors	NLR			MLR			PLR		
	Low NLR $N = 62$	High NLR $N = 84$	*p*-value	Low MLR $N = 76$	High MLR $N = 70$	*p*-value	Low PLR $N = 74$	High PLR $N = 72$	*p*-value
IIIA	10 (16.1)	16 (19.0)		11 (14.5)	15 (21.4)		14 (18.9)	12 (16.7)	
IIIB	3 (4.8)	6 (7.1)		6 (7.9)	3 (4.3)		4 (5.4)	5 (6.9)	
Pathologic T stage, eighth/ninth			0.034			0.654			0.583
1a	1 (1.6)	2 (2.4)		2 (2.6)	1 (1.4)		1 (1.4)	2 (2.8)	
1b	12 (19.4	9 (10.7)		12 (15.8)	9 (12.9)		9 (12.2)	12 (16.7)	
1c	21 (33.9)	16 (19.0)		21 (27.6)	16 (22.9)		24 (32.4)	13 (18.1)	
2a	13 (21.0)	26 (31.0)		16 (21.1)	23 (32.9)		17 (23.0)	22 (30.6)	
2b	10 (16.1)	14 (16.7)		13 (17.1)	11 (15.7)		12 (16.2)	12 (16.7)	
3	5 (8.1)	9 (10.7)		9 (11.8)	5 (7.1)		7 (9.5)	7 (9.7)	
4	0	8 (9.5)		3 (3.9)	5 (7.1)		4 (5.4)	4 (5.6)	
Pathologic N stage, ninth			0.045			0.094			0.136
0	32 (51.6)	28 (33.3)		38 (50.0)	22 (31.4)		31 (41.9)	29 (40.3)	
1	19 (30.6)	43 (51.2)		26 (34.2)	36 (51.4)		32 (43.2)	30 (41.7)	
2a	6 (9.7)	10 (11.9)		9 (11.8)	7 (10.0)		10 (13.5)	6 (8.3)	
2b	5 (8.1)	3 (3.6)		3 (3.9)	5 (7.1)		1 (1.4)	7 (9.7)	
Pathology, *n* (%)			0.343			0.009			0.804
ADC	5 (8.1)	7 (8.3)		6 (7.9)	6 (8.6)		5 (6.8)	7 (9.7)	
SCC	46 (74.2)	69 (82.1)		54 (71.1)	61 (87.1)		59 (79.7)	56 (77.8)	
Other	11 (17.7)	8 (9.5)		16 (21.1)	3 (4.3)		10 (13.5)	9 (12.5)	
Tumor size, cm, mean ± SD	3.09 ± 1.29	3.78 ± 1.70		3.31 ± 1.45	3.63 ± 1.67		3.41 ± 1.48	3.51 ± 1.69	
Degree of differentiation, *n* (%)			0.082			0.011			0.221
High	1 (1.6)	9 (10.7)		2 (2.6)	8 (11.4)		2 (2.7)	8 (11.1)	
Middle	35 (56.5)	43 (51.2)		40 (52.6)	38 (54.3)		43 (58.1)	35 (48.6)	
Low	19 (30.6)	28 (33.3)		24 (31.6)	23 (32.9)		24 (32.4)	23 (31.9)	
Unknown	7 (11.3)	4 (4.8)		10 (13.2)	1 (1.4)		5 (6.8)	6 (8.3)	
LOS, days, mean ± SD	13.06 ± 5.46	12.88 ± 6.64	0.457	12.64 ± 5.06	13.30 ± 7.17	0.958	13.58 ± 7.55	12.32 ± 4.21	0.761
Thoracic close drainage, days, mean ± SD	7.77 ± 4.85	8.89 ± 6.58	0.054	8.12 ± 4.74	8.74 ± 7.00	0.467	9.12 ± 7.53	7.69 ± 3.49	0.910
Total postoperative thoracic drainage, mL, mean ± SD	1740.03 ± 957.49	1997.17 ± 1513.45	0.486	1636.38 ± 868.26	2161.13 ± 1623.30	0.043	1996.15 ± 1514.45	1776.79 ± 1056.23	0.607
OS, months, mean ± SD	74.94 ± 33.90	60.74 ± 36.39	0.021	73.75 ± 35.25	59.19 ± 35.36	0.016	71.38 ± 35.79	62.03 ± 35.70	0.088
DFS, months, mean ± SD	70.71 ± 36.15	56.74 ± 38.63	0.043	70.05 ± 37.29	54.66 ± 37.61	0.024	68.20 ± 38.27	56.99 ± 37.35	0.076

Note: As the data was generated using statistical software, the percentage may be inaccurate. Counting data were tested by chi-square test. Rank sum test was used for stratified data. Mann–Whitney U test was used for continuous variables.
Abbreviations: ADC, adenocarcinoma; BMI, body mass index; DFS, disease-free survival; LN, lymph node; LOS, length of stay; MLR, monocyte lymphocyte ratio; NLR, neutrophil lymphocyte ratio; OS, overall survival; PLR, platelet lymphocyte ratio; SCC, squamous cell carcinoma; SD, standard deviation; TNM, tumor node metastasis.

TABLE 4 Patients were divided into different groups according to the cutoff value for DFS.

Factors	NLR			MLR			PLR		
	Low NLR $N = 100$	High NLR $N = 46$	*p*-value	Low MLR $N = 71$	High MLR $N = 75$	*p*-value	Low PLR $N = 103$	High PLR $N = 43$	*p*-value
Age, years, mean ± SD	59.20 ± 10.84	62.52 ± 7.76	0.111	57.83 ± 11.41	62.53 ± 8.02	0.019	60.79 ± 9.64	58.95 ± 11.02	0.043
Sex, *n* (%)			0.429			0.236			0.001
Male	93 (93.0)	41 (89.1)		63 (88.7)	71 (94.7)		100 (97.1)	34 (79.1)	
Female	7 (7.0)	5 (10.9)		8 (11.3)	4 (5.3)		3 (2.9)	9 (20.9)	
Smoking history, *n* (%)			0.579			0.020			0.011
Yes	81 (81.0)	39 (84.8)		18 (25.4)	8 (10.7)		90 (87.4)	30 (69.8)	
No	19 (19.0)	7 (15.2)		53 (74.6)	67 (89.3)		13 (12.6)	13 (30.2)	
BMI, mean ± SD	24.98 ± 3.24	23.55 ± 3.35	0.020	25.27 ± 3.33	23.84 ± 3.21	0.009	24.88 ± 3.25	23.69 ± 3.42	0.021
Tumor location, *n* (%)			0.445			0.750			0.245
Right upper lobe	70 (70.7)	27 (58.7)		46 (65.7)	51 (68.0)		73 (71.6)	24 (55.8)	
Involved the right middle lobe									
Left upper lobe	13 (13.1)	7 (15.2)		11 (15.7)	9 (12.0)		11 (10.8)	9 (20.9)	
Right lower lobe	5 (5.1)	4 (8.7)		3 (4.3)	6 (8.0)		6 (5.9)	3 (7.0)	
Left lower lobe	11 (11.1)	8 (17.4)		10 (14.3)	9 (12.0)		12 (11.8)	7 (16.3)	
Surgical approach, *n* (%)			0.797			0.243			0.903
Thoracoscopic surgery	22 (22.0)	11 (23.9)		19 (26.8)	14 (18.7)		23 (22.3)	10 (23.3)	
Open thoracotomy	78 (78.0)	35 (76.1)		52 (73.2)	61 (81.3)		80 (77.7)	33 (76.7)	
Operation time, min, mean ± SD	186.99 ± 62.91	201.17 ± 53.86	0.064	196.62 ± 71.48	186.57 ± 47.55	0.765	186.28 ± 63.56	203.86 ± 50.53	0.011
Number of LN dissection, mean ± SD	20.98 ± 8.84	23.11 ± 9.95	0.334	20.46 ± 9.05	22.77 ± 9.30	0.061	22.19 ± 9.60	20.35 ± 8.22	0.324
Number of LNs dissection stations, mean ± SD	5.73 ± 1.39	5.98 ± 1.37	0.371	5.69 ± 1.41	5.92 ± 1.36	0.441	5.92 ± 1.32	5.53 ± 1.50	0.130
Pathologic TNM stage, ninth			0.376			0.125			0.064
IA	26 (26.0)	6 (13.0)		20 (28.2)	12 (16.0)		24 (23.3)	8 (18.6)	
IB	10 (10.0)	5 (10.9)		9 (12.7)	6 (8.0)		11 (10.7)	4 (9.3)	
IIA	23 (23.0)	12 (26.1)		15 (21.1)	20 (26.7)		24 (23.3)	11 (25.6)	
IIB	22 (22.0)	11 (23.9)		12 (16.9)	21 (28.0)		25 (24.3)	8 (18.6)	
IIIA	14 (14.0)	6 (13.0)		12 (16.9)	8 (10.7)		16 (15.5)	4 (9.3)	
IIIB	5 (5.0)	6 (13.0)		3 (4.2)	8 (10.7)		3 (2.9)	8 (18.6)	
Pathologic TNM stage, eighth			0.176			0.205			0.566
IA	26 (26.0)	6 (13.0)		20 (28.2)	12 (16.0)		24 (23.9)	8 (18.6)	
IB	10 (10.0)	5 (10.9)		9 (12.7)	6 (8.0)		11 (10.7)	4 (9.3)	
IIA	5 (5.0)	6 (13.0)		5 (7.0)	6 (8.0)		9 (8.7)	2 (4.7)	
IIB	37 (37.0)	16 (34.8)		21 (29.6)	32 (42.7)		36 (35.0)	17 (39.5)	

(Continues)

TABLE 4 (Continued)

Factors	NLR			MLR			PLR		
	Low NLR $N = 100$	High NLR $N = 46$	*p*-value	Low MLR $N = 71$	High MLR $N = 75$	*p*-value	Low PLR $N = 103$	High PLR $N = 43$	*p*-value
IIIA	18 (18.0)	8 (17.4)		10 (14.1)	16 (21.3)		19 (18.4)	7 (16.3)	
IIIB	4 (4.0)	5 (10.9)		6 (8.5)	3 (4.0)		4 (3.9)	5 (11.6)	
Pathologic T stage, eighth/ninth			0.016			0.473			0.102
1a	3 (3.0)	0		2 (2.8)	1 (1.3)		3 (2.9)	0	
1b	13 (13.0)	8 (17.4)		11 (15.5)	10 (13.3)		11 (10.7)	10 (23.3)	
1c	32 (32.0)	5 (10.9)		19 (26.8)	18 (24.0)		30 (29.1)	7 (16.3)	
2a	24 (24.0)	15 (32.6)		15 (21.1)	24 (32.0)		26 (25.2)	13 (30.2)	
2b	16 (16.0)	8 (17.4)		13 (18.3)	11 (14.7)		20 (19.4)	4 (9.3)	
3	10 (10.0)	4 (8.7)		9 (12.7)	5 (6.7)		9 (8.7)	5 (11.6)	
4	2 (2.0)	6 (13.0)		2 (2.8)	6 (8.0)		4 (3.9)	4 (9.3)	
Pathologic N stage, ninth			0.759			0.141			0.200
0	42 (42.0)	18 (39.1)		35 (49.3)	25 (33.3)		45 (43.7)	15 (34.9)	
1	43 (43.0)	19 (41.3)		24 (33.8)	38 (50.7)		43 (41.7)	19 (44.2)	
2a	9 (9.0)	7 (15.2)		9 (12.7)	7 (9.3)		12 (11.7)	4 (9.3)	
2b	6 (6.0)	2 (4.3)		3 (4.2)	5 (6.7)		3 (2.9)	5 (11.6)	
Pathology, *n* (%)			1.000			0.015			0.195
ADC	8 (8.0)	4 (8.7)		5 (7.0)	7 (9.3)		7 (6.8)	5 (11.6)	
SCC	79 (79.0)	36 (78.3)		51 (71.8)	64 (85.3)		85 (82.5)	30 (69.8)	
Other	13 (13.0)	6 (13.0)		15 (21.1)	4 (5.3)		11 (10.7)	8 (18.6)	
Tumor size, cm, mean ± SD	3.23 ± 1.33	3.96 ± 1.94	0.044	3.35 ± 1.52	3.57 ± 1.64	0.358	3.43 ± 1.43	3.54 ± 1.90	0.765
Degree of differentiation, *n* (%)			0.011			0.043			0.333
High	2 (2.0)	8 (17.4)		2 (2.8)	8 (10.7)		6 (5.8)	4 (9.3)	
Middle	57 (57.0)	21 (45.7)		38 (53.5)	40 (53.3)		59 (57.3)	19 (44.2)	
Low	33 (33.0)	14 (30.4)		22 (31.0)	25 (33.3)		32 (31.3)	15 (34.9)	
Unknown	8 (8.0)	3 (6.5)		9 (12.7)	2 (2.7)		6 (5.8)	5 (11.6)	
LOS, d,ays mean ± SD	13.01 ± 6.50	12.85 ± 5.35	0.970	12.90 ± 5.09	13.01 ± 7.04	0.522	13.24 ± 6.83	12.28 ± 4.04	0.855
Thoracic close drainage, days, mean ± SD	8.31 ± 6.38	8.65 ± 4.82	0.220	8.32 ± 4.83	8.51 ± 6.82	0.980	8.65 ± 6.59	7.86 ± 3.86	0.914
Total postoperative thoracic drainage, mL, mean ± SD	1812.82 ± 1237.19	2051.35 ± 1453.50	0.379	1656.13 ± 890.58	2107.45 ± 1583.05	0.100	1993.56 ± 1341.77	1635.05 ± 1203.78	0.021
OS, months, mean ± SD	72.78 ± 35.31	53.70 ± 34.11	0.003	74.90 ± 35.21	59.07 ± 35.12	0.008	70.64 ± 35.92	57.49 ± 34.65	0.030
DFS, months, mean ± SD	69.51 ± 37.08	37.8 ± 36.38	0.003	71.42 ± 36.76	54.39 ± 37.73	0.009	67.85 ± 38.21	50.26 ± 35.27	0.011

Note: As the data was generated using statistical software, the percentage may be inaccurate. Counting data were tested by chi-square test. Rank sum test was used for stratified data. Mann–Whitney U test was used for continuous variables.
Abbreviations: ADC, adenocarcinoma; BMI, body mass index; DFS, disease-free survival; LN, lymph node; LOS, length of stay; MLR, monocyte lymphocyte ratio; NLR, neutrophil lymphocyte ratio; OS, overall survival; PLR, platelet lymphocyte ratio; SCC, squamous cell carcinoma; SD, standard deviation; TNM, tumor node metastasis.

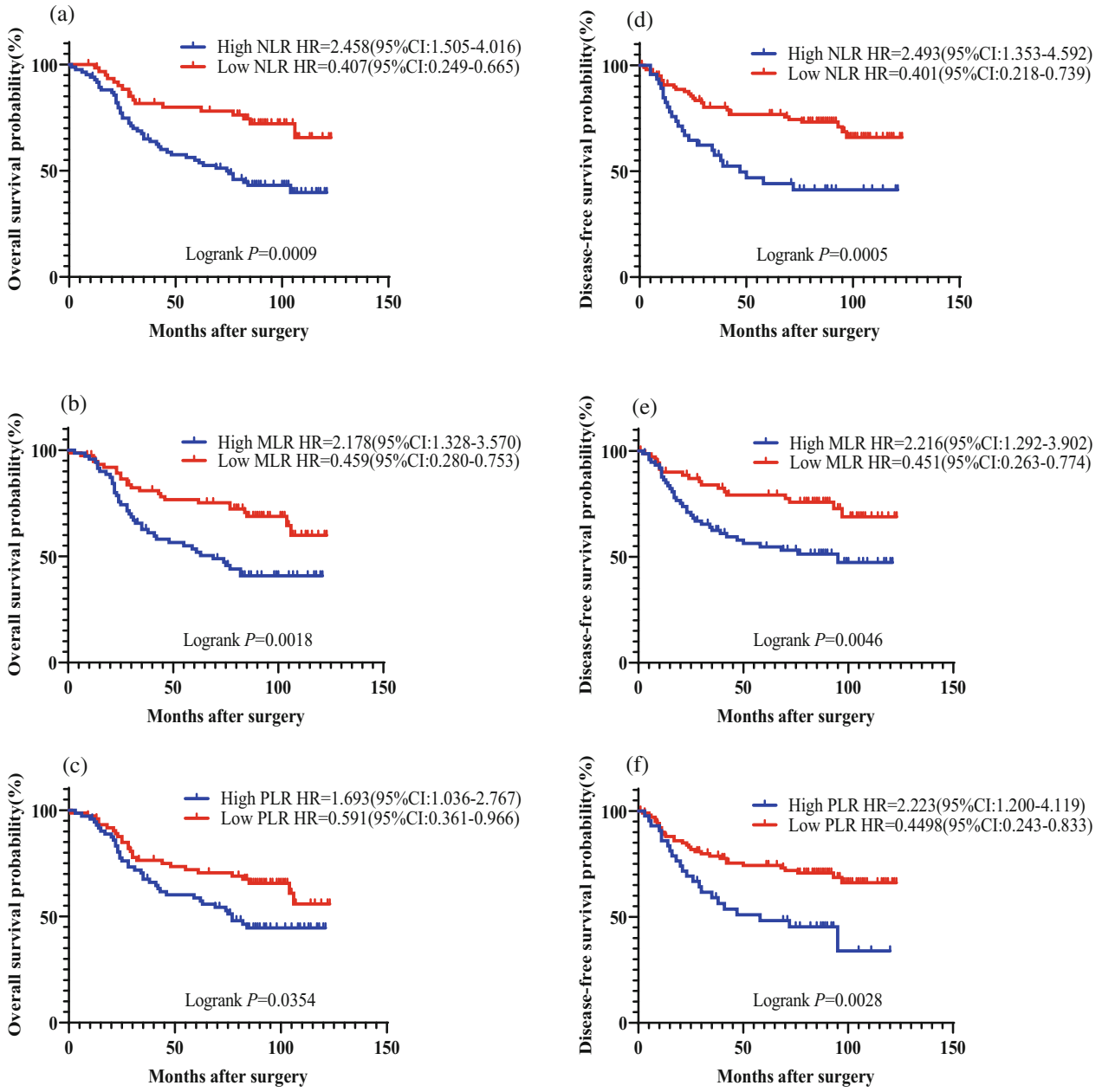

FIGURE 2 (a) Neutrophil lymphocyte ratio (NLR) diagnoses overall survival (OS) in groups based on cutoff values ($p = 0.0009$). (b) Monocyte lymphocyte ratio (MLR) diagnoses OS in groups based on cutoff values ($p = 0.0018$). (c) Platelet lymphocyte ratio (PLR) diagnoses OS in groups based on cutoff values ($p = 0.0354$). (d) NLR diagnoses disease-free survival (DFS) in groups based on cutoff values ($p = 0.0005$). (e) MLR diagnoses DFS in groups based on cutoff values ($p = 0.0046$). (f) PLR diagnoses DFS in groups based on cutoff values ($p = 0.0028$).

TABLE 5 Univariable and multivariable COX analysis for OS.

	Univariable		Multivariable	
Factors	**Hazard ratio (95% CI)**	***p*-value**	**Hazard ratio (95% CI)**	***p*-value**
Age (others vs. <60 years)	1.563 (0.927–2.637)	0.094		
Pathology (others vs. SCC)	1.252 (0.701–2.235)	0.448		
NLR (≥2.196 vs. <2.196)	2.469 (1.416–4.306)	<0.001	2.036 (1.072–3.864)	0.030
MLR (≥0.2763 vs. <0.2763)	2.192 (1.319–3.643)	0.002		
PLR (≥126.11 vs. <126.11)	1.696 (1.029–2.795)	0.038		

Abbreviations: CI, confidence interval; MLR, monocyte lymphocyte ratio; NLR, neutrophil lymphocyte ratio; OS, overall survival; PLR, platelet lymphocyte ratio; SCC, squamous cell carcinoma.

TABLE 6 Univariable and multivariable COX analysis for DFS.

Factors	Univariable		Multivariable	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
pN stage (others vs. N0)	3.163 (1.660–6.027)	<0.001	3.098 (1.619–5.928)	<0.001
NLR (≥3.010 vs. <3.010)	2.530 (1.468–4.360)	<0.001		
MLR (≥0.2708 vs. <0.2708)	2.229 (1.260–3.944)	0.006		
PLR (≥161.99 vs. <161.99)	2.249 (1.300–3.889)	0.004		

Abbreviations: CI, confidence interval; DFS, disease-free survival; MLR, monocyte lymphocyte ratio; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio.

neutrophils release vascular endothelial growth factor and other cytokines, whereas lymphocytes are essential for tumor defense because they trigger cytotoxic cell death. Therefore, increased lymphocytes are considered a favorable prognostic factor, indicating anticancer activity.[9,21] Our study indicates that higher NLR is linked to poor OS and DFS in central-type NSCLC undergoing SL. Furthermore, elevated NLR is a distinct risk indicator within central-type NSCLC undergoing SL.

There have been reports linking thrombocytosis to a bad prognosis for a number of malignancies.[23–26] Fang et al.[27] found that a worse outcome for stomach cancer is linked to higher PLR, alongside PLR showing higher diagnostic value than traditional markers like carcinoembryonic antigen (CEA) and carbohydrate antigen19-9 (CA19-9). Platelets may be involved in LN metastasis in lung adenocarcinoma (ADC).[28] Bahar et al.[29] reported that preoperative elevated PLR is connected to recurrence in non-small cell lung cancer. Platelets promote tumor metastasis through secreting growth factors, protecting tumor cells from immune attacks, and facilitating tumor cell growth and movement by blocking endothelial cells.[30] Our analysis confirms other research findings by indicating that higher PLR is linked to poor OS and DFS in sufferers of NSCLC following SL.

It has been reported that elevated MLR is a separate variable affecting the OS of sufferers after gallbladder cancer surgery.[31] Additionally, higher MLR has been shown by Yang et al. (2018) to be a distinct indicator of OS in patients having liver resection for hepatocellular carcinoma. Chen et al.[32] discovered that elevated MLR is associated alongside poor survival and recurrence after surgery for NSCLC. Cheng et al. reported that elevated MLR was discovered to be a distinct risk element after surgery for NSCLC, alongside a more significant impact in the lymph node-positive subgroup. Wang et al.[12] found in their study on early-stage NSCLC that low MLR is associated with good OS, consistent with our research findings. We found that elevated MLR in NSCLC patients undergoing SL was linked to poor prognosis within the High-MLR group, despite the fact that the multivariate analysis did not reveal higher MLR to have a separate predictive function. Although some scholars have proposed that increased N stage is associated with adverse OS in NSCLC,[33] the population in our study received radical chemotherapy and radiotherapy after surgery to varying degrees, which to some extent affected the OS of the overall population.

There are several restrictions on this study. Due to its retrospective cohort construction, there may be recall bias, and surgical data were obtained from different surgeons, leading to a lack of generalizability and consistency in the data. Additionally, the determination of threshold value for NLR, MLR, and PLR depended on a single-center investigation of 146 sufferers, which may have introduced some systematic errors. Despite these limitations, we have proposed for the first time the predictive function of hematological indicators within the prognosis for individuals undergoing SL, warranting further confirmation of our findings through large-scale multicenter prospective studies.

In conclusion, our preliminary research indicates that NLR, MLR, and PLR play a convenient and cost-effective predictive role in the survival and recurrence of sufferers undergoing SL for central-type NSCLC, with NLR being a separate risk variable for predicting OS within central-type NSCLC sufferers undergoing SL. Therefore, larger-scale multicenter prospective studies are warranted.

AUTHOR CONTRIBUTIONS

Juwei Mu and Jiagen Li: Contributed to study design. Rui Han and Fan Zhang: Contributed to drafting of the article. Chang Zhan, Chenguang Zhao, Fuquan Wang and Sining Zhang: Contributed to data collection. Rui Han, Qian Hong and Fang Li: Participated in data analysis and interpretation and led the revision of the article. Visar Djaferi: Contributed to the revision, correction and polishing the language of the article. All authors reviewed and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The research protocol and consent form were reviewed and approved by the Medical Ethics Committees of National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

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