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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

A prognostic score system with lymph node ratio in stage IIIA-N2 NSCLC patients after surgery and adjuvant chemotherapy

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Abstract

Purpose The survival of patients with IIIA-N2 non-small cell lung cancer after surgery followed by adjuvant chemotherapy is heterogeneous. The aim of this study is to form a prognostic system and a heat map method to visualize the overall survival rates in those patients.

Methods Univariate and multivariate Cox hazards regression models and the associated Wald Chi square coefficient were used to form the prognostic score system. Recursive partitioning analysis was used to determine the cutoff values of lymph node ratio and prognostic score in SEER cohort and validated in FDUSCC cohort. Meanwhile, a heat map method was used to visualize the overall survival probabilities of 3, 5 and 10 years for individual patient of both cohorts.

Results Lymph node ratio (with cutoff of 0.36) significantly correlates with overall survival of these patients. In addition, in patients with the same level of N2 disease, lymph node ratio still significantly affects survival. Also, after the multivariate analysis in SEER cohort, six factors were independent prognostic factors including age, sex, type of surgery, size, lymph node ratio and differentiation. A prognostic sore system with these factors (with cutoff of 12) was validated as a predictor for overall survival in FDUSCC cohort.

Conclusions This prognostic score system including lymph node ratio can predict the survival rates of IIIA-N2 patient after surgery and post-operative chemotherapy. Lymph node ratio could be a useful supplementation in TNM stage classification for IIIA-N2 patients. The heat map method can visualize the predicted overall survival of an individual patient.

Keywords Non-small cell lung cancer · Surgery · Adjuvant chemotherapy · Mediastinal lymph node metastasis

Abbreviations

NSCLC	Non-small cell lung cancer
SEER	Surveillance, epidemiology, and end results
FDUSCC	Fudan University Shanghai Cancer Center
LNR	Lymph node ratio

Introduction

Lung cancer remains the leading cause of cancer, both in incidence and mortality, occupying nearly 1 in 5 (18.4%) cancer deaths in 2018 (Bray et al. 2018). Non-small cell lung cancer (NSCLC) is the major histological type of lung cancer. According to the guideline (Postmus et al. 2017), for pathological IIIA-N2 NSCLC patients, adjuvant chemotherapy is a recommendation and considered to improve survival (Arriagada et al. 2010). Nonetheless, stage IIIA-N2 patients have various outcomes and some patients could not gain benefits from adjuvant chemotherapy. Hence, it is a crucial question to recognize the patients who could merely benefit from adjuvant chemotherapy. Owing to the timely recognition, these patients could get more individualized treatment strategy, for instance, receiving more frequent follow-ups, more intensive chemotherapy regimens or other treatment strategies. Lymph node ratio (LNR) was considered to have prognostic value in IIIA-N2 stage NSCLC patients after

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surgery followed by adjuvant radiotherapy (Deng et al. 2018). However, the role of LNR in the patients with IIIA-N2 NSCLC after surgery followed by adjuvant chemotherapy is not clear. Therefore, we try to build a prognostic score system with LNR in those patients and create a heat map method to visualize the predicted 3-, 5- and 10-year overall survival rates of individual patient.

Materials and methods

Patients

In all, we included two cohorts of patients, a training group of patients from Surveillance, Epidemiology, and End Results (SEER) and a validation group of patients from Fudan University Shanghai Cancer Center (FDUSCC). The detailed clinical and pathological characteristics of SEER cohort (Table 1) and FDUSCC cohort (Table 2) were provided.

Table 1 Clinical and pathological characteristics of patients in SEER cohort

Parameter	*N*/all (%)
Number	2804
Age	
<65	1374 (49.00)
≥65	1430 (51.00)
Gender	
Female	1535 (54.74)
Male	1269 (45.26)
Laterality	
Right	1504 (53.64)
Left	1300 (46.36)
Type of surgery	
Sub-lobar resection	323 (11.52)
Lobectomy/bi-lobectomy	2303 (82.13)
Pneumonectomy	178 (6.35)
Size	
T1	1684 (60.06)
T2	1120 (39.93)
Pathology	
Adenocarcinoma	1979 (70.58)
Squamous cell carcinoma	469 (16.72)
Other	356 (12.70)
Differentiation	
Well/moderately differentiated	1415 (50.46)
Poorly differentiated/undifferentiated/unknown	1389 (49.54)
Adjuvant radiotherapy	
Yes	1398 (49.86)
No	1406 (50.14)

Table 2 Clinical and pathological characteristics of patients in FDUSCC cohort

Parameter	*N*/all (%)
Number	365
Age	
<65	81 (22.19)
≥65	284 (77.81)
Gender	
Female	146 (40)
Male	219 (60)
Laterality	
Right	209 (57.26)
Left	156 (42.74)
Type of surgery	
Lobectomy/bi-lobectomy	338 (92.6)
Pneumonectomy	27 (7.4)
Size	
T1	129 (35.34)
T2	236 (64.66)
Pathology	
Adenocarcinoma	270 (73.97)
Squamous cell carcinoma	74 (20.27)
Other	21 (5.76)
Differentiation	
Well/moderately differentiated	253 (69.32)
Poorly differentiated/undifferentiated/unknown	112 (30.68)
Adjuvant radiotherapy	
Yes	95 (26.03)
No	270 (73.97)

A total of 2804 stage IIIA-N2 patients from 2004 to 2015 recorded in SEER were included in this study. The inclusive criteria are as follows: (1) confirmed with the pathology of NSCLC, with histological subtype ICD-O-3 of adenocarcinoma (8140, 8250, 8252, 8253, 8255, 8260, 8310, 8480–8481, 8490 and 8574), squamous cell carcinoma (8070, 8071, 8072, 8074 and 8050), other (8000, 8010, 8012–8014, 8020, 8022, 8031, 8033, 8570, 8046, 8082–8083, 8240, 8245, 8246, 8249, 8323 and 8550); (2) pathological IIIA-N2 stage [restaged according to 8th TNM classification (Goldstraw et al. 2016)]; (3) without neo-adjuvant therapy; (4) with surgery followed by adjuvant chemotherapy; (5) without history of malignancy; (6) with available data of positive lymph node, examined lymph node and follow-up data of overall survival.

As for the FDUSCC cohort, 365 patients with pathological IIIA-N2 stage NSCLC without malignant history, from August 2006 to January 2015 recorded at FDUSCC were included in this study, who received surgery followed by adjuvant chemotherapy. None of those patients

underwent neo-adjuvant therapy. The pathological TNM stage was based on 8th classification (Goldstraw et al. 2016).

Qualified and experienced surgeons performed surgeries for patients. Lymph nodes were rigorously and systematically dissected with routine frozen section during the operation (Liu et al. 2016). On the right lobes, mediastinal station 2R, 4R, 7, 8, 9 and N1 lymph nodes are dissected. On the left lobes, mediastinal lymph node station 4L, 5, 6, 7, 8, 9 and N1 lymph nodes, dissection is required. The lymph node stations were based on the International Association for the Study of Lung Cancer (IASLC) node map in the Seventh Edition of the TNM Classification (Rusch et al. 2009).

The Institutional Review Board of the Fudan University Shanghai Cancer Center (Fudan University Shanghai Cancer Center IRB#090977-1) approved this retrospective study.

Follow-up

In the SEER cohort, the median follow-up time was 29 months. In the FDUSCC cohort, the median follow-up time was 36 months. Three periods composed the entire follow-up time. During the initial 2 years after surgery, 3 ± 1 months were the regular follow-up time. Starting from the third to the fifth year postoperatively, 6 ± 1 months were the determined follow-up time. Finally, from the sixth year after surgery, the recommended follow-up time was extended to 12 ± 3 months. Clinic visit of the outpatients and telephone calls to the other available patients were the follow-up methods.

Statistical analysis

Excel (2016, Microsoft), SPSS Statistics (23, IBM), GraphPad Prism 7 and R (Version 3.5.1) were the software used for the analysis in this study. Recursive partitioning analysis was the method used to determine the cutoff values for the lymph node ratio (LNR) and the prognostic score (Keles and Segal 2002). Univariate and multivariate analyses were conducted by Cox proportional hazards regression model. Prognostic score system was formed based on the Wald Chi square values of significant variables in the multivariate analysis as the method performed in multiple previous studies (Deng et al. 2018; Wong et al. 2010; Xi et al. 2017) and 10-year overall survival probabilities were predicted by statistically significant variables derived from multivariate Cox proportional hazards regression model. Overall survival curve was compared with the log-rank test. *P* value was at the level of 0.05 with two-sided. Survival curves and the heat maps were drawn by R (Version 3.5.1).

Result

Lymph node ratio significantly correlates with overall survival of IIIA-N2 patient both in SEER (training set) and FDUSCC cohort (validation set)

The definition of LNR is the number of pathologically positive lymph nodes divided by the number of all lymph nodes examined during the surgery. We utilize SEER cohort as the training set. After recursive partitioning analysis, 0.36 was determined as the cutoff value from the training cohort. In the SEER cohort, patients with high LNR (≥ 0.36) had significantly worse overall survival compared with patients with low LNR (< 0.36) ($P < 0.001$, Fig. 1). In addition, we used the FDUSCC cohort as the validation cohort. Consistent with the finding in the training group, patients with low LNR (< 0.36) have significantly better overall survival than patients with high LNR (≥ 0.36) ($P < 0.001$, Fig. 1).

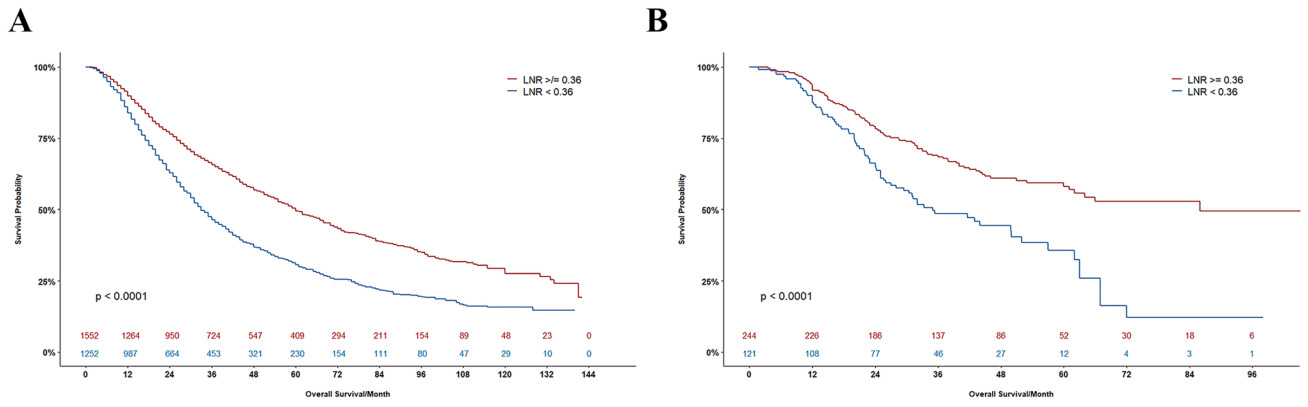

Fig. 1 **a** Overall survival plot of patients with high LNR (≥ 0.36) versus low LNR (< 0.36) in SEER cohort (training cohort). **b** Overall survival plot of patients with high LNR (≥ 0.35) versus low LNR (< 0.35) in FDUSCC cohort (validation cohort)

Lymph node ratio still correlates with overall survival of IIIA-N2 patients even in those with the same level of N2 lymph node metastasis status in FDUSCC cohort

As we all know, in IIIA patients, single and multiple level of N2 status showed significantly different overall survival rates (Zheng et al. 2018). To eliminate the possibility that worse prognosis of the high LNR (≥0.36) group was because of the difference in the composition of the patients' level of N2 status, we further tested LNR in the single- and multiple-level N2 patients. However, the SEER cohort did not contain the data of the level of N2 status. Hence, we tested LNR in patients with single- and multiple-level N2 from the FDUSCC cohort. Patients with low LNR (<0.36) had statistically better overall survival than the patients with high LNR (≥0.36) both in single- ($P=0.021$, Fig. 2) and multiple-level ($P=0.039$ Fig. 2) N2 patients.

Univariate and multivariate Cox proportional hazards regression model in SEER cohort

Age, sex, laterality, type of surgery, size, pathology, LNR and differentiation were the variables included in the analysis. After univariate analysis, age (HR 1.435; 95% CI 1.297–1.589; $P<0.001$; Table 3), sex (HR 1.372; 95% CI 1.241–1.518; $P<0.001$; Table 3), sub-lobar resection ($P=0.001$; Table 3), size (HR 1.139; 95% CI 1.029–1.262; $P=0.012$; Table 3), LNR (HR 1.646; 95% CI 1.487–1.821; $P<0.001$; Table 3) and differentiation (HR 1.192; 95%

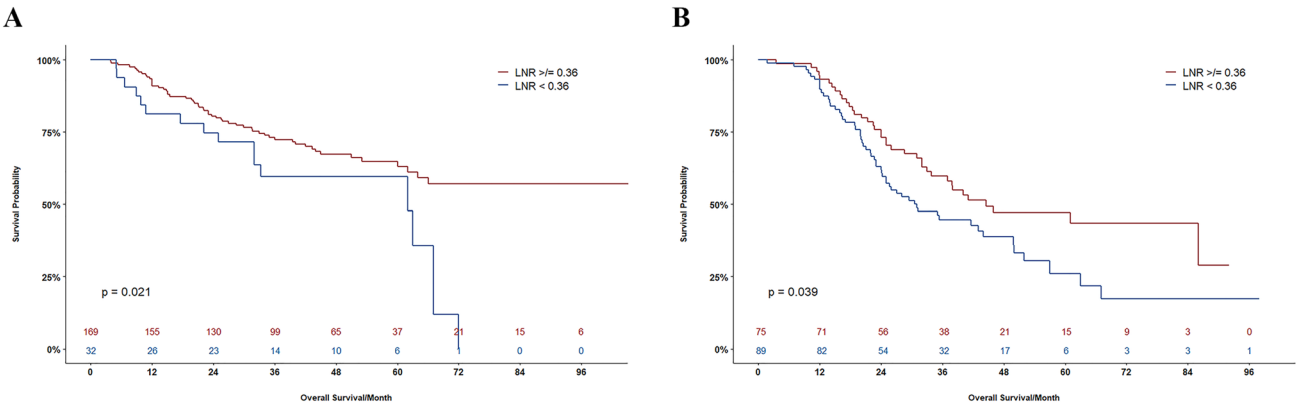

Fig. 2 **a** Overall survival plot of single-level N2 patients with high LNR (≥0.36) versus low LNR (<0.36) in FDUSCC cohort. **b** Overall survival plot of multiple-level N2 patients with high LNR (≥0.36) versus low LNR (<0.36) in FDUSCC cohort

Table 3 Univariable and multivariable Cox proportional hazards regression model of prognostic factors for overall survival

	HR	95% CI	*P* value	HR	95% CI	Wald Chi square	Score	*P* value
Age(≥65)	1.435	1.297–1.589	**< 0.001**	1.397	1.262–1.547	41.51	7.35	**< 0.001**
Sex (male)	1.372	1.241–1.518	**< 0.001**	1.359	1.228–1.505	34.89	6.18	**< 0.001**
Laterality (right)	0.992	0.897–1.098	0.880					
Type of surgery								
Sub-lobar resection			**0.001**					
Lobectomy/bi-lobectomy	1.240	0.983–1.566	0.70	1.204	0.947–1.530			
Pneumonectomy	0.929	0.764–1.128	0.455	1.011	0.830–1.232			
Size (T2)	1.139	1.029–1.262	**0.012**	1.135	1.022–1.260	5.65	1	**0.018**
Pathology								
Adenocarcinoma			0.159					
Squamous cell carcinoma		0.805–1.105	0.467					
Other		0.887–1.293	0.477					
LNR (≥0.35)	1.646	1.487–1.821	**< 0.001**	1.617	1.459–1.791	84.39	14.94	**< 0.001**
Differentiation (poorly differentiated/undifferentiated/unknown)	1.192	1.078–1.319	**0.001**	1.151	1.040–1.273	7.37	1.30	**0.007**
Adjuvant radiotherapy	1.014	0.917–1.122	0.781					

CI 1.078–1.319; $P = 0.001$; Table 3) have shown statistically significant difference, and then were included in the multivariate analysis. Finally, age (HR 1.397; 95% CI 1.262–1.547; $P < 0.001$; Table 3), sex (HR 1.359; 95% CI 1.228–1.505; $P < 0.001$; Table 3), size (HR 1.135; 95% CI 1.022–1.260; $P = 0.018$; Table 3), LNR (HR 1.617; 95%: 1.459–1.91; $P = < 0.001$; Table 3) and differentiation (HR 1.151; 95%: 1.040–1.273; $P = 0.007$; Table 3) showed a statistically significant difference. Meanwhile, these significant factors were enrolled in the prognostic score system.

Prognostic score system correlates with overall survival both in SEER cohort (training set) and FDUSCC cohort (validation set)

Independent prognostic factors derived from the multivariate Cox proportional hazards regression model of the SEER cohort (training set) comprise the prognostic score system and the weighted scores of each variable were based on the Wald Chi square in the multivariate model. The cutoff value of 12 in the prognostic score system was determined according to the result of recursive partitioning analysis. Patients with prognostic score equal or greater than 12 are called the 'high risk' group, while patients with prognostic score fewer than 12 are called the 'low risk' group. In the SEER cohort (training set), patients in the high-risk group have worse prognosis compared with low-risk group ($P < 0.001$, Fig. 3). Furthermore, this prognostic score system was validated in the FDUSCC cohort (validation set). Compared with the high-risk group, the low-risk group showed significantly better overall survival ($P < 0.001$, Fig. 3).

A heat map method to visualize the predicted 3-, 5- and 10-year overall survival rate

In both SEER and FDUSCC cohort, 3-, 5- and 10-year overall survival rates for individual patients were predicted by significant prognostic factors in the multivariate Cox proportional hazards regression model. Then, we used a heat map method to visualize the overall survival rates with the *X* axis of the number of positive lymph nodes examined and the *Y* axis of the number of negative lymph nodes examined. It can be seen from the heat map that the overall survival rate decreases with the number of positive lymph nodes increasing (Fig. 4).

Discussion

We elucidated that a prognostic score system with LNR can predict the overall survival rates of stage IIIA-N2 patients after surgery and post-operative chemotherapy. Meanwhile, we formed a heat map method to visualize the 3-, 5- and 10-year overall survival probability. Our previous work finds that IIIA patients with upfront surgery followed by adjuvant therapy are heterogeneous (Zheng et al. 2018). In this study, we indicated that a prognostic score system with LNR significantly correlates with overall survival in stage IIIA-N2 patients after surgery followed by adjuvant chemotherapy. Hence, it can provide evidence for doctors to develop more individualized treatment strategies for patients who could merely benefit from chemotherapy. For example, a treatment strategy with a closer follow-up schedule, more intensive

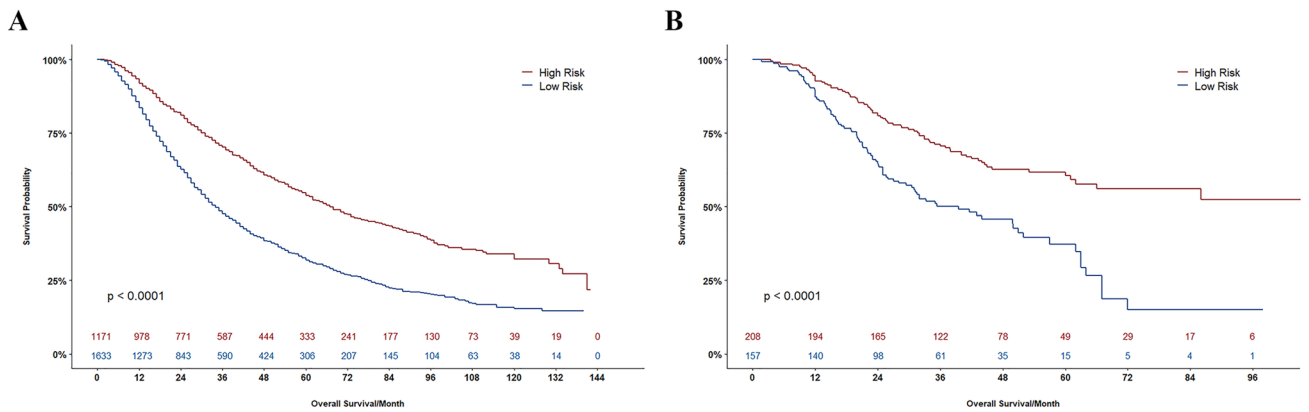

Fig. 3 **a** Survival plot of high risk versus low risk in SEER cohort (training set). **b** Survival plot of high risk versus low risk in FDUSCC cohort (validation set)

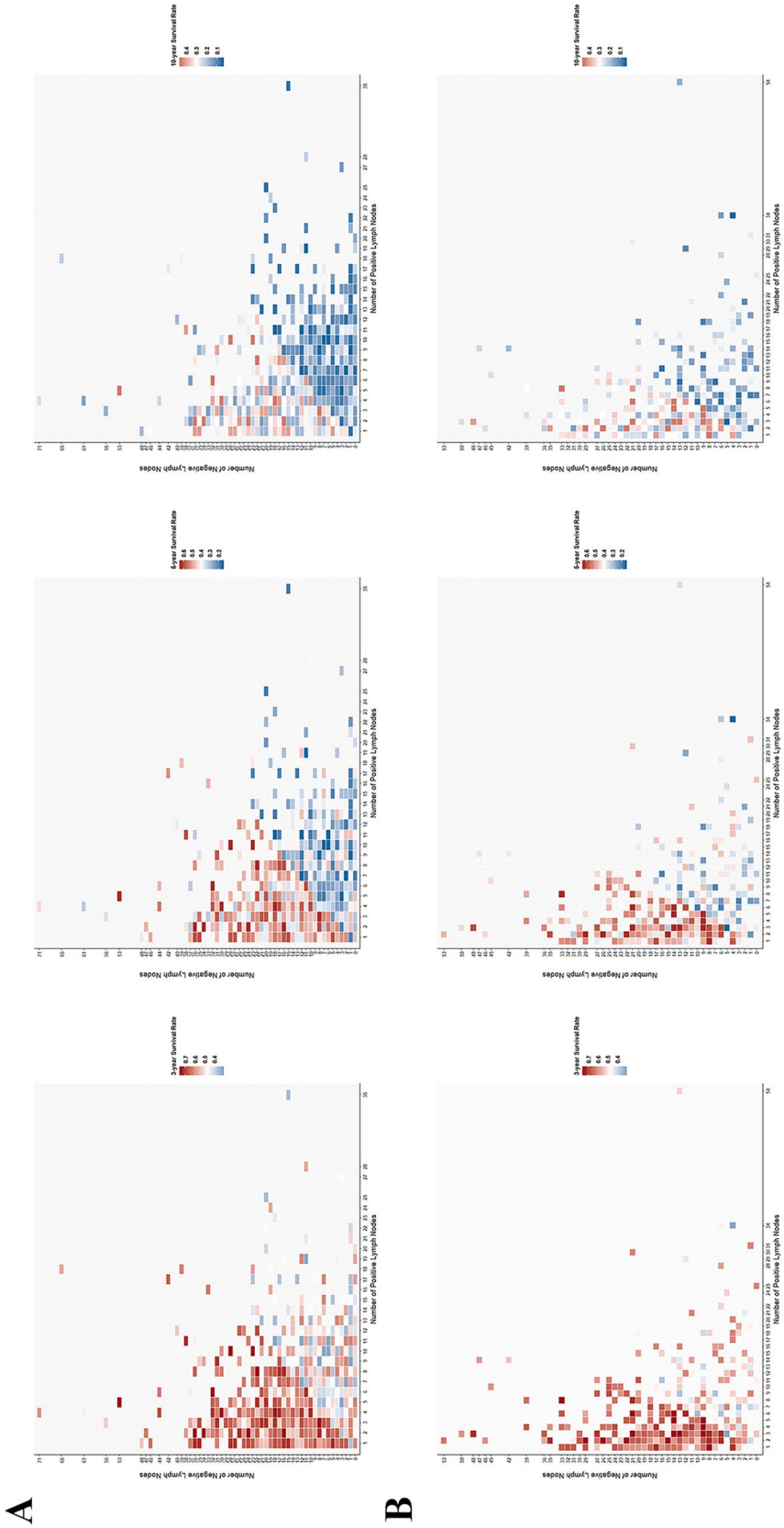

Fig. 4 **a** Heat maps of predicted 3-, 5- and 10-year overall survival rates of SEER cohort. **b** Heat maps of predicted 3-, 5- and 10-year overall survival rates of FDUSCC cohort

chemotherapy regimens or the combination of therapies may be more suitable for patients with high risk and LNR.

The prognostic value of LNR in NSCLC patients has been reported by several studies (Nwogu et al. 2012; Qiu et al. 2013; Taylor et al. 2013; Urban et al. 2013; Zhao et al. 2017). However, no previous research has explored the role of LNR in IIIA-N2 patients after surgery and adjuvant chemotherapy. Also found in this study, LNR can be a predictor of overall survival in patients with the same level of N2 disease status. That is to say, in the patients with the same level of metastatic mediastinal lymph nodes status, different LNRs still influence survival. Therefore, we suppose that LNR can be a useful supplementation for N stage of the stage IIIA-N2 patients, which has significant prognosis value.

There are some limitations in this study. First, this is a retrospective study. Second, some information is not available in SEER cohort, such as the level of the N2 disease. Third, details about the chemotherapy regimens have not been mentioned. Fourth, the dose of adjuvant radiotherapy is not specific. Adjuvant chemotherapy is a crucial part of the treatment strategy for patients with IIIA-N2 NSCLC. As can be acknowledged from the clinical practice, not all the patients can benefit from adjuvant chemotherapy. Therefore, it is a key question to clarify what kind of predictor significantly correlates with survival in IIIA-N2 patients. From our research, we suppose that the prognostic score system with LNR may be the potential clinical indicator that strongly correlated with overall survival in patients with IIIA-N2 NSCLC after surgery and adjuvant chemotherapy.

In conclusion, a prognostic score system with LNR significantly correlates with overall survival for stage IIIA-N2 NSCLC patients after surgery followed by adjuvant chemotherapy, which could be implemented in clinical practice. Patients with high risk and LNR are strongly associated with poor prognosis. We also developed a heat map method to visualize the predicted 3-, 5- and 10-year overall survival probabilities for individual patients.

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Compliance with ethical standards

Conflict of interest Han Han declares that he has no conflict of interest. Yue Zhao declares that he has no conflict of interest. Zhendong Gao declares that he has no conflict of interest. Difan Zheng declares that he has no conflict of interest. Fangqiu Fu declares that he has no conflict of interest. Zitong Zhao declares that he has no conflict of interest. Ya Tang declares that he has no conflict of interest. Jiaqing Xiang declares that he has no conflict of interest. Yihua Sun declares that he has no conflict of interest. Hong Hu declares that he has no conflict of interest. Haiquan Chen declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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