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Original Article

A biomarker-based prediction model for risk of locoregional recurrence in pathologic stage IIIA-N2 non-small cell lung cancer

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Abstract: Objective: To investigate risk factors for locoregional recurrence (LRR) of pathologic stage IIIA-N2 non-small cell lung cancer (pIIIA-N2 NSCLC) and construct a prediction model for risk score to determine a patient's risk for LRR and guide the selection of postoperative radiotherapy (PORT). Methods: The clinical, pathologic, and biological data of 107 patients with pIIIA-N2 NSCLC treated at Fujian Provincial Hospital between May 2012 and December 2018 were analyzed retrospectively. None of the patients had positive surgical margins, and none received preoperative treatment or PORT. The Kaplan-Meier method was used for a univariate analysis of possible factors for locoregional recurrence-free survival (LRFS). The Cox regression model was used in a multivariate analysis to identify independent risk factors for LRFS, which were used to construct a prediction model for risk score. The concordance index was calculated to evaluate discrimination. Results: The median follow-up time was 31.2 months. During the follow-up, 69 (64.5%) patients had LRR and/or distant metastasis (DM). Among them, 46 (43%) patients had LRR (with or without DM), and 56 (52.3%) patients had DM (with or without LRR). The 1-year LRFS, distant metastasis-free survival, disease-free survival, and overall survival rates were 78.2%, 78%, 69.8%, and 90.2%, respectively; the 3-year rates were 50.6%, 41.2%, 31.2%, and 66.3%, respectively. Multivariate analysis showed that surgical approach (hazard ratio [HR], 0.348; 95% confidence interval [CI], 0.175-0.693; P = 0.003), metastatic N2 lymph node ratio (HR, 3.597; 95% CI, 1.832-7.062; P = 0.000), epidermal growth factor receptor status (HR, 3.666; 95% CI, 1.724-7.797; P = 0.001), and lymphocyte-to-monocyte ratio (HR, 2.364; 95% CI, 1.221-4.574; P = 0.011) were independent risk factors for LRFS. These independent risk factors were used to construct a prediction model for risk score and stratify patients into the low-risk group (risk score: 0-2), medium-risk group (risk score: 3-5), and high-risk group (risk score: 6-13). The 1-year LRFS rates of these groups were 91.9%, 85.3%, and 54.6%, respectively; the 3-year LRFS rates were 71.4%, 57.3%, and 13.6%, respectively. These between-group differences were significant (P = 0.000). The prediction model showed good discrimination (concordance index = 0.747, 95% CI, 0.678-0.816). Conclusion: Our prediction model for risk score based on characteristics of pIIIA-N2 NSCLC patients may help clinicians predict a patient's risk for LRR. Further investigations of PORT with patients in different risk groups are warranted.

Keywords: Non-small cell lung cancer, pathologic stage IIIA-N2 disease, locoregional recurrence, risk factors, prediction model

Introduction

Lung cancer has the highest morbidity and mortality of malignant tumors worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers [2]. In accordance with the 2009 lung cancer staging of the International Association for the Study of Lung Cancer (IASLC), pathologic stage IIIA-N2 (pIIIA-N2) NSCLC is defined as primary NSCLC with subcarinal and/or ipsilateral mediastinal lymph node metastasis (including T1-3N2M0) that is diagnosed by pathologic examination of a surgical specimen in patients with no preoperative induction therapy [3]. pIIIA-N2 NSCLC is locally advanced NSCLC and encompasses a group of heterogeneous diseases with distinct clinical, pathologic, and biological characteristics as well as significant variation in treatment response and outcomes.

The 5-year survival rate is 24.1% to 47.4% [4-10]. Surgery is the main treatment for pIIIA-N2 NSCLC, and postoperative locoregional recurrence (LRR) and/or distant metastasis (DM) are the main causes of treatment failure and adverse prognosis. Several randomized clinical trials and meta-analyses have shown that platinum-based adjuvant chemotherapy increases the survival rate of patients with pIIIA-N2 NSCLC [11-13]. However, the LRR rate is still as high as 40% to 50% even after surgery and adjuvant chemotherapy [6, 14]. Therefore, postoperative radiotherapy (PORT) is often recommended to reduce LRR. However, researchers still debate its benefit on survival [15-19]. There are no prospective phase III study data on whether PORT improves survival. Some studies show that for locally advanced NSCLC, improved local control is related to longer overall survival (OS) [20, 21], suggesting that reducing LRR may improve OS. These data indicate that in addition to better radiotherapy equipment and technology, LRR risk stratification of pIIIA-N2 NSCLC and proper selection of the patient population indicated for PORT will help reduce LRR, improve local control, and extend survival.

Some studies on the effective predictors of LRR risk in patients with pIIIA-N2 NSCLC have focused on clinical and pathologic factors, including age [22], smoking [23], pathologic type [24], tumor differentiation [22], microscopic margin status [25], pathologic T staging [26], clinical N status [9, 23], number of mediastinal lymph node stations involved [9, 22, 24], the region of mediastinal lymph node involvement [8, 26], skip metastasis [26-28], metastatic lymph node ratio (LNR) [22, 23], extranodal extension [29, 30], and number of N1 lymph nodes involved [25, 26]. However, these studies reached different conclusions, so further research is needed on the predictive value of these factors. Previous studies have shown that the status of the tumor biomarker epidermal growth factor receptor (EGFR) gene [31, 32]; preoperative systemic inflammation biomarkers such as the neutrophil-to-lymphocyte ratio (NLR) [33], platelet-to-lymphocyte ratio (PLR) [34], and lymphocyte-to-monocyte ratio (LMR) [35]; and preoperative prognostic nutritional index (PNI) [PNI = serum albumin (g/L) + 5 × lymphocyte count (/nL)] [36] are related to postoperative recurrence of NSCLC. However, no studies have been conducted to investigate the relationship between these biomarkers and LRR of pIIIA-N2 NSCLC.

In this study, we analyzed the relationship between clinical, pathologic, and biological factors and LRR and constructed a prediction model for risk score to help clinicians identify a patient's risk for LRR and guide the selection of PORT.

Patients and methods

Patient selection

The clinical, pathologic, and biological data of NSCLC patients who underwent surgery at Fujian Provincial Hospital between May 2012 and December 2018 were screened retrospectively. Eligible patients were selected based on the inclusion and exclusion criteria. Inclusion criteria included: (1) undergoing lung resection + lymph node dissection; (2) negative margins; (3) NSCLC diagnosed based on postoperative pathologic examination according to the 2015 World Health Organization Classification of Lung Cancer [37]; (4) pT1-3N2M0, stage IIIA according to the IASLC tumor, node, metastasis (TNM) classification (Edition 7) [38]; and (5) Eastern Cooperative Oncology Group Performance Status score 0 to 1. Exclusion criteria included: (1) positive visual or microscopic margins; (2) small cell carcinoma or mixed non-small and small cell carcinoma based on postoperative pathologic examination; (3) preoperative anti-tumor therapy such as radiotherapy, chemotherapy, or PORT; (4) history of malignancy; (5) concurrent second primary tumor or second primary tumor during follow-up; (6) perioperative death; or (7) incomplete follow-up data. In the end, a total of 107 patients were included in this study. The study was approved by the hospital ethics committee, and patients provided written informed consent.

Before surgery, the patients underwent a series of exams, including hematological examination, enhanced chest computed tomography (CT), enhanced upper-abdomen CT or abdominal ultrasonography, enhanced brain CT or magnetic resonance imaging (MRI), whole-body bone scan, and bronchoscopy, as well as positron emission tomography (PET)-CT in some cases. We reviewed electronic medical

records, imaging data, pathologic reports, and blood tests to collect data for this study. We referenced the IASLC lymph node map (2009) to map the N1 and N2 lymph nodes [39]. Specifically, the N1 lymph nodes include five groups of lymph nodes from stations 10 to 14, and the N2 lymph nodes include nine groups of lymph nodes from stations 1 to 9. The N2 lymph nodes cover the superior mediastinum, aortopulmonary window, subcarinal region, and inferior mediastinum. Regional N2 metastasis was defined as metastasis to the superior mediastinum or the aortopulmonary window of an upper-left-lobe tumor, metastasis to the superior mediastinum of an upper-right-lobe tumor, metastasis to the superior mediastinum or subcarinal region of a middle-right-lobe tumor, or metastasis to the subcarinal region or inferior mediastinum of a lower-left- or lower-right-lobe tumor. Non-regional N2 metastasis was defined as metastasis to the subcarinal region or inferior mediastinum of an upper-left- or upper-right-lobe tumor, metastasis to the inferior mediastinum of a middle-right-lobe tumor, metastasis to the superior mediastinum or the aortopulmonary window of a lower-left-lobe tumor, or metastasis to the superior mediastinum of a lower-right-lobe tumor. Clinical N1 (cN1) and N2 (cN2) were determined mainly based on imaging studies and criteria, including short diameter of lymph nodes ≥ 1 cm and lymph nodes with visibly high metabolism on PET-CT (maximum standardized uptake value > 2.5).

Treatments

All patients underwent lung resection and lymph node dissection by thoracotomy or video-assisted thoracoscopic surgery (VATS). A total of 90 patients underwent lobectomy, nine underwent bilobectomy, three underwent pneumonectomy, four underwent sleeve resection, and one underwent wedge resection. Moreover, 39 patients underwent systemic lymph node dissection, which included three stations of N1 lymph nodes and three stations of N2 lymph nodes (including station 7 lymph nodes), along with the surrounding adipose tissue. Among the other 68 patients, fewer than three stations of N2 lymph nodes were dissected in six patients, fewer than three stations of N1 lymph nodes were dissected in 61 patients. In the last patient, three stations of N2 lymph nodes were dissected, but station 7 lymph nodes were untouched, and fewer than three groups of N1 lymph nodes were dissected. After surgery, 81 patients underwent adjuvant chemotherapy for a median of 4 cycles (range 1-6 cycles) with a platinum-based regime combined with third-generation chemotherapy drugs. Moreover, 10 patients received targeted EGFR-tyrosine kinase inhibitors (TKIs) therapy (gefitinib [Iressa]: n = 9; erlotinib [Tarceva]: n = 1). Sixteen patients did not receive postoperative adjuvant therapy due to poor performance status or patient refusal.

Follow-up

A postoperative follow-up assessment was generally performed every 3 months during the first 2 years, every 6 months during years 3-5, and then every year after year 5. Follow-up procedures included physical examination, serum tumor markers, chest CT, and abdominal CT or ultrasonography. Moreover, patients with suspected brain and bone metastasis underwent brain CT or MRI and whole-body bone scan. Patients with no signs of brain or bone metastasis underwent brain CT or MRI and whole-body bone scan every year. The follow-up time (months) was defined as the time from surgery to LRR, DM, death, or last follow-up. The outcome measures were LRR, DM, and death. Data related to no recurrence, no metastasis, non-cancer-related death, and survival at the last follow-up were censored data. LRR was defined as tumor recurrence at stumps and/or regional lymph nodes, including hilar, mediastinal, and supraclavicular lymph nodes. Intrapulmonary metastasis in the affected lung was not considered LRR. DM was defined as non-regional tumor recurrence, including metastases to cervical lymph nodes, the contralateral lung, pleura, brain, bone, liver, or adrenal glands. Tumor recurrence and metastasis were diagnosed mainly based on imaging studies, and suspected recurrence and metastasis were confirmed with pathologic examination or imaging studies over time.

Statistical analysis

SPSS version 20 software (IBM Co., Armonk, NY, USA) was used for data analysis. Locoregional recurrence-free survival (LRFS) was defined as the time from surgery to the first LRR or the last follow-up. Distant metastasis-free survival (DMFS) was defined as the time from surgery to the first DM or the last follow-

Table 1. Baseline characteristics of all enrolled patients

Characteristic	No. of patients (n = 107)
Age (years), median (range)	61 (29~80)
Gender, n (%)	
Male	59 (55.1)
Female	48 (44.9)
Smoking history, n (%)	
No	74 (69.2)
Yes	33 (30.8)
ECOG PS, n (%)	
0	46 (43)
1	61 (57)
Laterality, n (%)	
Left	37 (34.6)
Right	70 (65.4)
Location of primary tumor, n (%)	
Left upper lobe	23 (21.5)
Left lower lobe	14 (13.1)
Right upper lobe	35 (32.7)
Right middle lobe	13 (12.1)
Right lower lobe	22 (20.6)
Tumor gross type, n (%)	
Central-type	19 (17.8)
Peripheral-type	88 (82.2)
N clinical stastus, n (%)	
cN0	46 (43.0)
cN1	11 (10.3)
cN2	50 (46.7)
Surgical approach, n (%)	
Thoracotomy	25 (23.4)
VATS	65 (60.7)
VATS conversion to Thoracotomy	17 (15.9)
Extent of surgical resection, n (%)	
Wedge resection	1 (0.9)
Lobectomy	90 (84.1)
Bilobectomy	9 (8.4)
Pneumonectomy	3 (2.8)
Sleeve resection	4 (3.7)
Adjuvant therapy, n (%)	
Not performed	16 (15.0)
Platinum-based chemotherapy	81 (75.7)
Targeted EGFR-TKIs therapy	10 (9.3)
Dissection of LNs, n (%)	
Non-SLND	68 (63.6)
SLND	39 (36.4)
Total no. of stations dissected, median (range)	6 (3~9)
No. of N2 stations dissected, median (range)	4 (1~6)
No. of N1 stations dissected, median (range)	2 (1~4)
Total no. of LNs dissected, median (range)	23 (5~60)
No. of N2 LNs dissected, median (range)	15 (2~56)

up. Disease-free survival (DFS) was defined as the time from surgery to the first recurrence, last follow-up, or all-cause death. OS was defined as the time from surgery to all-cause death or last follow-up. Descriptive statistics were used to summarize tumor biomarkers, preoperative systemic inflammation biomarkers, and other clinical and pathologic characteristics. The Kaplan-Meier method was used to analyze LRFS, DMFS, DFS, and OS and to plot survival curves. The optimal cutoff values of the number of lymph nodes dissected, the number of metastatic lymph nodes, metastatic LNR, pathologic tumor size, Ki67, NLR, PLR, LMR, and PNI were determined using the X-tile software [40]. The Kaplan-Meier method was used for univariate analysis of possible factors for LRFS, and the log-rank sum test was run to analyze the difference in LRFS. Significant variables identified with univariate analysis were incorporated into the Cox regression model for multivariate analysis to identify independent risk factors for LRFS. All tests were two-tailed, and $P<0.05$ was considered statistically significant. The multivariate Cox regression model was used to estimate the regression coefficient of each independent risk factor and calculate the additive risk score. The Harrell's concordance index (C-index) was calculated to evaluate the discrimination ability of the prediction model.

Results

Clinical, pathologic, and biological characteristics

Among the 107 patients with pIIIA-N2 NSCLC, 59 (55.1%) were men and 48 (44.9%) were women (male:female ratio:

No. of N1 LNs dissected, median (range)	6 (2~27)
Total no. of metastatic LNs, median (range)	4 (1~35)
No. of metastatic N2 LNs, median (range)	2 (1~28)
No. of metastatic N1 LNs, median (range)	1 (0~11)
Total LNR (%), median (range)	20 (2.2~89.7)
N2-LNR (%), median (range)	17.4 (2.5~100)
N1-LNR (%), median (range)	25 (0~100)
No. of metastatic N2 stations, n (%)	
Single	39 (36.4)
Multiple	68 (63.6)
No. of metastatic N2 regions, n (%)	
Single	84 (78.5)
Multiple	23 (21.5)
Distribution of Metastatic N2 regions, n(%)	
Regional	82 (76.6)
Non-regional	25 (23.4)
Subcarinal LNs metastasis, n (%)	
No	61 (57.0)
Yes	46 (43.0)
Skip N2 metastasis, n (%)	
No	75 (70.1)
Yes	32 (29.9)
Pathologic tumor size (cm), median (range)	3.5 (0.7~15)
Pathologic T stage, n (%)	
pT1	24 (22.4)
pT2	74 (69.2)
pT3	9 (8.4)
Histologic subtype, n (%)	
Squamous cell carcinoma	19 (17.8)
Adenocarcinoma	70 (65.4)
Large cell carcinoma	5 (4.7)
Adenosquamous carcinoma	6 (5.6)
Others	7 (6.5)
Visceral pleural invasion, n (%)	
No	43 (40.2)
Yes	64 (59.8)
Lymphovascular invasion, n (%)	
No	81 (75.7)
Yes	26 (24.3)
Neurological invasion, n (%)	
No	100 (93.5)
Yes	7 (6.5)
Tumor necrosis, n (%)	
No	78 (72.9)
Yes	29 (27.1)
Ki67, n (%)	
<50%	65 (60.7)
≥ 50%	29 (27.1)
Unknown	13 (12.1)

1.23:1). The median age of the patients was 61 years (range 29-80 years). Most patients had peripheral lung cancer (88, 82.2%). Before surgery, 46 patients (43%) had clinical node negativity (cN0), 11 (10.3%) had cN1, and 50 (46.7%) had cN2. Most patients underwent VATS (65, 60.7%), and 17 patients (15.9%) were converted to thoracotomy during operation due to interference from lymph nodes and/or extensive thoracic adhesions. Most patients underwent lobectomy (90, 84.1%), and one patient (0.9%) underwent wedge reception due to advanced age. The median total number of lymph nodes dissected, N2 lymph nodes dissected, and N1 lymph nodes dissected was 23, 15, and 6. The median total numbers of lymph node stations dissected, N2 lymph node stations dissected, and N1 lymph node stations dissected were 6, 4, and 2. The median total numbers of metastatic lymph nodes, metastatic N2 lymph nodes, and metastatic N1 lymph nodes were 4, 2, and 1. Most patients had adenocarcinoma (70, 65.4%), followed by squamous cell carcinoma (19, 17.8%). A total of 84 patients (78.5%) underwent EGFR gene testing; the results showed that 42 patients (39.3%) had one mutant EGFR and one wild type EGFR allele. EGFR status was unknown in the other 23 patients (21.5%). The median tumor size was 3.5 cm. Before surgery, the median concentrations of albumin, neutrophils, lymphocytes, monocytes, and platelets were 44 g/L, 4.2 × 10^9/L, 1.9 × 10^9/L, 0.41 × 10^9/L, and 244 × 10^9/L. After surgery, 81 patients (75.7%) received platinum-based double-drug chemotherapy, and 10 (9.3%) received targeted

EGFR status, n (%)	
Mutation	42 (39.3)
Exon18 G719X	1 (0.9)
Exon19 del	17 (15.9)
Exon20 ins	2 (1.9)
Exon21 L858R	21 (19.6)
Exon20 T790M and Exon21 L858R	1 (0.9)
Wild-type	42 (39.3)
Unknown	23 (21.5)
Blood cell count/Biochemistry	
Albumin (g/L), median (range)	44 (34~50.5)
Neutrophil count (10^9/L), median (range)	4.2 (1.7~10.7)
Lymphocyte count (10^9/L), median (range)	1.9 (0.7~7.1)
Monocyte count (10^9/L), median (range)	0.41 (0.18~1.15)
Platelet count (10^9/L), median (range)	244 (128~450)
Nutrition/inflammation index	
NLR, median (range)	2.09 (0.71~8.82)
PLR, median (range)	128.82 (33.66~308.57)
LMR, median (range)	4.4 (1.63~12.38)
PNI, median (range)	53.5 (38.5~81.5)

Abbreviations: ECOG: eastern cooperative oncology group, PS: performance status, VATS: video-assisted thoracoscopic surgery, EGFR: epidermal growth factor receptor, TKIs: tyrosine kinase inhibitors, SLND: systemic lymph node dissection, LNs: lymph nodes, LNR: lymph node ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, LMR: lymphocyte-to-monocyte ratio, PNI: prognostic nutritional index.

Table 2. Patterns of First recurrence and Distribution of Recurrence sites

Item	No. of patients
Patterns of First recurrence, n (%)	
Locoregional recurrence alone	13 (18.8)
Distant metastasis alone	23 (33.3)
Both	33 (47.8)
Sites of Locoregional recurrence, n (%)	
Mediastinal LNs	39 (84.8)
Hilar LNs	12 (26.1)
Supraclavicular LNs	11 (23.9)
Stump	11 (23.9)
Sites of Distant metastasis, n (%)	
Lung	23 (41.1)
Brain	16 (28.6)
Bone	9 (16.1)
Pleura	8 (14.3)
Adrenal	7 (12.5)
Liver	6 (10.7)
Non-regional LNs	2 (3.6)
Kidney	1 (1.8)
Spleen	1 (1.8)

Abbreviations: LNs: lymph nodes.

EGFR-TKIs therapy. The detailed clinical, pathologic, and biological characteristics are presented in **Table 1**.

Patterns of first recurrence and the distribution of recurrence sites

The median follow-up time was 31.2 months. During follow-up, 69 patients (64.5%) had LRR and/or DM, of whom 13 patients (18.8%) had only LRR, 23 (33.3%) had only DM, and 33 (47.8%) had both LRR and DM. A total of 46 patients (43%) had LRR (with or without DM), which occurred within 1 year of surgery in 22 patients (47.8%) and within 3 years of surgery in 41 patients (89.1%). Mediastinal lymph nodes were the most common recurrence site (39, 84.8%), followed by hilar lymph nodes (12, 26.1%), supraclavicular lymph nodes (11, 23.9%), and stumps (11, 23.9%). A total of 56 patients (52.3%) had DM (with or without LRR), which occurred within 1 year of surgery in 22 patients (39.3%) and within 3 years of surgery in 50 patients (89.3%). The most common metastatic sites were lung (23, 41.1%) and brain (16, 28.6%), followed by bone (9, 16.1%), pleura (8, 14.3%), adrenal gland (7, 12.5%), liver (6, 10.7%), non-regional lymph nodes (2, 3.6%), kidney (1, 1.8%), and spleen (1, 1.8%) (**Table 2**).

Survival analysis

The patients were followed up through July 10, 2019. The median LRFS, DMFS, DFS, and OS were 17, 19.6, 16.3, and 31.2 months, respectively. The 1-year LRFS, DMFS, DFS, and OS rates were 78.2%, 78%, 69.8%, and 90.2%, respectively; the 3-year rates were 50.6%, 41.2%, 31.2%, and 66.3%, respectively (**Figure 1**).

Univariate and multivariate analysis of the risk factors for LRFS

Univariate and multivariate analysis were conducted to identify LRFS-related clinical, patho-

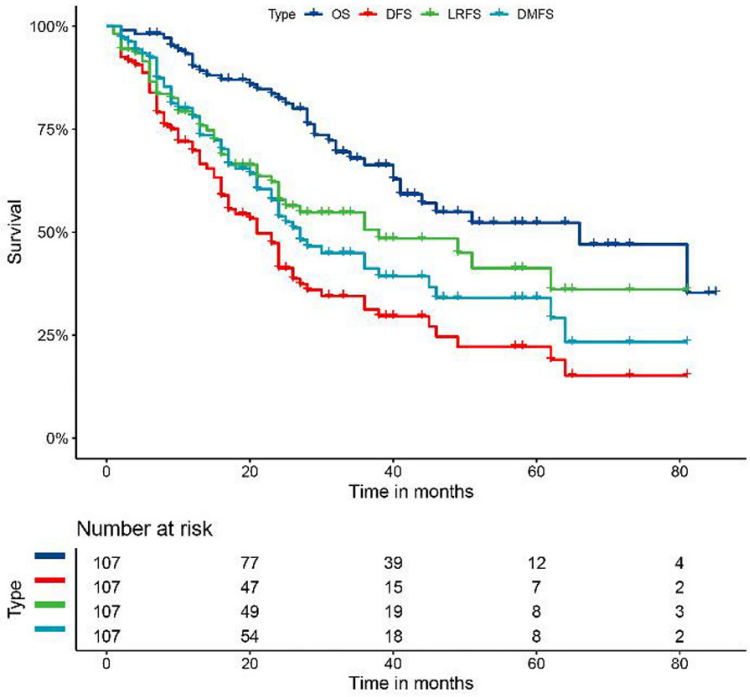


Figure 1. Kaplan-Meier curve for LRFS, DMFS, DFS, OS of pIIIA–N2 NSCLC patients.

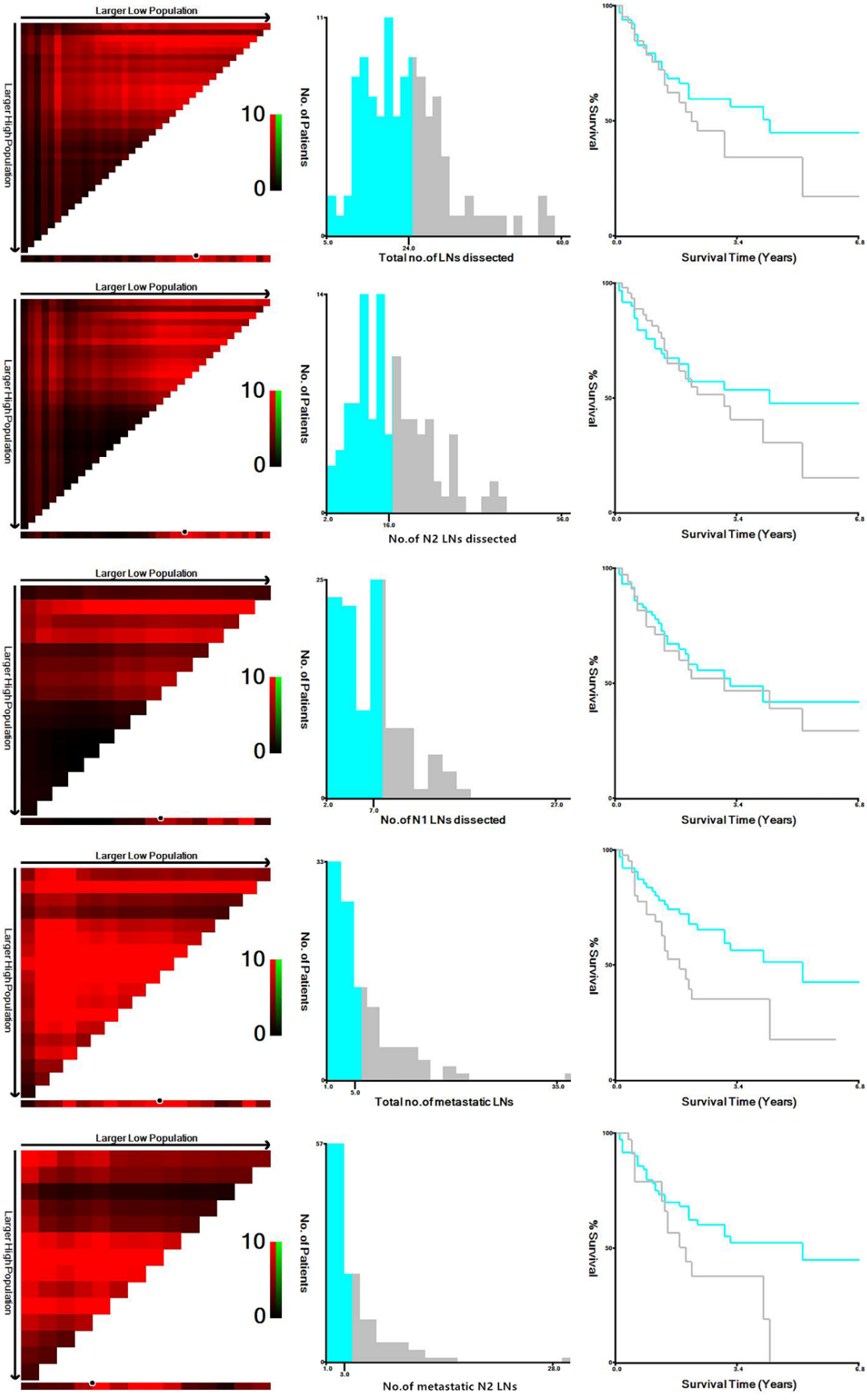
logic, and biological factors. The optimal cut-off values of the total number of lymph nodes dissected, the number of N2 lymph nodes dissected, the number of N1 lymph nodes dissected, the total number of metastatic lymph nodes, the number of metastatic N2 lymph nodes, the number of metastatic N1 lymph nodes, total LNR, N2-LNR, N1-LNR, pathologic tumor size, Ki67, NLR, PLR, LMR and PNI were determined using the X-tile. The results were 24, 16, 7, 5, 3, 2, 36.4%, 38.9%, 75%, 5 cm, 50%, 2.39, 252, 4.69 and 43.5, respectively (**Figure 2**). Univariate analysis showed that surgical approach (χ^2 = 14.983, P = 0.001; **Figure 3A**), extent of surgical resection (χ^2 = 10.207, P = 0.037), pathologic tumor size (χ^2 = 4.627, P = 0.031), tumor necrosis (χ^2 = 6.979, P = 0.008), the total number of metastatic lymph nodes (χ^2 = 9.977, P = 0.002), total LNR (χ^2 = 6.051, P = 0.014), N2-LNR (χ^2 = 6.544, P = 0.011; **Figure 3B**), the number of metastatic N1 lymph nodes (χ^2 = 3.923, P = 0.048), cN2 (χ^2 = 13.702, P<0.001), cN1 (χ^2 = 6.098, P = 0.014), EGFR status (χ^2 = 11.328, P = 0.003; **Figure 3C**), NLR (χ^2 = 6.194, P = 0.013), and LMR (χ^2 = 7.376, P = 0.007; **Figure 3D**) were risk factors for LRFS (**Table 3**). Significant factors identified by univariate analysis were incorporated into the Cox regression model for multivariate analysis. The results showed that surgical approach, N2-LNR, EGFR status, and LMR were independent risk factors for LRFS. VATS (hazard ratio [HR], 0.348; 95% confidence interval [CI], 0.175-0.693; P = 0.003) was associated with a higher LRFS rate, while N2-LNR ≥ 38.9% (HR 3.597; 95% CI, 1.832-7.062; P = 0.000), wild-type EGFR (HR 3.666; 95% CI, 1.724-7.797; P = 0.001), and LMR<4.69 (HR 2.364; 95% CI, 1.221-4.574; P = 0.011) were associated with a lower LRFS rate (**Table 4**).

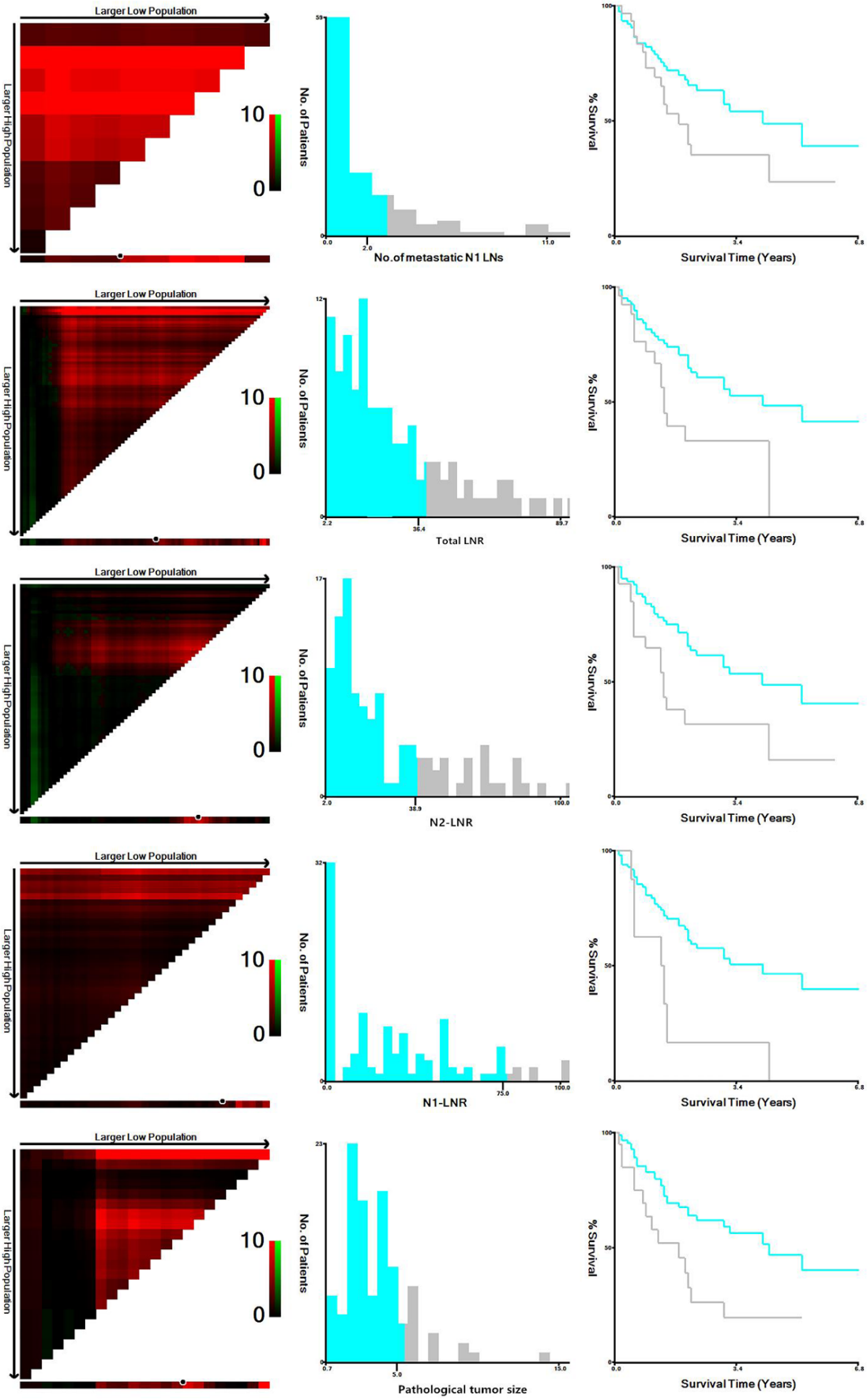
Construction of a prediction model for LRR risk score in patients with pIIIA-N2 NSCLC

We incorporated the independent risk factors identified by multivariate analysis into a prediction model for LRR risk score. The additive risk score was calculated based on the regression coefficient of each independent risk factor (**Table 5**). We used X-tile to stratify the 107 patients into the low-risk group (risk score: 0-2; 37, 34.6%), medium-risk group (risk score: 3-5; 28, 26.2%), and high-risk group (risk score: 6-13; 42, 39.2%). The Kaplan-Meier method was used to plot LRFS curves, which showed that a lower risk level was associated with longer LRFS. In the low-, medium-, and high-risk groups, the 1-year LRFS rates were 91.9%, 85.3%, and 54.6%, respectively; and the 3-year LRFS rates were 71.4%, 57.3%, and 13.6%, respectively. These between-group differences were significant (P = 0.000) (**Figure 4**; **Table 6**). By internal bootstrap validation, the C-index was 0.747 (95% CI, 0.678-0.816), indicating good discrimination of the prediction model.

Discussion

In this retrospective study, we analyzed the clinical, pathologic, and biological data of 107 patients with pIIIA-N2 NSCLC. Our pertinent findings are summarized as follows. First, the LRR rate was 43%, which was similar to previ-


Larger Low Population
Larger High Population
10
0
No. of Patients
Total no.of LNs dissected
% Survival
Survival Time (Years)
Larger Low Population
Larger High Population
10
0
No. of Patients
No.of N2 LNs dissected
% Survival
Survival Time (Years)
Larger Low Population
Larger High Population
10
0
No. of Patients
No.of N1 LNs dissected
% Survival
Survival Time (Years)
Larger Low Population
Larger High Population
10
0
No. of Patients
Total no.of metastatic LNs
% Survival
Survival Time (Years)
Larger Low Population
Larger High Population
10
0
No. of Patients
No.of metastatic N2 LNs
% Survival
Survival Time (Years)


Larger Low Population
Larger High Population
10
0
No. of Patients
No. of metastatic N1 LNs
% Survival
Survival Time (Years)
Larger Low Population
Larger High Population
10
0
No. of Patients
Total LNR
% Survival
Survival Time (Years)
Larger Low Population
Larger High Population
10
0
No. of Patients
N2-LNR
% Survival
Survival Time (Years)
Larger Low Population
Larger High Population
10
0
No. of Patients
N1-LNR
% Survival
Survival Time (Years)
Larger Low Population
Larger High Population
10
0
No. of Patients
Pathological tumor size
% Survival
Survival Time (Years)

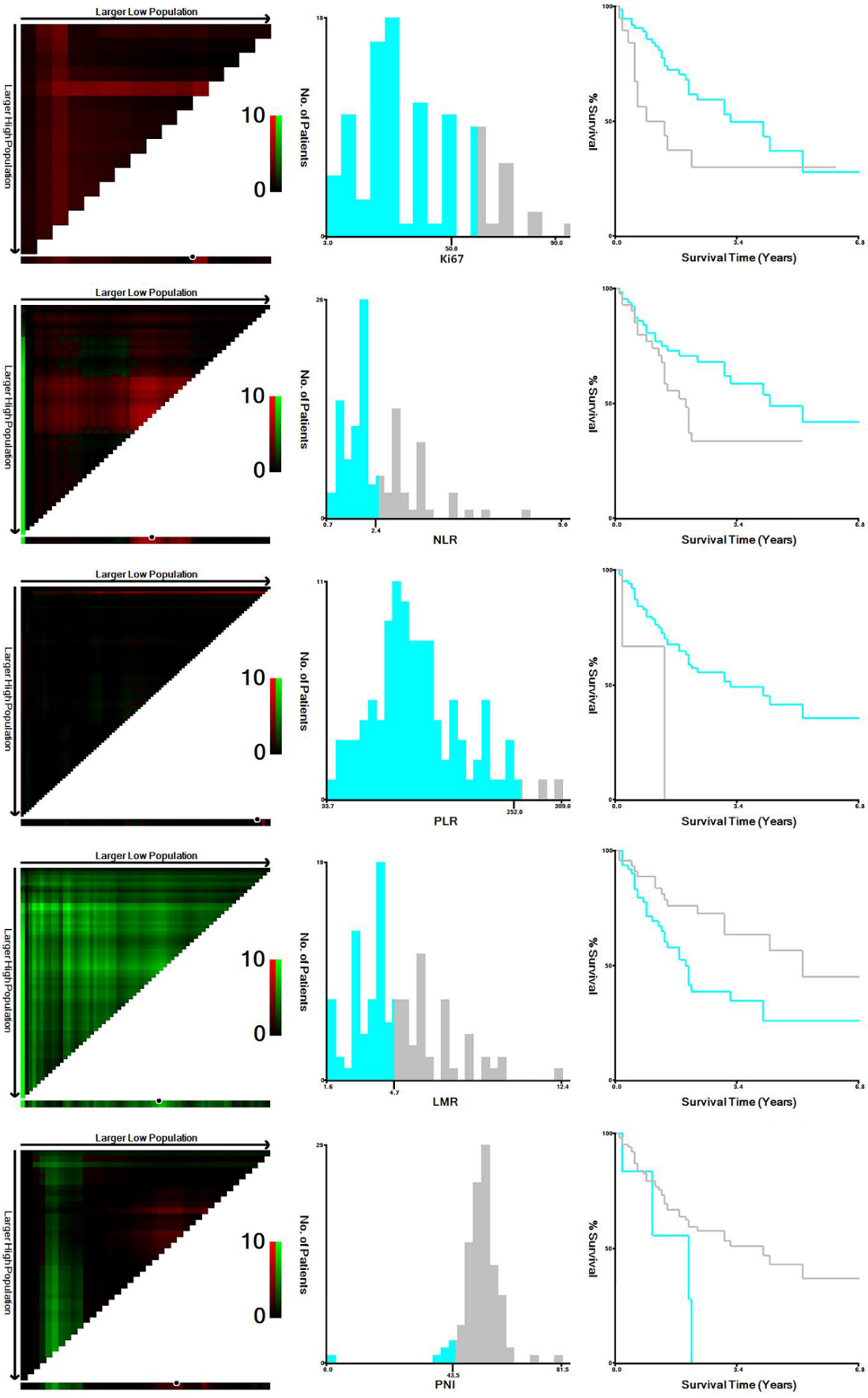

Larger Low Population
Larger High Population
10
0
No. of Patients
Ki67
% Survival
Survival Time (Years)
NLR
PLR
LMR
PNI

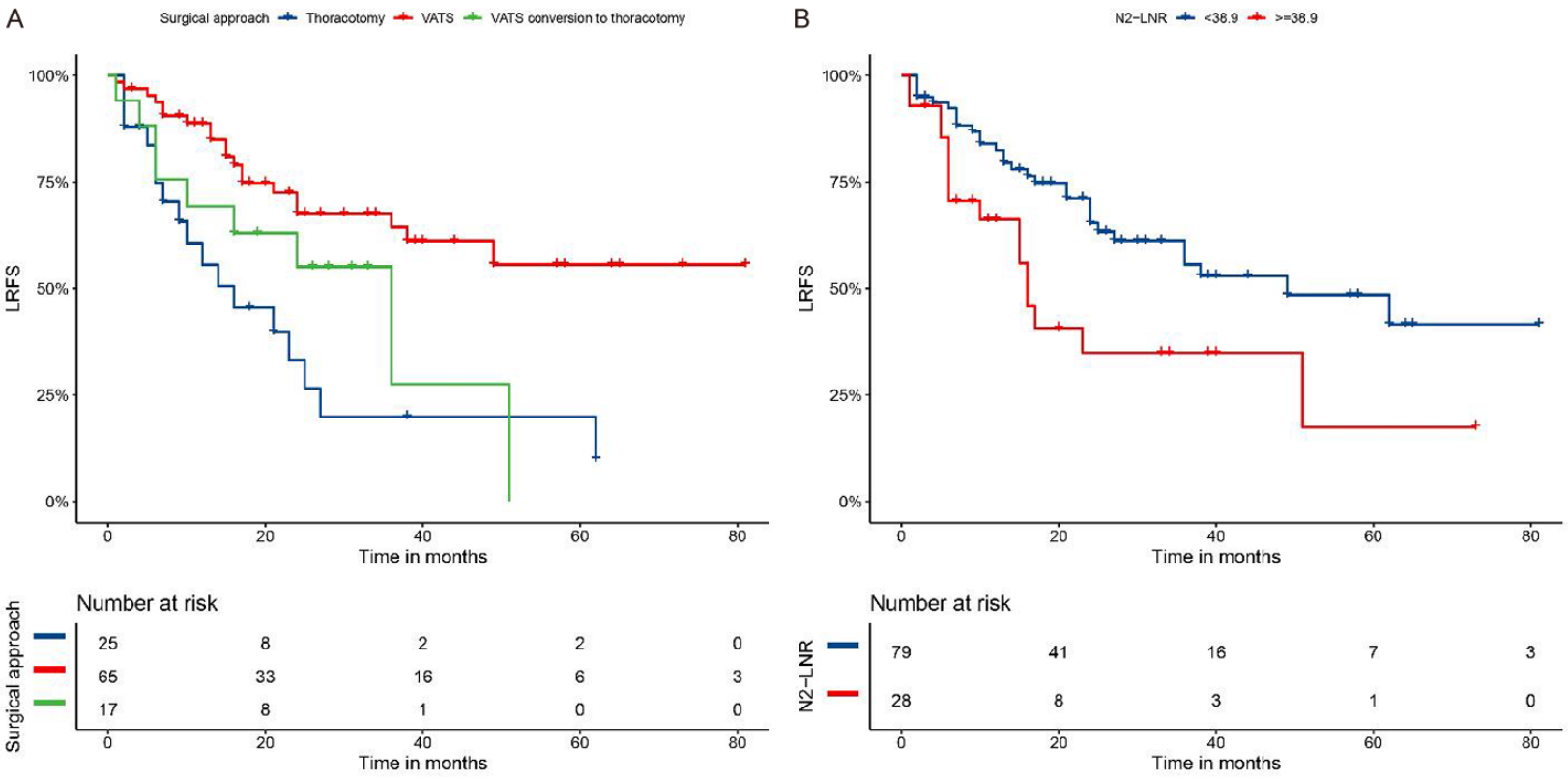
Figure 2. X-tile analyses of LRFS were performed using patients' data to determine the optimal cut-off values for the number of lymph nodes dissected, the number of metastatic lymph nodes, LNR, pathologic tumor size, Ki67, NLR, PLR, LMR and PNI. The optimal cut-off values highlighted by the black circles in left panels are shown in histograms of the entire cohort (middle panels), and Kaplan-Meier plots are displayed in right panels. The optimal cut-off values for the total number of lymph nodes dissected, the number of N2 lymph nodes dissected, the number of N1 lymph nodes dissected, the total number of metastatic lymph nodes, the number of metastatic N2 lymph nodes, the number of metastatic N1 lymph nodes, total LNR, N2-LNR, N1-LNR, pathologic tumor size, Ki67, NLR, PLR, LMR and PNI were 24, 16, 7, 5, 3, 2, 36.4%, 38.9%, 75%, 5 cm, 50%, 2.39, 2.52, 4.69 and 43.5, respectively.

ous literature reports (6, 14). Nearly 50% (22/46) of LRR cases occurred within 1 year of surgery. Second, the 1-year LRFS, DMFS, DFS, and OS rates were 78.2%, 78%, 69.8%, and 90.2%, respectively, and the 3-year rates were 50.6%, 41.2%, 31.2%, and 66.3%, respectively. Surgical approach, N2-LNR, EGFR status, and LMR were shown to be independent risk factors for LRFS. Third, we constructed a prediction model for risk score based on the four independent risk factors to predict a patient's risk for LRR.

VATS has been used in clinical practice since the 1990s. In 2006, the National Comprehensive Cancer Network guidelines started to recommend VATS as a practical surgical approach for early-stage NSCLC, thereby affirming the value of VATS. With ongoing improvements to medical devices and equipment and as surgeons gain more experience and skill with VATS, VATS is increasingly used to treat locally advanced NSCLC. Several studies have shown that VATS is safe and practical for locally advanced NSCLC [41-45], with similar DFS and OS performance as for thoracotomy [43-45]. However, few studies have been conducted to investigate the role of surgical approach in postoperative LRFS in patients with locally advanced NSCLC. This study showed that surgical approach was an independent risk factor for LRFS. The 1- and 3-year LRFS rates were higher in the VATS group than in the thoracotomy group (86.2% vs. 55.6%, 64.4% vs. 17.4%; P = 0.001). Tumor recurrence was closely related to the resection range. Both VATS and thoracotomy achieved R0 resection, with no significant difference in the range or extent of lymph node dissection. VATS was associated with lower LRR risk, which was probably related to EGFR status and LMR, because a higher proportion of patients in the VATS group (relative to the thoracotomy group) had EGFR mutation and a high LMR, both favorable prognostic factors for LRR (**Table 7**).

While the number of metastatic lymph nodes is considered an important predictor of survival and prognosis [6, 46-49], it is associated with the number of lymph nodes examined in the surgical specimen, the extent of lymph node dissection during surgery, and pathologic sectioning. These problems can be avoided by using LNR, which makes LNR a better prognostic predictor. LNR has been used to predict the OS of patients with pIIIA-N2 NSCLC [50-52], but few researchers have looked at the role of LNR in LRFS. LNR includes total LNR, N2-LNR, and N1-LNR. No unified cut-off value has been established for LNR, and different values have been used in different studies. Feng et al. [23] used 20% as the cut-off value for LNR (≤ 20% vs. > 20%), but they did not specify the type of LNR investigated. Wei et al. [22] advocated an N2-LNR cut-off value of 1/3 (≤ 1/3 vs. > 1/3). Both studies showed that LNR was an independent risk factor for LRFS and that high LNR was an adverse prognostic factor, but neither study described the method used to determine the cut-off value. In this study, we used X-tile to determine the cut-off value of N2-LNR (38.9%) with the minimum *P* value in the log-rank sum test. Survival analysis showed that the 1- and 3-year LRFS rates were significantly lower in the N2-LNR ≥ 38.9% group than in the N2-LNR<38.9% group (62.1% vs. 82.5%, 26.8% vs. 55.7%; P = 0.011). N2-LNR was independently correlated with LRFS in patients with pIIIA-N2 NSCLC (HR = 3.597, P = 0.000), while the number of metastatic N2 nodes and the number of N2 nodes dissected were not correlated with LRFS, suggesting that LNR is a better predictor of LRR risk in patients with pIIIA-N2 NSCLC. These cut-off values of LNR are clinically relevant, although large, multicenter, and prospective studies are needed to validate the results. Further research is also needed to identify the most clinically relevant LNR.

EGFR status is an excellent predictor of patient prognosis and response to EGFR-TKI therapy in patients with unresectable advanced NSCLC,


A
Surgical approach
Thoracotomy
VATS
VATS conversion to thoracotomy
100%
75%
50%
25%
0%
LRFS
0
20
40
60
80
Time in months
Number at risk
Surgical approach
25
8
2
2
0
65
33
16
6
3
17
8
1
0
0
20
40
60
80
Time in months
B
N2−LNR
<38.9
>=38.9
100%
75%
50%
25%
0%
LRFS
0
20
40
60
80
Time in months
Number at risk
N2−LNR
79
41
16
7
3
28
8
3
1
0
0
20
40
60
80
Time in months

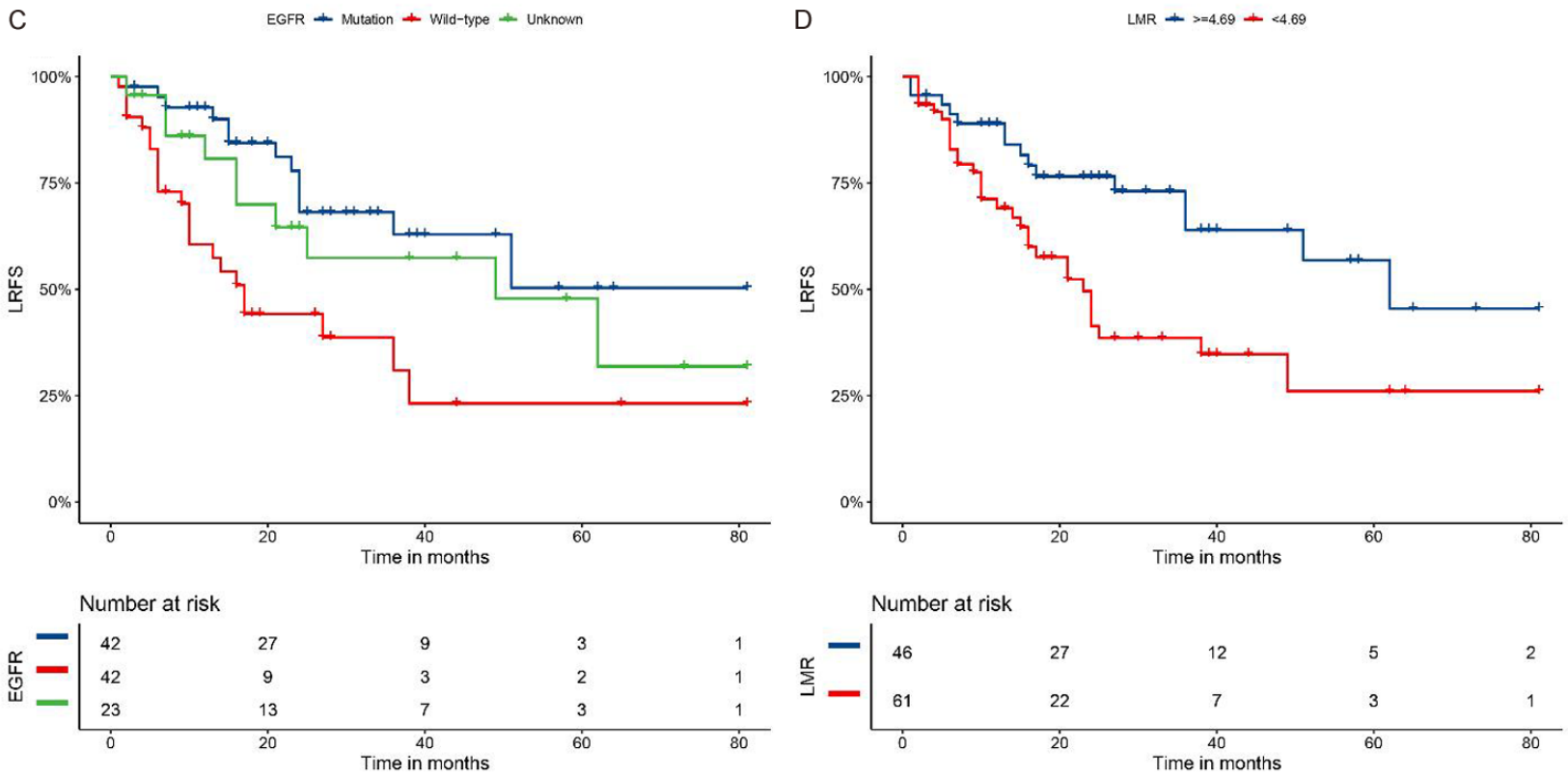


Figure 3. Kaplan-Meier curve for LRFS of pIIIA-N2 NSCLC patients stratified by surgical approach, N2-LNR, EGFR status, and LMR. A. Kaplan-Meier curve for LRFS stratified by surgical approach (P = 0.001). B. Kaplan-Meier curve for LRFS stratified by N2-LNR (P = 0.011). C. Kaplan-Meier curve for LRFS of pIIIA-N2 NSCLC patients stratified by EGFR status (P = 0.003). D. Kaplan-Meier curve for LRFS of pIIIA-N2 NSCLC patients stratified by LMR (P = 0.007).

Table 3. Risk factors: univariate analysis

Characteristic	No. of patients	LRFS (%)			
		1-year	3-year	χ^2	*P*-value
Age (years)				1.649	0.199
<65	66	72	45.1		
≥ 65	41	84.7	57.4		
Gender				2.804	0.094
Male	59	66.2	46.1		
Female	48	89.7	56.9		
Smoking history				2.918	0.088
No	74	88.9	56.5		
Yes	33	61.5	NA		
ECOG PS				5.416	0.200
0	46	85.7	61.8		
1	61	71.5	40.6		
Laterality				0.804	0.370
Left	37	80.8	53.5		
Right	70	75.8	46.7		
Location of primary tumor				0.098	0.952
Upper lobe	58	78	48.2		
Middle lobe	13	66.5	23.4		
Lower lobe	36	77.6	48.2		
Tumor gross type				1.891	0.169
Central-type	19	56.4	35.9		
Peripheral-type	88	81.2	51.9		
Surgical approach				14.893	0.001
Thoracotomy	25	55.6	17.4		
VATS	65	86.2	64.4		
VATS conversion to Thoracotomy	17	67.2	27.6		
Extent of surgical resection				10.207	0.037
Lobectomy	90	79.7	55.9		
Wedge resection	1	NA	NA		
Bilobectomy	9	55.9	NA		
Pneumonectomy	3	45.4	NA		
Sleeve resection	4	33.3	NA		
Adjuvant therapy				5.288	0.071
Not performed	16	58.5	29		
Platinum-based chemotherapy	81	76.4	49.1		
EGFR-TKIs targeted therapy	10	NA	83.3		
Dissection of LNs				0.321	0.571
Non-sLND	68	78.5	53.9		
sLND	39	73.4	NA		
Total no. of LNs dissected				3.747	0.053
<24	60	78.5	58.6		
≥ 24	47	74	34.9		
Total no. of metastatic LNs				9.977	0.002
<5	60	84.3	62.7		
≥ 5	47	68.1	25.9		
Total LNR				6.051	0.014

<36.4%	80	80.1	55.6		
≥ 36.4%	27	69.1	18.2		
No. of N2 LNs dissected				0.509	0.476
<16	55	72.8	55		
≥ 16	52	80.8	45.5		
No. of metastatic N2 LNs				3.348	0.067
<3	57	78.2	56.4		
≥ 3	50	76.5	36.5		
N2-LNR				6.544	0.011
<38.9%	79	82.5	55.7		
≥ 38.9%	28	62.1	26.8		
No. of N1 LNs dissected				0.042	0.837
<7	55	81	52.3		
≥ 7	52	73.5	48.6		
No. of metastatic N1 LNs				3.923	0.048
<2	59	82.3	61.3		
≥ 2	48	71.6	35		
N1-LNR				1.813	0.178
<75%	95	79.7	51.8		
≥ 75%	12	61.5	28.8		
No. of metastatic N2 stations				0.047	0.829
Single	39	77	42.6		
Multiple	68	76.9	51.7		
No. of metastatic N2 regions				1.192	0.275
Single	84	78.4	53.5		
Multiple	23	74	NA		
Distribution of Metastatic N2 regions				1.207	0.272
Regional	82	77.9	53.8		
Non-regional	25	75.8	NA		
Subcarinal LNs metastasis				0.078	0.780
No	61	80.5	50.1		
Yes	46	74.2	44		
Skip N2 metastasis				1.018	0.313
No	75	75	42.6		
Yes	32	80.3	60.5		
Clinical N2				13.702	<0.001
No	57	88.9	69.5		
Yes	50	63.9	30.2		
Pathologic tumor size (cm)				4.627	0.031
<5	79	80.9	59.6		
≥ 5	28	63.3	29.7		
Pathologic T stage				3.676	0.159
1	24	88.3	NA		
2	74	74.8	52.1		
3	9	55.5	20		
Histologic subtype				0.342	0.558
Non-squamous cell carcinoma	88	77.6	51.7		
Squamous cell carcinoma	19	71.8	41.4		
Visceral pleural invasion				0.105	0.746

No	43	80.5	48		
Yes	64	74.1	52.1		
Tumor necrosis				6.979	0.008
No	78	83	58.2		
Yes	29	59.6	25.6		
Lymphovascular invasion				0.472	0.492
No	81	81.7	50.8		
Yes	26	63	NA		
Neurological invasion				1.117	0.290
No	100	77	49.4		
Yes	7	NA	NA		
Ki67				1.722	0.423
<50%	65	81.8	49.5		
≥ 50%	29	64.1	42.3		
Unknown	13	75.8	NA		
EGFR status				11.328	0.003
Mutation	42	90.5	62.9		
Wild-type	42	58.5	30.9		
Unknown	23	80.7	53		
NLR				6.194	0.013
<2.39	63	79.2	62.8		
≥ 2.39	44	72.9	NA		
PLR				1.275	0.259
<252	103	78.4	51.3		
≥ 252	4	48.2	NA		
LMR				7.376	0.007
≥ 4.69	46	84.8	63.9		
<4.69	61	69.1	35.3		
PNI				1.404	0.236
<43.5	4	50	NA		
≥ 43.5	103	77.2	52		

Abbreviations: ECOG: eastern cooperative oncology group, PS: performance status, VATS: video-assisted thoracoscopic surgery, EGFR: epidermal growth factor receptor, TKIs: tyrosine kinase inhibitors, SLND: systemic lymph node dissection, LNs: lymph nodes, LNR: lymph node ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, LMR: lymphocyte-to-monocyte ratio, PNI: prognostic nutritional index, NA: not available.

and EGFR mutation is related to a better treatment response and prognosis [53-56]. However, researchers are still debating the extent to which EGFR status predicts postoperative recurrence in NSCLC patients. Takamochi et al. analyzed the data of 939 patients with lung adenocarcinoma and found that the RFS rate was significantly higher in patients with EGFR mutation than in patients with wild-type EGFR [31]. A multicenter retrospective analysis of 1155 patients with pN0-1 lung adenocarcinoma showed that the RFS rate was significantly lower in patients with EGFR mutation than in patients with wild-type EGFR [32]. A multicenter matched cohort study showed that EGFR status was unrelated to postoperative RFS in NSCLC patients [57]. A subsequent meta-analysis [58] and the study by Zhu et al. [48] reached similar conclusions. This is the first study to investigate the role of EGFR status in LRFS in patients with pIIIA-N2 NSCLC. We analyzed the predictive value of EGFR status for LRR in patients with pIIIA-N2 NSCLC. The results showed that 1- and 3-year LRFS rates were lower in patients with wild-type EGFR than in patients with EGFR mutation (58.5% vs. 90.5%, 30.9% vs. 62.9%; P = 0.003) and that EGFR status was an independent risk factor for LRFS (HR = 3.666, P = 0.001), suggesting that the risk of postopera-

Table 4. Risk factors: multivariate analysis

Characteristic	Beta	SE	Wald	*P*-value	HR (95% CI)
Surgical approach					
Thoracotomy					1.000
VATS	-1.056	0.351	9.033	0.003	0.348 (0.175-0.693)
VATS conversion to Thoracotomy	-0.654	0.450	2.109	0.146	0.520 (0.215-1.257)
N2-LNR					
<38.9%					1.000
≥ 38.9%	1.280	0.344	13.837	0.000	3.597 (1.832-7.062)
EGFR status					
Mutation					1.000
Wild-type	1.299	0.385	11.387	0.001	3.666 (1.724-7.797)
Unknown	0.211	0.443	0.227	0.634	1.235 (0.518-2.941)
LMR					
≥ 4.69					1.000
<4.69	0.860	0.337	6.521	0.011	2.364 (1.221-4.574)

Abbreviations: VATS: video-assisted thoracoscopic surgery, LNR: lymph node ratio, EGFR: epidermal growth factor receptor, LMR: lymphocyte-to-monocyte ratio, HR: hazard ratio, CI: confidence interval.

Table 5. Risk factor calculation

Characteristic	*P*-value	HR (95% CI)	Score
Surgical approach			
Thoracotomy		1.000	3
VATS	0.003	0.348 (0.175-0.693)	0
VATS conversion to Thoracotomy	0.146	0.520 (0.215-1.257)	0
N2-LNR			
<38.9%		1.000	0
≥ 38.9%	0.000	3.597 (1.832-7.062)	4
EGFR status			
Mutation		1.000	0
Wild-type	0.001	3.666 (1.724-7.797)	4
Unknown	0.634	1.235 (0.518-2.941)	0
LMR			
≥ 4.69		1.000	0
<4.69	0.011	2.364 (1.221-4.574)	2

Abbreviations: VATS: video-assisted thoracoscopic surgery, LNR: lymph node ratio, EGFR: epidermal growth factor receptor, LMR: lymphocyte-to-monocyte ratio, HR: hazard ratio, CI: confidence interval.

tive LRR was higher in patients with wild-type EGFR than in patients with EGFR mutation.

Inflammation is closely related to tumor growth, development, invasion, and metastasis [59]. As a peripheral blood indicator of systemic inflammation status, LMR is a proven prognostic predictor for many malignancies, including lung cancer [60]. For lung cancer, most studies have focused on the relationship between LMR and OS, and few investigated the relationship between LMR and postoperative recurrence in NSCLC patients [61, 62]. LMR is related to postoperative occurrence in NSCLC patients, and a low LMR is an adverse prognostic factor [35]; however, the role of LMR in LRR in patients with pIIIA-N2 NSCLC is unknown. The current study was first to investigate the clinical value of preoperative LMR in predicting LRR in patients with pIIIA-N2 NSCLC. We used X-tile to determine the optimal cut-off value of LMR (4.69) with the minimum *P* value from the log-rank sum test for LRFS analysis and found that the 1- and 3-year LRFS rates were significantly lower in the low-LMR group (LMR<4.69) than in the high-LMR group (LMR ≥ 4.69) (69.1% vs. 84.8%, 35.3% vs. 63.9%; P = 0.007) and that LMR was an independent risk factor for LRFS (HR = 2.364, P = 0.011), suggesting that a low LMR was associated with high LRR risk. LMR may be used as a biomarker to predict LRR in patients with pIIIA-N2 NSCLC. Moreover, LMR can be measured with blood samples and is cost-effective. Nevertheless, data on the predictive value of LMR for LRR in patients with pIIIA-N2 NSCLC are still limited, and large, multicenter, prospective studies are

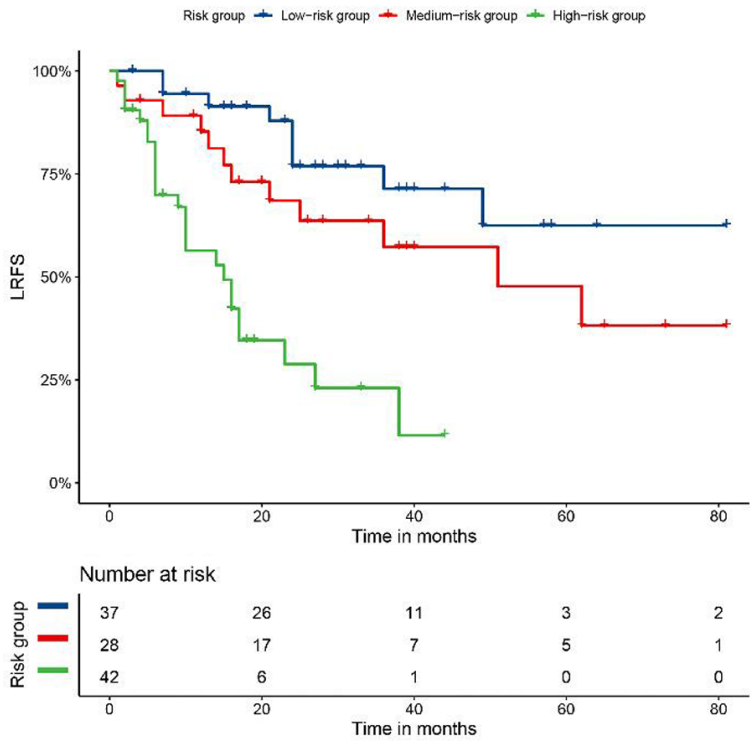


Figure 4. Kaplan-Meier curve for LRFS of pIIIA-N2 NSCLC patients with different risk groups (P = 0.000).

needed to further validate the clinical value and cut-off value of LMR.

A prediction model plays an important role in guiding individualized treatment. Two previous studies [25, 63] have constructed prediction models based on relevant clinical and pathologic factors to guide the selection of PORT in patients with pIIIA-N2 NSCLC. However, none of the models incorporate biological indicators, even though test samples for these biomarkers are easy to collect in clinical practice. In this study, we constructed a new prediction model that may be more accurate and useful than previous models by incorporating relevant clinical, pathologic, and biological factors. Its C-index is 0.747 (95% CI, 0.678-0.816), indicating good discrimination of the new prediction model. We categorize risk into low-, medium-, and high-risk groups. If the patient's estimated risk for LRR is low, the clinicians may select regular follow-up, whereas high-risk estimates may support being actively recommended PORT, because high-risk patients may benefit most from PORT. For medium-risk estimates, it may be necessary to weigh the advantages and disadvantages and consider the economics, physical condition and treatment willingness of patients before making the PORT decision. However, prospective studies are needed to investigate PORT in these patients.

As far as we know, this is the first study to construct a prediction model for risk score including clinical, pathologic, and biological factors in patients with pIIIA-N2 NSCLC. However, our study had some limitations. First, it was a single-center, retrospective study, thus the sample size was small and it may had selection bias. Second, the median follow-up time was 31.2 months, with only short- to intermediate-term survival data. Studies with a longer follow-up time are needed to investigate long-term survival. Third, our prediction model was based on the results of a single-center population-based study. We did only internal verification of the prediction model. However, there were certain difficulties in collecting case data from other centers, so no external validation was done. In the future, we will collect data from other centers to further validate our model.

Conclusion

The surgical approach (VATS vs. thoracotomy), N2-LNR (≥ 38.9% vs. <38.9%), EGFR status (wild-type vs. mutation), and LMR (<4.69 vs. ≥ 4.69) are significantly related to LRR in patients with pIIIA-N2 NSCLC. The prediction model for risk score based on the four independent risk factors may help identify a patient's risk for LRR and play an important role in guiding individualized treatment. Further research is needed to validate the clinical value of this model to further improve it and benefit more patients.

Acknowledgements

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Table 6. Risk group stratification and comparison of LRFS rate according to risk classification

Risk group	Risk score	No. of patients	1-year LRFS	3-year LRFS	Reference	*P*-value
Low-risk group	0~2	37	91.9%	71.4%	Vs. high risk	0.000
Medium-risk group	3~5	28	85.3%	57.3%	Vs. low risk	0.149
High-risk group	6~13	42	54.6%	13.6%	Vs. medium risk	0.002

Table 7. N2-LNR, EGFR status, LMR and lymph node dissection conditions of the two groups

Characteristic	Thoracotomy Group	VATS Group	χ^2	*P*-value
N2-LNR, n (%)			1.336	0.248
≥ 38.9%	4 (16)	18 (27.7)		
<38.9%	21 (84)	47 (72.3)		
EGFR status, n (%)			12.687	<0.001
Wild-type	13 (52)	18 (27.7)		
Mutation	2 (8)	34 (52.3)		
LMR, n (%)			5.769	0.016
<4.69	20 (80)	34 (52.3)		
≥ 4.69	5 (20)	31 (47.7)		
Total no. of stations dissected, median (range)	6 (3~9)	6 (3~9)		
Total no. of LNs dissected, median (range)	23 (10~60)	23 (5~40)		
No. of N2 stations dissected, median (range)	4 (1~6)	4 (2~6)		
No. of N2 LNs dissected, median (range)	15 (6~56)	15 (2~30)		
No. of N1 stations dissected, median (range)	2 (1~4)	2 (1~3)		
No. of N1 LNs dissected, median (range)	6 (2~27)	6 (2~14)		

Abbreviations: LNR: lymph node ratio, EGFR: epidermal growth factor receptor, LMR: lymphocyte-to-monocyte ratio.

Disclosure of conflict of interest

None.

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