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Significance of metastatic lymph nodes ratio in overall survival for patients with resected nonsmall cell lung cancer: a retrospective cohort study

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Objective **The tumor, node and metastasis stage is widely applied to classify lung cancer and is the foundation of clinical decisions. However, increasing studies have pointed out that this staging system is not precise enough for the N status. In this study, we aim to build a convenient survival prediction model that incorporates the current items of lymph node status.**

Methods **We performed a retrospective cohort study and collected the data from resectable nonsmall cell lung cancer (NSCLC) (IA-IIIB) patients from the Surveillance, Epidemiology, and End Results database (2006–2015). The x-tile program was applied to calculate the optimal threshold of metastatic lymph node ratio (MLNR). Then, independent prognostic factors were determined by multivariable Cox regression analysis and enrolled to build a nomogram model. The calibration curve as well as the Concordance Index (C-index) were selected to evaluate the nomogram. Finally, patients were grouped based on their specified risk points and divided into three risk levels. The prognostic value of MLNR and examined lymph node numbers (ELNs) were presented in subgroups.**

Results Totally, **40853 NSCLC patients after surgery were finally enrolled and analyzed. Age, metastatic lymph node ratio, histology type, adjuvant treatment and American Joint Committee on Cancer 8th T stage were deemed as independent prognostic parameters after multivariable Cox regression analysis. A nomogram was built using those variables, and its efficiency in predicting patients' survival was better than the conventional American Joint Committee on Cancer stage system after evaluation. Our new model has a significantly higher concordance Index (C-index) (training set, 0.683 v 0.641, respectively; $P < 0.01$; testing set, 0.676 v 0.638, respectively; $P < 0.05$). Similarly, the calibration curve shows the nomogram was in better accordance with the actual observations in both cohorts. Then, after risk stratification, we found that MLNR is more reliable than ELNs in predicting overall survival.**

Conclusion **We developed a nomogram model for NSCLC patients after surgery. This novel and useful tool outperforms the widely used tumor, node and metastasis staging system and could benefit clinicians in treatment options and cancer control.** ***European Journal of Cancer Prevention*** **33: 376–385 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Lung cancer remains the leading cause of cancer-related morbidity and mortality worldwide, with a 5-year survival rate of 14–17% (Miller *et al*., 2022; Oliver, 2022). Nonsmall cell lung cancer (NSCLC) is the most common histological type and represents 85% of all lung cancer cases. Although the application of advanced imaging techniques has significantly developed early detection, the 5-year survival rate of early-stage NSCLC patients with surgical excision is only 30–75% (Narjust *et al*., 2019; Ettinger *et al*., 2022).

Accurate assessment of lymph node metastasis is important for determining the optimal treatment strategies and providing prognostic information to NSCLC patients (Narjust *et al*., 2019; Ettinger *et al*., 2022). The tumor, node and metastasis (TNM) staging system is widely used to predict the outcome of NSCLC (Padinharayil *et al*., 2022). However, patients in the same stage often show different survival times. In the updated eighth edition of the TNM classification of NSCLC, lymph node stages are the same as those in the previous edition and based solely on the anatomical location of lymph node involvement (Rusch *et al*., 2016).

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Several previous studies have pointed out that the count of positive lymph nodes and examined lymph nodes can reveal the effectiveness of lymphadenectomy and oncological outcomes (Fukui *et al*., 2006; Liang *et al*., 2017). However, the number of metastatic lymph nodes is limited by the number of resected lymph nodes. In cases where few lymph nodes were removed, the number of metastatic lymph nodes could not be accurately assessed (Raymond, 1798; Chukwumere *et al*., 2012). To address the potential limitation, the ratio of metastatic lymph nodes (MLNR), defined as the ratio between the metastatic lymph nodes and the retrieved lymph nodes, takes into account both the parameters and has been suggested to represent a powerful prognostic factor in many solid tumors such as breast cancer, esophageal carcinoma and medullary thyroid cancer (Chen *et al*., 2019; Li *et al*., 2019). In recent years, the MLNR has also been evaluated in the survival impact of NSCLC (Zhou *et al*., 2020, 2022). However, few studies have investigated the predictive effect of examined lymph node numbers (ELNs) and MLNR in the long-term survival outcomes for NSCLC patients after surgery.

A nomogram is a reliable tool to quantify risk, which can reduce statistical predictive models into a single numerical estimate of the probability of an event (Iasonos *et al*., 2008). By creating precise prediction, that is, to say, combining independent prognostic factors such as patients' age, histological type, and other potential prognostic factors, it can provide essential information for therapy regime options and cancer control. Compared with the conventional TNM staging system, nomogram prognostic models can confer better survival prediction. However, nomograms for predicting long-term survival outcomes for NSCLC patients after surgery are scarce.

In this retrospective cohort study, we aimed to explore the ability of ELNs and MLNR to predict prognosis for NSCLC patients after surgery employing a cohort from the population-based Surveillance, Epidemiology, and End Results (SEER) program. We present the following article in accordance with the STROBE reporting checklist, Supplementary Material, Supplemental digital content 1, *http://links.lww.com/EJCP/A430*.

Methods

Data source and collection

We performed a retrospective cohort study, and data was collected from the SEER database. It was supported by the Surveillance Research Program which provides national leadership in the science of cancer surveillance as well as analytical tools and methodological expertise in collecting, analyzing, interpreting, and disseminating reliable population-based statistics (Enewold *et al*., 2020). Because SEER is a public database, the ethics committee of the second affiliated hospital of Fujian Medical University waived individual informed consent. NSCLC cases between 2006 and 2015 in the SEER public access database and their corresponding details were identified with the use of SEERSTAT version 8.3.5 software. Patients were uniformly reviewed and staged according to the 8th edition of the TNM classification.

Including criteria

The extent of surgery was analyzed by regional nodes positive (1988+) and RX Summ-Surg Prim Site (1998+) (Zhu *et al*., 2020). Only patients diagnosed with NSCLC who underwent radical resection were enrolled in the study.

Excluding criteria

Patients were excluded when some of the criteria were met: (1) patients with local advanced or metastatic disease (TNM stage IIIC or stage IV), because surgery was no standard procedure for these patients; (2) patients had more than one primary tumor; (3) missing information on extracted variables and (4) fewer than one examined lymph node was eligible.

Variables and follow-up

Totally 40853 NSCLC patients after surgery were finally enrolled, demographic characters (age, gender and race), the number of metastatic lymph nodes, the number of examined lymph nodes, the 8th edition TNM classification and oncological outcomes were obtained from the SEER database. We deemed the endpoint of NSCLC patients as the time from histological diagnosis to the date of death from lung cancer.

Statistical analysis

All statistical analysis was performed with R software (www.r-project.org) version 3.6.1 and RStudio (www.rstudio.com) version 1.1.456. Categorical variables were shown as frequency and percentage. Continuous variables were transformed into categorical variables based on recognized cutoff values (for age) or median number (examined lymph nodes lymph node station). The X-tile program was applied to calculate the optimal threshold for MLNR and risk levels with maximum specificity and sensitivity. The variables with $P < 0.05$ from the univariate analysis were chosen for the next step to build the Cox proportional hazards regression model to find risk factors linked to the prognosis of NSCLC.

The nomogram prediction model was constructed based on chosen prognostic factors by multivariate Cox regression analysis from the training set. The accuracy of nomograms was evaluated by Harrell's concordance index (C-index) calculated through the rcorrcens function in Hmisc package version 4.3-1. The predicted survival rates were compared with actual survival rates determined using a Kaplan–Meier analysis and calibrations were generated in the training set and testing set through the calibrate function in rms package version 5.1-4. Bootstraps

were used for these analyses at 1000 reiterations. Kaplan–Meier survival curves were constructed for chosen variables through the ggsurvplot function included in package survminer version 0.4.6 and were compared with Cox's regression through the coxph function included in package survival version 3.1-8. A comparison of the C-index of two different models was based on methods previously described (Hanley and McNeil, 1983). Continuous variables fitting a normal distribution between binary groups were compared using a *t*-test. Otherwise, the Mann–Whitney U test or Kruskal–Wallis test was applied.

Tests were two-sided and $P < 0.05$ was considered as statistically significant in all analyses mentioned above.

Results

Clinical characteristics of patients

From 2006 to 2015, a total of 456090 NSCLC patients undergoing radical surgical resection were collected from the SEER database. Patients without lymphadenectomy or clear ELNs and MLNR, unknown staging information, stage IIIC or IV disease, multiple primary cancers and distant metastases were excluded. According to the inclusion criteria, 40853 patients with a history of surgical resection were finally identified. Based on the 8th TNM staging system, the proportion of patients at the T1, T2, T3 and T4 stage was 42.24% (*n* = 17255), 33.39% (*n* = 13653), 14.28% (*n* = 5837) and 10.06% (*n* = 4108), respectively. The most predominant histological type was adenocarcinoma (*n* = 22767, 55.729%). The median ELNs and MLNR were 8 (1–90) and 0 (range from 0 to 1), respectively. Among the 4351 patients who accepted adjuvant therapy, 1081 patients received radiotherapy, 2225 patients received chemotherapy, and 1045 received both. Detailed information on demographic features and clinicopathological characteristics is presented in Table 1.

Cutoff points for metastatic lymph node ratio

Patient cohorts were made up of a training set and a testing set. Those two groups were randomly generated, with 29181 (71%) in the former set and 11672 (29%) in the latter one. The discrepancy in clinical and oncological characteristics between those two parts was very small with $P > 0.05$ (shown in Tables 1 and 2). The optimal cutoff value for MLNR (0, 0.31) in the training set was calculated using X-tile software

Table 1 **Demographic and clinicopathological characteristics of patients with nonsmall cell lung cancer**

Characteristics	Total [*n* (%)]	Training cohort [*n* (%)]	Validation cohort [*n* (%)]	*P* value
Age				0.949
<60	10909 (26.7)	7799 (26.7)	3110 (26.6)	
60–70	14758 (36.1)	10549 (36.2)	4209 (36.1)	
>70	15186 (37.1)	10833 (37.1)	4353 (37.3)	
Sex				0.842
Female	21170 (51.8)	15112 (51.8)	6058 (51.9)	
Male	19683 (48.2)	14069 (48.2)	5614 (48.1)	
Race				0.405
White	33903 (82.98)	24255 (83.1)	9648 (82.7)	
Black	3729 (9.12)	2629 (9)	1100 (9.4)	
Others	3221 (7.88)	2297 (7.9)	924 (7.9)	
Assistant treatment				0.985
Neither	22767 (55.729)	20070 (68.8)	8018 (68.7)	
Radiotherapy	1081 (2.64)	711 (2.4)	279 (2.4)	
Chemotherapy	2225 (5.44)	5499 (18.8)	2214 (19)	
Both	1045 (2.55)	2901 (9.9)	1161 (9.9)	
Histological type				0.254
Adenocarcinoma	22767 (55.729%)	16283 (55.8)	6484 (55.6)	
Adenosquamous carcinoma	1081 (2.64%)	736 (2.5)	345 (3)	
Bronchi alveolar carcinoma	2225 (5.44%)	1578 (5.4)	647 (5.5)	
Large cell carcinoma	1045 (2.55%)	753 (2.6)	292 (2.5)	
NSCLC (unspecified)	1134 (2.77%)	815 (2.8)	319 (2.7)	
Squamous cell carcinoma	10632 (26.02%)	7588 (26)	3044 (26.1)	
Other	1969 (4.81%)	1428 (4.9)	541 (4.6)	
MLNR				
Median (range)	0 (0-1)	0 (0-1)	0 (0-1)	0.586
ELNs				
Median (range)	8 (0-90)	8 (0-90)	8 (0-90)	0.432
AJCC 8th T stage				0.957
T1a	1687 (4.13)	1199 (4.1)	488 (4.2)	
T1b	8744 (21.41)	6255 (21.4)	2489 (21.3)	
T1c	6824 (16.70)	4862 (16.7)	1962 (16.8)	
T2a	10567 (25.86)	7583 (26)	2984 (25.6)	
T2b	3086 (7.53)	2185 (7.5)	901 (7.7)	
T3	5837 (14.28)	4159 (14.3)	1678 (14.4)	
T4	4108 (10.06)	2938 (10.1)	1170 (10)	

ELNs, examined lymph node numbers; MLNR: metastatic lymph node ratio; NSCLC, nonsmall cell lung carcinoma; NSCLC (unspecified), non-small cell lung carcinoma (unspecified but not listed above); Other, other malignant tumors categories other than above and small cell lung cancer in SEER database.

Table 2 Univariate and multivariate Cox regression analyses of OS of nonsmall cell lung carcinoma patients

	N	Univariate Cox			Multivariate Cox		
Variables	(40853)	HR	95% CI	*P* value	HR	95% CI	*P* value
Age							
<60	10909 (26.7)	1	–	–	1	–	–
60–70	14758 (36.1)	1.275	1.222–1.329	<0.001	1.328	1.273–1.386	<0.001
>70	15186 (37.1)	1.779	1.710–1.852	<0.001	1.924	1.847–2.006	<0.001
Sex							
Female	21170 (51.8)	1	–	–	1	–	–
Male	19683 (48.2)	1.522	1.476–1.569	< 0.001	1.361	1.319–1.404	0.052
Race							
White	33903 (82.98)	1	–	–			
Black	3729 (9.12)	0.965	0.915–1.018	0.189			
Others	3221 (7.88)	0.773	0.726–0.823	< 0.001			
Assistant treatment							
Neither	22767 (55.729)	1	–	–	1	–	–
Radiotherapy	1081 (2.64)	2.397	2.215–2.595	<0.001	1.54	1.421–1.67	<0.001
Chemotherapy	2225 (5.44)	1.290	1.241–1.341	<0.001	0.82	0.784–0.857	<0.001
Both	1045 (2.55)	2.002	1.915–2.094	<0.001	1.047	0.991–1.106	0.103
Histological type							
Adenocarcinoma	22767 (55.729%)	1	–	–	1	–	–
Adenosquamous carcinoma	1081 (2.64%)	1.534	1.408–1.671	<0.001	1.291	1.185–1.406	<0.001
Bronchi alveolar carcinoma	2225 (5.44%)	0.638	0.592–0.689	<0.001	0.756	0.704–0.816	<0.001
Large cell carcinoma	1045 (2.55%)	1.625	1.495–1.767	<0.001	1.589	1.461–1.728	<0.001
NSCLC (unspecified)	1134 (2.77%)	1.456	1.344–1.578	<0.001	1.284	1.184–1.392	<0.001
Squamous cell carcinoma	10632 (26.02%)	1.461	1.411–1.512	<0.001	1.228	1.185–1.273	<0.001
Other	1969 (4.81%)	0.876	0.808–0.948	0.001	0.909	0.839–0.985	0.02
MLNR							
0	30628 (74.97%)	1	-	-	1	-	-
0–0.31	6643 (16.26%)	1.858	1.789–1.930	<0.001	1.752	1.678–1.829	<0.001
≥0.31	3582 (8.76%)	2.698	2.581–2.820	<0.001	2.52	2.399–2.648	<0.001
ELNs							
<16	32819 (80.33%)	1	–	–	–	–	–
≥16	8034 (19.67%)	1.124	0.993–1.362	0.086	–		
AJCC 8th T stage							
T1a	1687 (4.13%)	1	–	–	1	–	–
T1b	8744 (21.41%)	1.297	1.163–1.446	<0.001	1.214	1.088–1.353	0.001
T1c	6824 (16.70%)	1.791	1.607–1.996	<0.001	1.534	1.376–1.71	<0.001
T2a	10567 (25.86%)	2.149	1.934–2.389	<0.001	1.769	1.591–1.967	<0.001
T2b	3086 (7.53%)	2.775	2.479–3.108	<0.001	2.116	1.887–2.371	<0.001
T3	5837 (14.28%)	3.121	2.803–3.476	<0.001	2.389	2.142–2.664	<0.001
T4	4108 (10.06)	3.748	3.362–4.179	<0.001	2.864	2.563–3.199	<0.001

AJCC, American Joint Committee on Cancer; CI, confidence interval; ELNs, examined lymph node numbers; HR, hazardous ratio; MLNR, metastatic lymph node ratio; NSCLC, nonsmall cell lung carcinoma; NSCLC (unspecified), nonsmall cell lung carcinoma (unspecified but not listed above); Other, other malignant tumors categories other than above and small cell lung cancer in SEER database.

($P < 0.001$, Fig. 1). After enrolling all the variables into univariate and multivariate analysis, factors such as MLNR ($P < 0.001$), age ($P < 0.001$), histological type ($P < 0.001$), T stage ($P < 0.001$) and assistant treatment ($P < 0.001$) were deemed as independent prognostic factors.

Construction of a new model of survival prediction

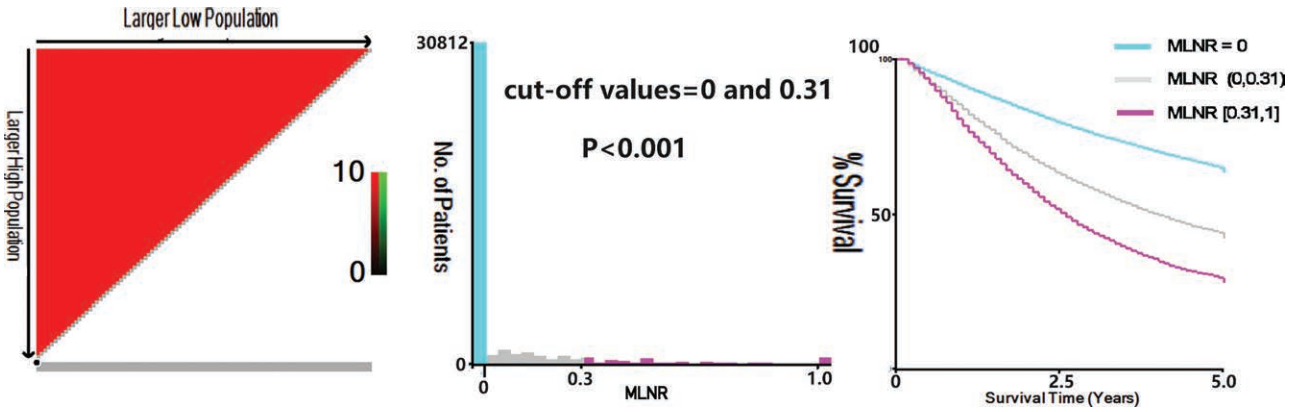
According to the outcome of multivariate analysis, patients' age, MLNR, T stage, histological type, and assistant treatment were identified as independent predictors. The above factors were applied to construct a nomogram (Fig. 2). The final risk point was the sum of the scores assigned to each independent parameter. Patients with higher T stage, higher MLNR, poor differentiation, radiotherapy only, and older age are more likely to get higher points which means poor prognosis. We can visually estimate the probability of death of patients individually by drawing a vertical line.

The calibration plots showed a well-matched 1-, 3-, and 5-year overall survival (OS) between nomogram prediction and clinical observation whether in the training set or testing set (Fig. 3a,b). Harrell's C-index, a classical index used to evaluate model performance, in our model was still superior to the usual TNM category prediction. C-index of 0.683 (95% CI, 0.678–0.688; $P < 0.001$) and 0.676 (95% CI, 0.649–0.665; $P < 0.001$) was observed in the two patient cohorts. However, in the American Joint Committee on Cancer (AJCC) TNM staging system (8th), C-index was 0.641 (95% CI, 0.636–0.646; $P < 0.001$) and 0.635 (95% CI, 0.627–0.643; $P = 0.02$), respectively (Table 3). These results indicated that our new model showed greater predictive accuracy than the AJCC 8th TNM staging system.

Stratification of risk groups

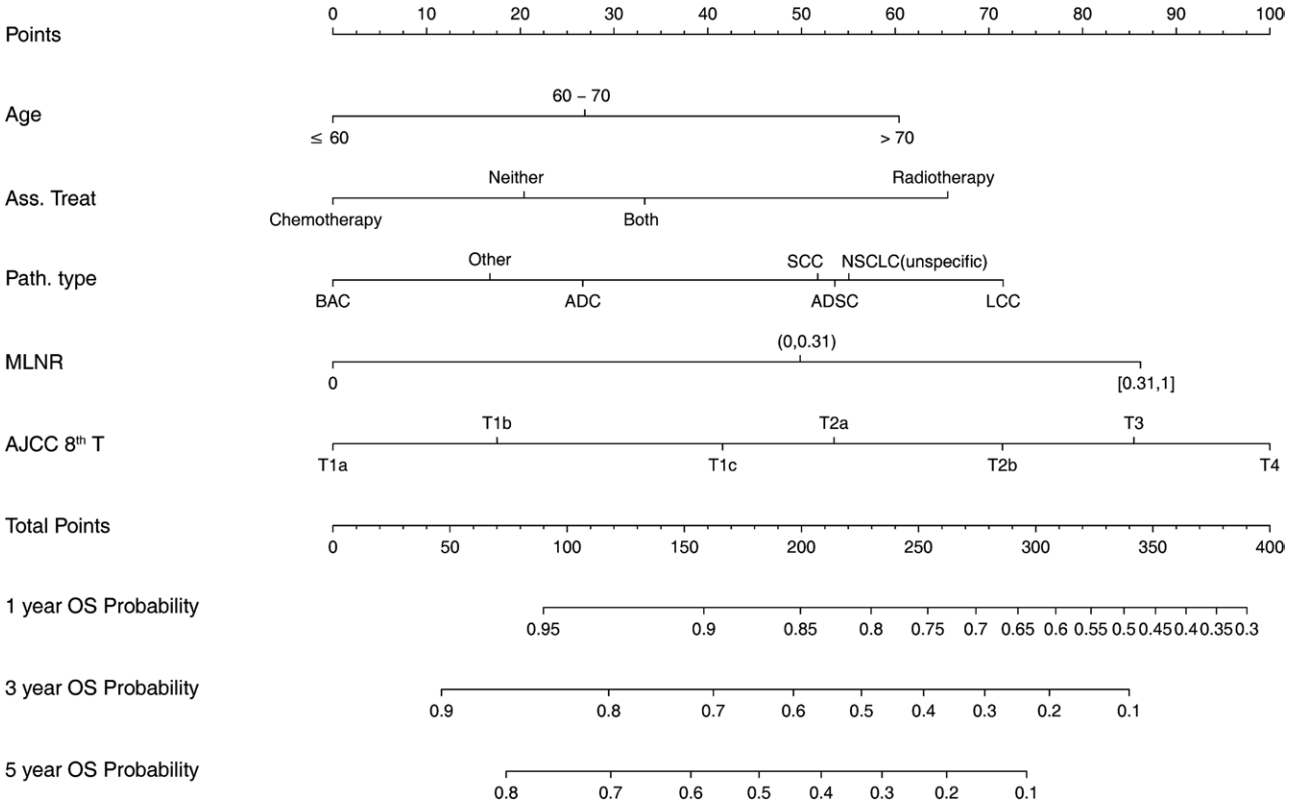
Based on the cutoff calculated via the X-tile program (Fig. 4), we finally made a risk stratification. Patients with NSCLC in both the training and testing cohorts were divided into three risk subgroups: low risk (score 0–127), moderate risk (score 127–225), and high risk

Fig. 1



X-tile analysis determining optimal MLNR cutoff values based on the overall survival. The optimal threshold was shown in blue(MLNR = 0), gray (MLNR, 0 ≤ and <0.31) and violet (MLNR ≥ 0.31) panels. MLNR, metastatic lymph node ratio.

Fig. 2

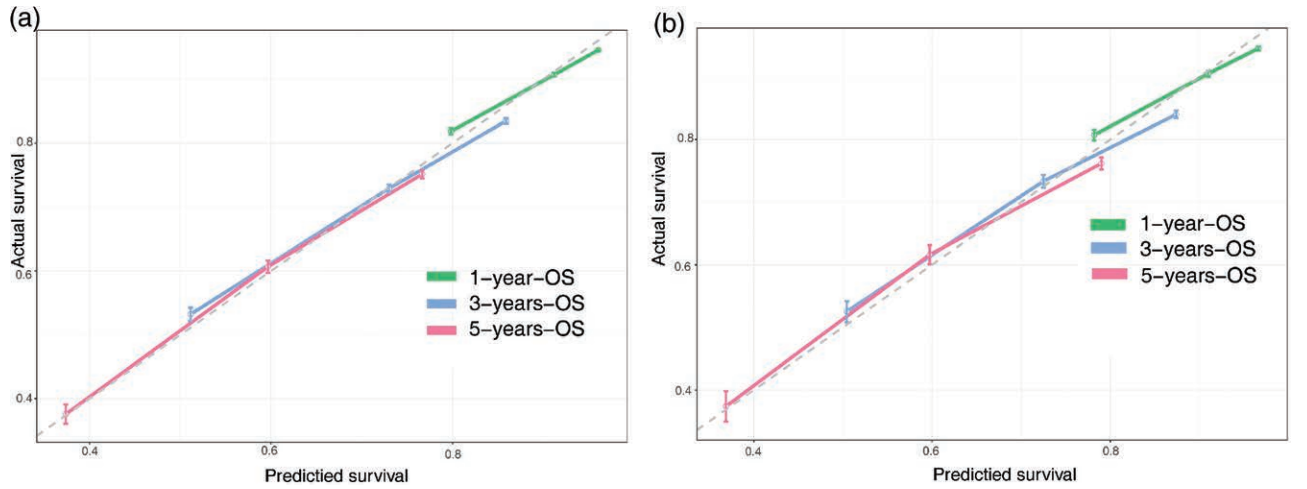


Overall survival-predicting model for postoperative NSCLC patients at stage IA-IIIB. ADC, adenocarcinoma; ADSC, adenosquamous carcinoma; BAC, bronchioloalveolar carcinoma; LC, large-cell carcinoma; MLNR, metastatic lymph node ratio; NSCLC, nonsmall cell lung carcinoma; SC, squamous carcinoma.

(score 225–367). Significant distinctions ($P < 0.001$) of Kaplan–Meier OS curves were observed among the different risk groups in the training set and the testing set (Fig. 5a,b).

Next, we stratified patients according to the risk level to identify how ELNs, MLNR and adjuvant therapy influenced their prognosis. As for ELNs, we could see from Fig. 6 that, in the total patient cohort

Fig. 3



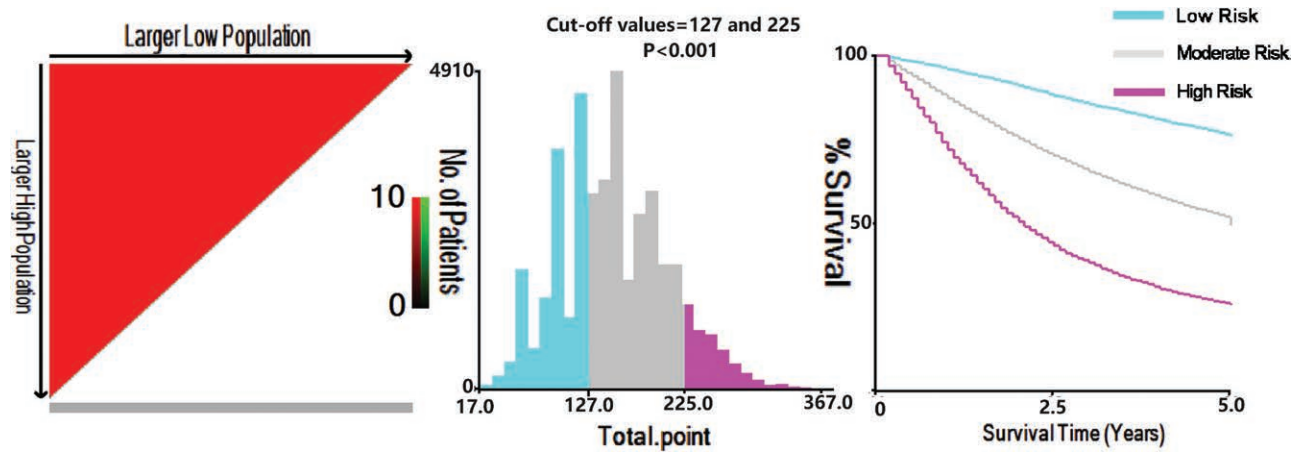
The calibration curves for predicting patient survival at each time point in the (a) training set and (b) testing set. Nomogram-predicted overall survival (OS) was plotted on the x-axis; actual OS was plotted on the y-axis. A plot along the 45-degree line shows that predicted probabilities are well matched the actual outcomes.

Table 3 **C-index of nomogram and American Joint Committee on Cancer 8th staging system**

	Nomogram			AJCC 8th stage			*P*.value
Category	C-Index	95% CI	*P*.value	C-Index	95% CI	*P*.value	(nomogram vs AJCC 8th stage)
OS							
Training Set	0.6828	0.6777–0.6878	<0.001	0.6413	0.6362–0.6464	<0.001	<0.001
Validation Set	0.6762	0.6485–0.6649	<0.001	0.6348	0.6267–0.6429	<0.001	0.020

AJCC, American Joint Committee on Cancer.

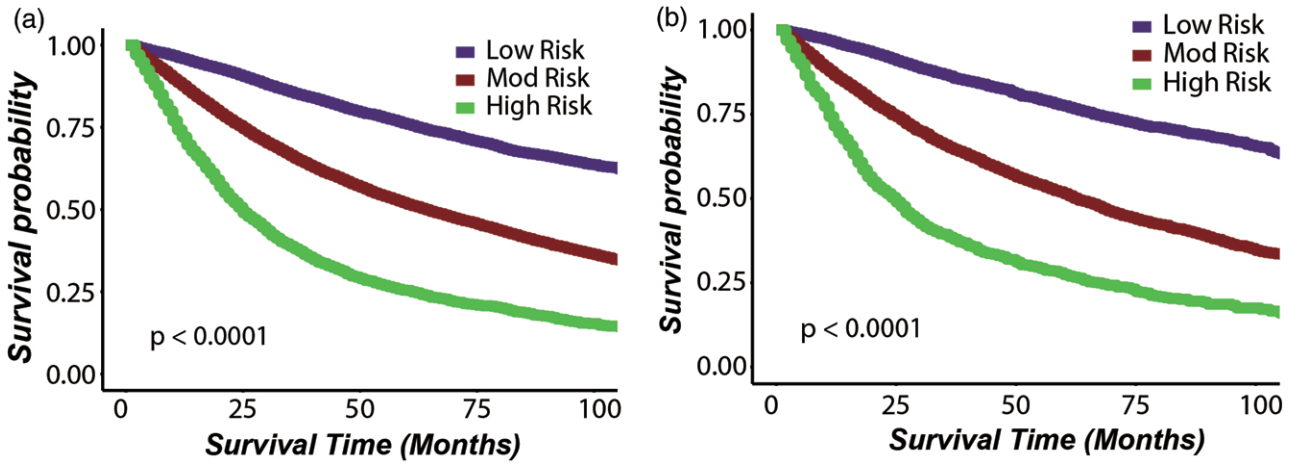
Fig. 4



X-tile analysis determining optimal cutoff values for risk stratification. The optimal threshold was shown in blue(low-risk group), gray (moderate-risk), and violet (high-risk group) panels.

($P = 0.12$) and high-risk ($P = 0.48$) group, there were no incremental benefits when the examined lymph node was higher. However, a greater number of ELNs was positively correlated with better OS among both patients with low risk and patients with moderate risk. MLNR which considered the examined lymph node

Fig. 5



Comparison of Kaplan–Meier curves between subgroups in the training set (a) and the testing set (b).

and positive lymph node presented as a very good predictor. Kaplan–Meier curves were significantly different among patients with different MLNR in the same risk stratification as we could see from Fig. 7. All those above proved that our new nomogram prognostic model could provide efficient information about cancer control and management.

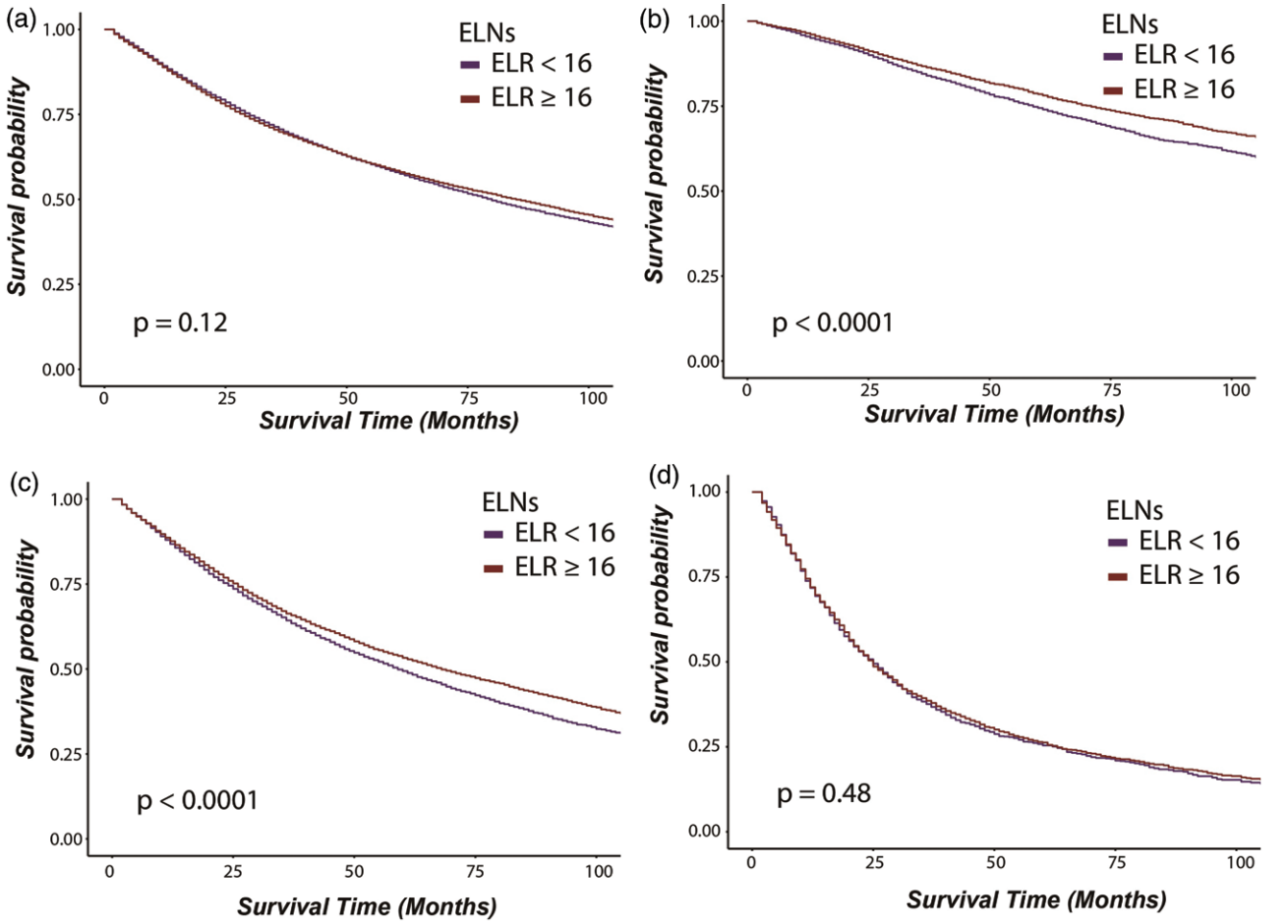
Discussion

Lung cancer is the leading cause of cancer-related death in both men and women. Accurate clinical staging plays an important role in the management and survivor prediction in lung cancer patients. The TNM staging system, a description of the anatomic extent of diseases, is the cornerstone of modern lung cancer management since its approval by the International Association for the Study of Lung Cancer (IASLC) and the AJCC. The 8th edition of TNM lung cancer staging modified the T classification and M descriptors, while the clinical nodal (N) classifier remained the same as in the previous editions, depending solely on the anatomic location of metastatic lymph nodes (LN) (Rusch *et al*., 2016). However, several studies have shown that this nodal classification method is unsatisfactory for distinguishing the heterogeneous N1 and N2 diseases in NSCLC. Additionally, NSCLC patients in the same stage often show different survival times (Brundage *et al*., 2002). Accurate assessment of lymph node metastasis rather than just the anatomical location is crucial for the prognosis of NSCLC patients after surgery. Since the TNM staging system is not precise enough, especially regarding lymph node status, we want to build a new predictive model to evaluate the survival of NSCLC patients. Although several researchers are trying to construct predictive models (Song *et al*., 2018; Wo *et al*., 2019), a nomogram that takes full account of the lymph node for NSCLC-operable patients is scarce. In our study, we established a model that combines the condition of the examined and positive lymph node for surgically resected NSCLC.

We obtained our data from the SEER database, which includes cancer incidence and survival data from 18 population-based cancer registries throughout America, covering about 27.8% of the US population. This huge database empowers our model to find out potential efficient predictor factors that influence a patient's survival. Patients in stage IV were out of consideration since for them surgery is not the first treatment option. In this retrospective study, we concentrate on the lymph node status in the respect that this item is an important component in the conventional AJCC stage system. Yanling has pointed out in their research that the current TNM classification only states the anatomic extent of lymph node metastasis. They suggest a positive lymph node count should be included especially for stage III patients (Fan *et al*., 2019). Examined lymph node count also cannot be neglected as reported in Wenhua's study. They analyzed data from a Chinese multi-institutional registry and the US SEER database and found ELN count is associated with improved outcomes in NSCLC (Padinharayil *et al*., 2022). They recommend 16 ELNs as the cut point for the evaluation of the quality of postoperative lymph node examination or prognostic stratification for patients with declared node-negative disease (Liang *et al*., 2017), which is consistent with our analyses as expected.

The difference between our study and the one referred to above is that we aimed to construct a nomogram that considered the condition of the number of examined lymph nodes and metastatic lymph nodes together. Using multivariable models, we found that MLNR can reflect more accurate node staging than other indexes such as ELNs. Marc reported that the number of lymph nodes is subject

Fig. 6

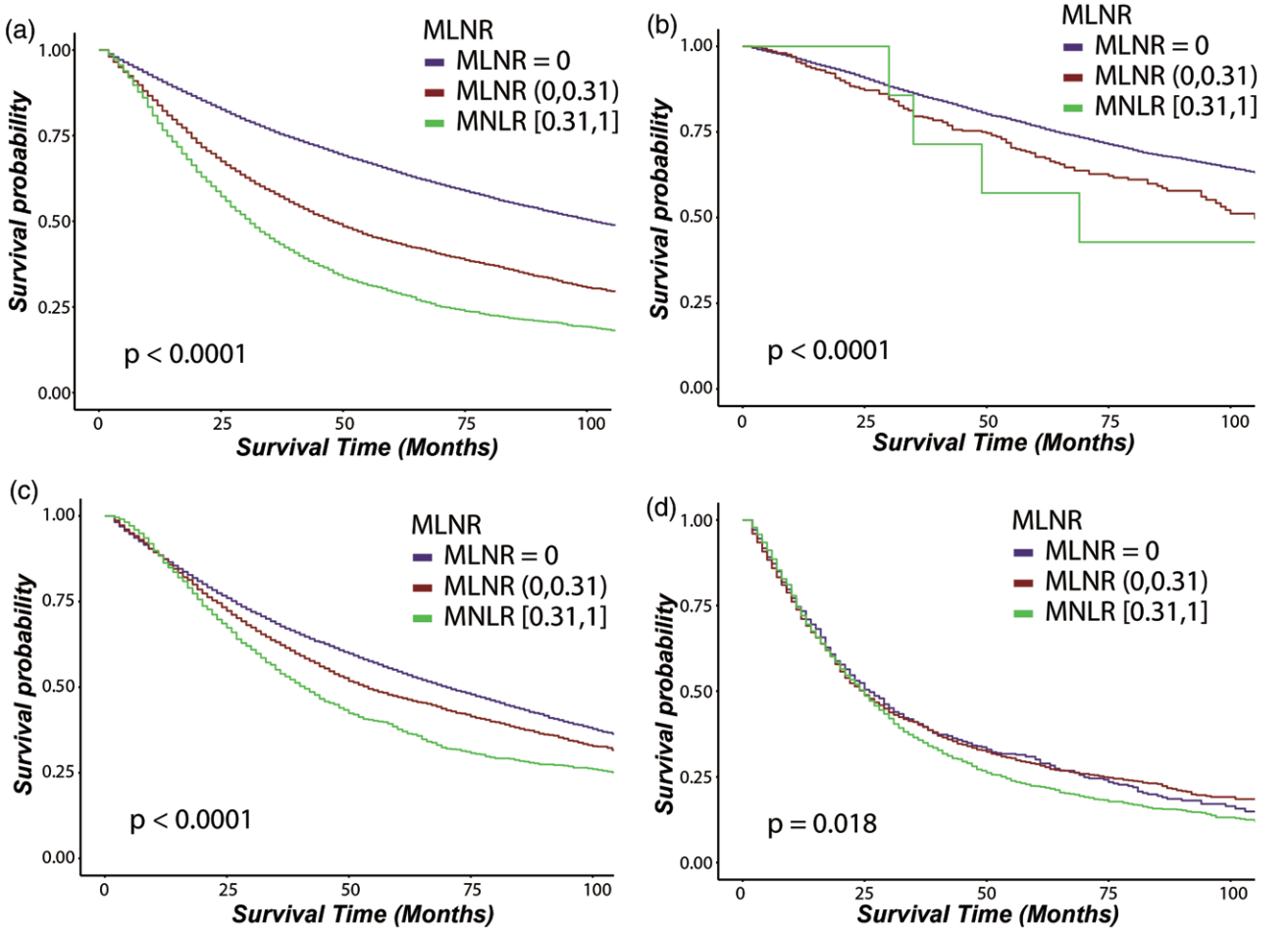


The Kaplan–Meier curves of OS for NSCLC patients after surgery. The prognostic value of examined lymph nodes number(ELNs) in total patient cohort ($n = 40583$, a), low-risk group ($n = 15610$, b), moderate-risk group ($n = 21031$, c), and high-risk group ($n = 4212$, d). NSCLC, nonsmall cell lung carcinoma; OS, overall survival.

to normally distributed interindividual variability, with no significant impact on OS (Riquet *et al.*, 2014). Likewise, through univariable analysis by Cox regression, ELNs have no association with the survival time of NSCLC patients ($P = 0.289$) in our study. After stratifying all the patients based on nomogram points, we managed to formulate three different risk-level groups. Using the cut-off value screened from the X-tile, patients with MLNR higher than 0.31 show better long-term survival despite their risk grade. Meanwhile, only moderate and low-risk patients can benefit from a greater examined lymph node. More lymph nodes examined means more exhaustive elimination of remnants and timely impart adjuvant chemotherapy. However, for high-risk NSCLC patients, as we know, adjuvant chemotherapy is imperative as long as there are signs of lymph node metastasis (Zaric *et al.*, 2013). It is speculated that for this group of NSCLC patients, an increased ELN does not present as a better survival time. The benchmark of ELNs we determined is eight which is different from others (Liu *et al.*, 2018). The lymph node number we recorded may not reflect the true situation since it is not easy to separate each lymph node after dissection, and crushed nodal tissues often mistaken as several completed ones. Therefore, recommending an ideal ELN may not be suitable.

We also found patients with different histological types showed different prognoses. Horiana recently reported in their study that the addition of histological subtypes enhances traditional TNM classification to provide a more accurate risk assessment of patients with early-stage NSCLC (Wo *et al.*, 2019). After taking into account competing risks, those with squamous histology have a higher risk of mortality than those with adenocarcinoma histology (Grosu *et al.*, 2020). Although the statistical method is different, we also found that the prognosis of lung squamous cell carcinoma was poor than that of lung adenocarcinoma. Additionally, large cell carcinoma was the most

Fig. 7



The Kaplan–Meier curves of OS for NSCLC patients after surgery. The prognostic value of metastatic lymph nodes ratio(MLNR) in total patient cohort ($n = 40583$, a), low-risk group ($n = 15610$, b), moderate-risk group ($n = 21031$, c), and high-risk group ($n = 4212$, d). NSCLC, nonsmall cell lung carcinoma; OS, overall survival.

influential predictor with the highest risk score, while bronchi alveolar carcinoma with the minimum risk. It suggested that specifying this element in our nomogram will make it more precise and reliable.

Our study still has some limitations due to its retrospective nature from using the SEER database. Moreover, the SEER database lacks some confounding factors such as smoking, postoperative complications, and access to perform limited resection (open or VATS). The results we get may be influenced to some extent and prospective studies are needed to further test the efficiency of our model.

Conclusion

All in all, to evaluate the survival time of NSCLC patients, it is not enough to just consider the anatomic extent of lymph node metastases. Here we performed a population-based study to summarize the clinical characteristics of NSCLC patients after surgery. Older age, higher MLNR, histological type, adjuvant treatment, and AJCC 8th stage were independent risk factors of NSCLC. The prognostic nomogram of these elements performed better than the traditional TNM staging system. Through risk stratification, we are also able to speculate that MLNR is more suitable than ELNs to predict the survival of NSCLC patients, especially for the high-risk one.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interests

There are no conflicts of interest.

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