Evaluation of Log Odds of Positive Lymph Nodes in Predicting the Survival of Neoadjuvant Therapy Patients with Non-Small Cell Lung Cancer After Surgery: A SEER Cohort-Based Study

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Research Article

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Abstract

Background

log odds of positive lymph nodes (LODDS) is a novel lymph node (LN) descriptor, demonstrating promising prognostic value in many tumors. However, there was limited information on LODDS in non-small cell lung cancer (NSCLC) patients, especially those receiving neoadjuvant therapy followed by lung surgery.

Methods

A total of 2,059 NSCLC patients who received neoadjuvant therapy and surgery were identified in the Surveillance, Epidemiology, and End Results (SEER) database. We used the X-tile software to calculate the cut-off value of LODDS. Kaplan-Meier survival analysis and receiver operating characteristics (ROC) curve were used to compare the predictive value of the American Joint Committee on Cancer (AJCC) N staging descriptor and LODDS. Univariate and multivariate Cox regression and inverse probability of treatment weighting (IPTW) analyses were conducted to construct the model predicting the prognosis.

Results

LODDS showed better differentiating ability in survival analysis than N staging descriptor (Log-rank test, $P<0.0001$ vs. $P=0.031$). The ROC curve demonstrated that the AUC of LODDS was significantly higher than the N staging descriptor in 1-year, 3-year, and 5-year survival analyses (All $P<0.05$). Univariate and multivariate Cox regression analysis showed that the LODDS was an independent risk factor for NSCLC patients receiving neoadjuvant therapy followed by surgery, both before and after IPTW (all $P<0.001$). A clinicopathological model with LODDS, age, gender, T, and radiotherapy could better predict the prognosis.

Conclusions

Compared with the AJCC N staging descriptor, LODDS exhibits better predictive ability for NSCLC patients receiving neoadjuvant therapy followed by surgery. A multivariate clinicopathological model with LODDS included demonstrates sound performance in predicting the prognosis.

Introduction

Lung cancer is the most common cause of death from cancer worldwide, causing 69,410 male deaths and 62,470 female deaths in the 2021 year of USA alone(1). As a prominent type of lung cancer, non-small cell lung cancer (NSCLC) accounts for about 85% of all types of lung cancer cases, with 60% for lung adenocarcinoma and 15% for lung squamous cell carcinoma (SCC) as the most common

histological subtypes(2). With the advent of the new era of targeted therapy and immunotherapy, the overall survival of NSCLC has gained a considerable increase for each stage(3). Despite the novel treatments, lung surgery remains the most substantial and supportive tool for NSCLC. For locally advanced NSCLC patients, neoadjuvant therapy plays a crucial role in downstaging lung cancer and providing an opportunity for surgery, which effectively improves the prognosis(4). Traditional neoadjuvant therapy included chemotherapy and chemoradiation, while molecular-targeted therapy and immunotherapy are evolving as revolutionary neoadjuvant treatments for NSCLC(5). However, there are limited tools and predictive models for predicting the prognosis of patients receiving neoadjuvant therapy followed by lung surgery.

The American Joint Committee on Cancer (AJCC) TNM staging system is the most commonly used tool for recurrence and survival prediction(6). For N descriptor, the lymph node (LN) is based on the lymphatic region involved, without any information of the number of dissected lymph nodes (NDLN) and the number of positive lymph nodes (NPLN)(7). Log odds of positive lymph nodes (LODDS) is a novel lymph node descriptor, showing advantages over N stating descriptor of TNM system in many malignancies, including rectal cancer(8), gallbladder cancer(9), gastric adenocarcinoma(10), cervical cancer(11), esophageal carcinoma(12), and so on. Wang et al. reported that the nomogram combining the TNM stage with LODDS+LNR performed better than AJCC 8th TNM stage in clinical practicability(13). In addition, Yu and his colleagues found that LODDS exhibited better predictive power than the N, NPLN, LNR staging system(14). However, there was no previous report on the application of LODDS in predicting the prognosis for patients receiving neoadjuvant therapy followed by lung surgery. In this study, we screened the suitable cases from the SEER database and compared the value of LODDS and TNM N descriptors. At last, we tried to construct a model combining LODDS with clinicopathological characteristics for a better prediction. This study was presented following the TRIPOD reporting checklist(15).

Materials And Methods

Patient selection

All patients were selected from the SEER database (http://seer.cancer.gov/). Eighteen population-based cancers were selected in the SEER database, with the SEER*Stat program (v 8.3.9) used to extract the information of patients with lung cancer. The extraction conditions were as follows: "the location of the disease: lung and bronchus" and "diagnosis year: 2004–2015." In the research, we enrolled patients with primary lung cancer who received neoadjuvant therapy and lung surgery between 2004 and 2015. Figure 1 shows the flowchart of the patient selection. Following variables were extracted: "Age recode with <1 year olds", "Race recode (White, Black, Other)", "Sex", "Marital status", "Derived AJCC T, 6th ed (2004-2015)", "Derived AJCC M, 6th ed (2004-2015)", "Primary Site – labeled", "Histologic Type ICD-O-3", "RX Summ–Surg Prim Site (1998+)", "CS tumor size (2004-2015)", "CS Tumor Size/Ext Eval (2004-2015)", "Grade (thru 2017)", "Survival months", "Vital status recode (study cut-off used)", "Regional nodes positive (1988+)", "Regional nodes examined (1988+)", “CS Reg Node Eval (2004-2015)”, "First malignant primary

indicator". And the AJCC TNM staging system was updated to the 8th version. The exclusion criteria were as follows: (a) patients with metastatic disease; (b) patients without lung surgery performed; (c) patients in whom lung cancer was not the one primary only tumor; (d) patients not receiving neoadjuvant therapy; (e) patients without information about the number of retrieved and positive lymph nodes; (f) patients with unknown race, marital status, tumor site, laterality, grade, T stage, and N stage.

Ethical statement

The informed consent was waived, and the institutional review board sought no ethical approval because SEER is a public database and all SEER data contained no personally-identifying information. We conducted this study following the Declaration of Helsinki and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization.

LODDS calculation

LODDS was calculated by the formula of ln([NPLN + 0.5]/[NDLN-NPLN + 0.5]), when NPLN meant the number of positive lymph nodes and NDLN meant the number of dissected lymph nodes. X-Tile software (version 3.6.1) was used to produce the optimal cut-off of LODDS with the maximal survival difference between different groups(16). LODDS was divided into three ranges: LODDS<-1.07, -1.07£LODDS<-0.27, and LODDS³-0.27.

Statistical analysis

R software (version 4.0.2) was used to in statistical analysis. A P value of less than 0.05 was considered statistically significant. Categorical variables were presented as proportions. Chi-square tests or Fisher's precision probability test were performed in different evaluations of categorical variables.Univariate and multivariate Cox regression analysis was conducted to screen the risk factors for the overall survival when the variables with P value less than 0.05 were finally incorporated into the risk model.

A Kaplan–Meier survival curve and the log-rank test were conducted to compare the overall survival of patients with different LODDS ranges and different N classifications. Receiver operating characteristics (ROC) was used to evaluate the predictive value of N classification, LODDS, and the multivariate model for the patients' long-term outcomes. Weighted mean rank (WMR) statistics were used to compare the area under the curve (AUC) of N classification, LODDS, and the multivariate model(17). To better balance the baseline of patients of different LODDS ranges, propensity scores were calculated using generalized boosted models, and inverse probability of treatment weighting (IPTW) was used to adjust the Cox regression analyses(18). In addition, prediction accuracy was compared by calculating the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI) between LODDS, N classification, and multivariate model.

Results

Demographical and clinicopathological characteristics

In table 1, we compared the demographical and clinicopathological characteristics of patients with different LODDS ranges. A total of 2059 patients in the SEER database were enrolled in this study and divided into three groups, patients with LODDS<-1.07, -1.07£LODDS<-0.27, and LODDS³-0.27. There was no difference between different groups in age, marital status, surgery type, and radiotherapy (all P>0.05). However, the variables of gender, race, laterality, primary site, histology type, differentiation, and chemotherapy were significantly different among the three groups (All P<0.05). The patients with LODDS³-0.27 had higher proportions of female, right laterality, the primary site of lower lobe, adenocarcinoma, low differentiation grade, low T1 stage, and chemotherapy. Since LODDS was calculated with the NDLN and the NPLN, the patients with LODDS³-0.27 had a higher N stage, more regional nodes examined and positive. We conducted the IPTW to eliminate the demographical and clinicopathological characteristics of patients with different LODDS ranges. As shown in Figure S1, the absolute standardized differences of variables were decreased under 0.2 and mostly under 0.1, indicating that the three groups were well matched after IPTW.

Univariate and multivariate Cox regression analysis

We conducted the univariate and multivariate Cox regression analysis to confirm the independent risk factors for the patients' survival, shown in Table 2 and Table 3. Before IPTW, the univariate analysis demonstrated that LODDS, age, gender, T stage, N stage, and radiotherapy were significantly associated with the OS of the patients (All P<0.05). However, the multivariate analysis showed that LODDS, age, gender, T stage, and radiotherapy were independent risk factors for patients' survival (All P<0.05), with N stage excluded.

After IPTW, the univariate analysis results were similar to the previous results, showing that LODDS, age, gender, T stage, N stage, and radiotherapy were variables with statistical significance, while the race, marital status, primary site, histologic type, differentiation, and surgery type were newly added variables (All P<0.05). Furthermore, the multivariate regression analysis indicated that LODDS, age, gender, race, marital status, primary site, differentiation, and T stage were independent risk factors for patients' survival (All P<0.05), with N stage excluded. Whether with or without IPTW, the LODDS was an independent risk factor for the prognosis of patients receiving neoadjuvant therapy followed by lung surgery.

We also conducted a subgroup analysis to validate the significance of LODDS further. By dividing the patients into different subgroups through the variable, we further compared the relative risk of different LODDS ranges. We found that the higher LODDS was associated with higher risks in most subgroups, as shown in Table 4. However, in subgroups of middle lobe, overlapping primary site, grade I differentiation, grade IV differentiation, and N3 stage, there was no statistical significance among different LODDS ranges, which could be caused by the relatively lower sample size.

Survival analysis

We compared the long-term survival of patients with different N classifications, shown in Figure 2A. Although the patients with different N stages presented different survival curves with a P value of 0.036, the curve was not separate and mostly overlapped. Nevertheless, when we divided the patients into three groups of LODDS ranges, we found that the curve was much more separate (Figure 2B). The patients with LODDS<-1.07 demonstrated the best survival status than the other two groups, while the middle group (-1.07£LODDS<-0.27) had better overall survival than the patients with LODDS³-0.27 (P<0.0001). Even after IPTW, the survival curve was still significant among three groups (P<0.0001), shown in Figure 3.

ROC analysis

In addition, we compared the accuracy and prognostic value of N classification, LODDS, and a multivariate model by ROC curve and AUC comparison. We used a multivariate model with five variables which had been shown to be independent prognostic indicatiors in multivariate analysis in Table 2: LODDS, age, gender, T stage, and radiotherapy. As shown in Figure 4, LODDS had significantly higher AUC than N classification in 1-year (P= 0.008), 3-year (P= 0.007), 5-year OS (P= 0.010), but not in 10-year OS (P=0.228). However, the multivariate model had significantly higher AUC than LODDS and N classification in 1-year, 3-year, 5-year, and 10-year OS (All P<0.001). We also compared the IDI and NRI of N classification, LODDS, and multivariate model, as shown in Table 5. When listing the LODDS as the reference, we found the IDI and NRI of N classification were negative. At the same time, those of the multivariate model was positive, suggesting that the LODDS had significantly higher predictive accuracy than N classification but was lower than the multivariate model (P<0.05).

Discussion

Controversies over the nodal status of the 8th TNM staging system have existed for many years. In summary, there are four commonly used nodal classifications in lung cancer, including N classification, NPLN, LNR, and LODDS(19). The N classification in the TNM staging system is the most commonly used prognostic tool for patients with lung cancer. The N classification is easy to understand and remember in lung cancer, which categorizes no metastasis to lymph node as N0, metastasis to ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes as N1, metastasis to ipsilateral mediastinal and/or subcarinal nodes as N2, metastasis to Contralateral mediastinal and/or hilar, as well as any supraclavicular lymph nodes as N3(20). The TNM staging system helps clinicians to decide the treatment and predict the prognosis. However, the N classification is based on the anatomic position of the positive nodes, without any quantity information, leading to inaccuracy and low discrimination power(21). In this study, we found that the AUC of N classification was only 0.493 95%CI (0.461–0.526), 0.538 95%CI (0.513–0.563), 0.549 95%CI (0.522–0.577), and 0.603 95%CI (0.554–0.651) in 1-year, 3-year, 5-year, and 10-year survival respectively. The low discriminative power of TNM staging N classification calls for a more accurate nodal status assessment tool.

For patients receiving radical lung cancer resection, systematic lymph node dissection (SND) is the standard procedure in surgical treatment for NSCLC(22), especially for patients receiving neoadjuvant

therapy, who were usually diagnosed with stage II-III, when systematic lymph node dissection is a must. In this study, 78.1% of patients received lobectomy, and 19.3% received pneumonectomy, with only 2.7% of patients having sublobectomy. Mun reported that lobe-specific mediastinal lymph node dissection (MLND) is vital for pN1 patients, while SND contributes to survival for pN2 patients after recurrence(23). The lymph nodes retrieved in the surgery provide sufficient knowledge about the nodal status with quantity information. NPLN stands for the number of positive lymph nodes, requiring retrieval of the lymph nodes from the surgery(14). However, the NPLN can be significantly affected by the surgical technique and the number of examined lymph nodes because the pathological results are dependent on the lymph node dissection. Using a Chinese multi-institutional registry and the US SEER database on stage I to IIIA resected NSCLC, Liang recommended 16 examined lymph nodes for prognostic stratification(24).

Ratio-based nodal evaluation methods are also used, not requiring the number of examined lymph nodes, including LNR and LODDS. LNR is calculated by dividing the NPLN with NDLN. LODDS is calculated using the formula: log(NPLN+0.50)/(NDLN−NPLN+0.50), so LODDS is the only indicator with the numbers of dissected, positive, and negative LNs included. The controversy over the comparison between LNR and LODDS consists since they demonstrate advantages against each other in different situations(25,26). However, the LODDS shows superiority over LNR for lung cancer in most studies. Yu and his colleagues demonstrated that LODDS showed better predictive performance than N, NPLN, and LNR among patients with node-positive SCC after surgery(14). Deng found that LODDS and LNR performed slightly differently in patients with different resected LNs. He proved that LODDS was slightly better than LNR for patients with <10 resected LNs, while LNR was slightly better than LODDS for patients with ≥10 resected LNs(27). When combined, LODDS and LNR had the highest prediction accuracy than other models for cancer-specific survival and overall survival of lung adenocarcinoma patients after surgery(13). However, there is no previous report on the predictive ability and accuracy of LODDS in patients receiving neoadjuvant therapy and surgery. In this study, we found that LODDS could effectively differentiate the patient's prognosis. Also, LODDS demonstrated a much higher AUC than N classification 1-year, 3-year, and 5-year prediction, but not in 10-year prediction. The univariate and multivariate Cox regression analysis demonstrated that LODDS was an independent risk factor for patients' overall survival. The subgroups analysis confirmed the results in different subgroups.

We noticed that the baseline characteristics and demographical data of patients with different LODDS ranges were significantly different. To eliminate the bias caused by the difference, we applied the IPTW to balance the baseline characteristics and demographical data. Whether before or after IPTW, the LODDS showed statistical significance in the Kaplan-Meier curve and regression analysis. Due to its excellent predictive ability, LODDS was incorporated into the multivariate model to construct a nomogram. Wang's nomogram included LODDS+LNR as the nodal status factor, which showed an excellent predictive ability with a high C-index (0.7222 for nomogram for CSS, 0.6920 for nomogram for OS) for patients with T1-4N0-2M0 lung adenocarcinoma after surgery(13). This study applied a multivariate model with five critical factors: LODDS, age, gender, T stage, and radiotherapy. This model showed higher AUC than N classification and LODDS. The multivariate model's predictive performance indicator IDI and NRI were

also higher than N classification and LODDS, which proved that LODDS is an independent and compatible factor for lymph node staging and could be incorporated into the risk assessment model well.

Several limitations of this study must be noted. On the one hand, many important data are absent from the SEER database, including smoking history, sequence of surgery and chemotherapy, novel treatments of tyrosine kinase inhibitors treatment, and immune checkpoint inhibitors. The missing data might lead to the worse predictive effect of the nomogram. We tried to construct a nomogram based on our findings but failed in this study because the C-index was very low. We suspected that the low C-index of the nomogram was caused by the heterogeneity of the patients, who received very different treatment regimens. On the other hand, the new era of tyrosine kinase inhibitors and immune checkpoint inhibitors bring the paradigm-shifting for the neoadjuvant therapy for NSCLC patients, which challenges the LODDS and other nodal status indicators.

Conclusions

For NSCLC patients receiving neoadjuvant therapy followed by surgery, LODDS presents better predictive ability than the AJCC N staging descriptor. A multivariate clinicopathological model with LODDS included demonstrates exemplary performance in predicting the prognosis. LODDS provides clinicians with more accurate nodal status information, while the nomogram and external validation are required in future studies.

Abbreviations

AIC Akaike information criterion

AJCC American Joint Committee on Cancer

CI confidence interval

C-index Harrell concordance index

HR hazard ratio

ICD-O-3 3rd edition of the International Classification of Diseases for Oncology

IDI integrated discrimination improvement

IQR interquartile range

IPTW inverse probability of treatment weighting

KM Kaplan-Meier

LNR lymph node ratio

LODDS log odds of positive lymph nodes

LR likelihood ratio

NDLN number of dissected lymph nodes

NPLN number of positive lymph nodes

NRI net reclassification improvement

NSCLC non-small cell lung cancer

OS overall survival

PRCDA purchased/referred care delivery areas

ROC receiver operating characteristics

SEER Surveillance, Epidemiology, and End Results

SCC squamous cell carcinoma

TNM tumor, node, metastasis

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. No approval by the institutional review board was sought, and no individual patient consent was required, because SEER is a public database and the data are de-identified. The authors confirm that they are accountable for all aspects of the work (if applied, including full data access, integrity of the data and the accuracy of the data analysis) in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is available in the SEER*Stat software (version 8.3.8; RRID:SCR_003293; https://seer.cancer.gov/resources/). The primary data can be accessed through SEER*Stat software with certain filter according to the methods in the manuscript.

Competing interests

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

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None.

Authors' contributions

QW, SW, and XZ conceived and designed the analysis, collected the data, performed the analysis and wrote the paper. ZS and QWconceived and designed the analysis, contributed data or analysis tools, performed the analysis. MC and SW interpreted the data and wrote the paper. QW and SW conceived and designed the analysis and interpreted the data. All authors read and approved the final manuscript.

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Tables

TABLE 1 Baseline characteristics of NSCLC patients underwent neoadjuvant therapy

Variables	LODDS<-1.07	-1.07≤LODDS<-0.27	LODDS≥-0.27	P
	n=866	n=895	n=298	
Age				0.359
≤60 years old	365 (42.1%)	405 (45.3%)	142 (47.7%)	
61-67 years old	218 (25.2%)	229 (25.6%)	70 (23.5%)	
≥68 years old	283 (32.7%)	261 (29.2%)	86 (28.9%)	
Gender				0.003
Female	381 (44.0%)	393 (43.9%)	163 (54.7%)	
Male	485 (56.0%)	502 (56.1%)	135 (45.3%)	
Race				0.029
White	729 (84.2%)	740 (82.7%)	243 (81.5%)	
Black	85 (9.8%)	84 (9.4%)	21 (7.0%)	
Other	52 (6.0%)	71 (7.9%)	34 (11.4%)	
Marital status				0.65
Married	543 (62.7%)	588 (65.7%)	189 (63.4%)	
Unmarried	121 (14.0%)	107 (12.0%)	37 (12.4%)	
Seperated/Divorced/Widowed	202 (23.3%)	200 (22.3%)	72 (24.2%)	
Laterality				<0.001
Right	481 (55.5%)	548 (61.2%)	207 (69.5%)	
Left	385 (44.5%)	347 (38.8%)	91 (30.5%)	
Primary site				<0.001
Main bronchus	24 (2.8%)	19 (2.1%)	6 (2.0%)	
Upper lobe	642 (74.1%)	584 (65.3%)	181 (60.7%)	
Middle lobe	22 (2.5%)	41 (4.6%)	20 (6.7%)	
Lower lobe	162 (18.7%)	227 (25.4%)	83 (27.9%)	
Overlapping lesion of lung	16 (1.8%)	24 (2.7%)	8 (2.7%)	
Histologic type				<0.001
Adenocarcinoma	343 (39.6%)	451 (50.4%)	205 (68.8%)	
Squamous cell	365 (42.1%)	291 (32.5%)	57 (19.1%)	

Other	158 (18.2%)	153 (17.1%)	36 (12.1%)	
Differentiation				0.032
Grade I	32 (3.7%)	29 (3.2%)	9 (3.0%)	
Grade II	224 (25.9%)	238 (26.6%)	101 (33.9%)	
Grade III	403 (46.5%)	417 (46.6%)	138 (46.3%)	
Grade IV	33 (3.8%)	23 (2.6%)	2 (0.7%)	
Unknown	174 (20.1%)	188 (21.0%)	48 (16.1%)	
T				<0.001
T1	91 (10.5%)	147 (16.4%)	58 (19.5%)	
T2	208 (24.0%)	257 (28.7%)	129 (43.3%)	
T3	279 (32.2%)	270 (30.2%)	67 (22.5%)	
T4	288 (33.3%)	221 (24.7%)	44 (14.8%)	
N				
N0	447 (51.6%)	178 (19.9%)	0 (0.0%)	<0.001
N1	112 (12.9%)	198 (22.1%)	42 (14.1%)	
N2	293 (33.8%)	502 (56.1%)	246 (82.6%)	
N3	14 (1.6%)	17 (1.9%)	10 (3.4%)	
Regional nodes examined	13.0 (9.0-20.0)	9.0 (4.0-15.0)	9.0 (5.0-15.0)	<0.001
Regional nodes positive	.0 (0.0-0.0)	1.0 (0.0-2.0)	5.0 (2.0-9.0)	<0.001
Surgery				0.418
Sublobectomy	23 (2.7%)	39 (4.4%)	11 (3.7%)	
Lobectomy	676 (78.1%)	691 (77.2%)	233 (78.2%)	
Pneumonectomy	167 (19.3%)	165 (18.4%)	54 (18.1%)	
Radiotherapy				0.082
No/Unknown	291 (33.6%)	275 (30.7%)	80 (26.8%)	
Yes	575 (66.4%)	620 (69.3%)	218 (73.2%)	
Chemotherapy				0.008
No/Unknown	24 (2.8%)	15 (1.7%)	0 (0.0%)	
Yes	842 (97.2%)	880 (98.3%)	298 (100.0%)	

Categorical variables are presented with number (percentage) and continuous variables are reported as median with interquartile range. NSCLC, non-small cell lung cancer; LODDS, log odds of positive lymph nodes.

TABLE 2 Cox regression analysis of NSCLC patients underwent neoadjuvant therapy before IPTW

Variables	Univariable analysis		Multivariable analysis	
	HR (95%CI)	P	HR (95%CI)	P
LODDS				
LODDS<-1.07	Reference		Reference	
-1.07≤LODDS<-0.27	1.387 (1.220-1.578)	<0.001	1.396 (1.220-1.598)	<0.001
LODDS≥-0.27	2.026 (1.719-2.388)	<0.001	2.116 (1.759-2.544)	<0.001
Age				
≤60 years old	Reference		Reference	
61-67 years old	1.300 (1.123-1.504)	<0.001	1.353 (1.168-1.568)	<0.001
≥68 years old	1.583 (1.385-1.808)	<0.001	1.716 (1.497-1.967)	<0.001
Gender				
Female	Reference		Reference	
Male	1.233 (1.098-1.384)	<0.001	1.246 (1.107-1.401)	<0.001
Race				
White	Reference			
Black	0.874 (0.715-1.069)	0.19		
Other	0.858 (0.685-1.075)	0.182		
Marital status				
Married	Reference			
Unmarried	1.106 (0.929-1.316)	0.259		
Seperated/Divorced/Widowed	1.064 (0.926-1.222)	0.383		
Laterality				
Right	Reference		Reference	
Left	0.900 (0.800-1.012)	0.078	0.958 (0.848-1.083)	0.495
Primary site				
Main bronchus	Reference		Reference	
Upper lobe	1.105 (0.736-1.659)	0.631	0.968 (0.642-1.460)	0.876
Middle lobe	1.436 (0.887-2.327)	0.141	1.204 (0.736-1.967)	0.46
Lower lobe	1.423 (0.939-2.158)	0.096	1.223 (0.803-1.861)	0.348

Overlapping lesion of lung	1.826 (1.083-3.079)	0.024	1.383 (0.814-2.348)	0.231
Histologic type				
Adenocarcinoma	Reference			
Squamous cell	0.986 (0.867-1.121)	0.825		
Other	0.935 (0.796-1.098)	0.411		
Differentiation				
Grade I	Reference		Reference	
Grade II	1.266 (0.888-1.803)	0.192	1.229 (0.861-1.753)	0.256
Grade III	1.403 (0.993-1.983)	0.055	1.358 (0.959-1.923)	0.085
Grade IV	1.342 (0.834-2.160)	0.225	1.431 (0.886-2.310)	0.143
Unknown	1.099 (0.764-1.580)	0.611	1.091 (0.757-1.574)	0.639
T				
T1	Reference		Reference	
T2	1.153 (0.954-1.392)	0.14	1.147 (0.948-1.389)	0.158
T3	1.277 (1.061-1.537)	0.01	1.363 (1.128-1.647)	0.001
T4	1.175 (0.969-1.424)	0.101	1.336 (1.094-1.632)	0.004
N				
N0	Reference		Reference	
N1	1.132 (0.951-1.348)	0.163	0.934 (0.778-1.120)	0.459
N2	1.223 (1.069-1.398)	0.003	1.021 (0.878-1.186)	0.791
N3	1.240 (0.819-1.877)	0.309	0.962 (0.631-1.468)	0.858
Surgery				
Sublobectomy	Reference			
Lobectomy	0.866 (0.648-1.159)	0.334		
Pneumonectomy	1.086 (0.796-1.482)	0.602		
Radiotherapy				
No/Unknown	Reference		Reference	
Yes	1.173 (1.035-1.330)	0.013	1.203 (1.054-1.372)	0.006
Chemotherapy				

No/Unknown	Reference	
Yes	0.927 (0.619-1.389)	0.715

NSCLC, non-small cell lung cancer; IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; LODDS, log odds of positive lymph nodes.

TABLE 3 Cox regression analysis of NSCLC patients underwent neoadjuvant therapy after IPTW

Variables	Univariable analysis		Multivariable analysis	
	HR (95%CI)	P	HR (95%CI)	P
LODDS				
LODDS<-1.07	Reference		Reference	
-1.07≤LODDS<-0.27	1.445 (1.325-1.577)	<0.001	1.437 (1.313-1.573)	<0.001
LODDS≥-0.27	2.318 (2.127-2.527)	<0.001	2.459 (2.227-2.715)	<0.001
Age				
≤60 years old	Reference		Reference	
61-67 years old	1.282 (1.177-1.397)	<0.001	1.360 (1.245-1.485)	<0.001
≥68 years old	1.591 (1.471-1.721)	<0.001	1.803 (1.659-1.959)	<0.001
Gender				
Female	Reference		Reference	
Male	1.318 (1.231-1.411)	<0.001	1.321 (1.227-1.422)	<0.001
Race				
White	Reference		Reference	
Black	0.919 (0.814-1.037)	0.169	0.989 (0.874-1.119)	0.86
Other	0.827 (0.723-0.946)	0.006	0.798 (0.694-0.917)	0.001
Marital status				
Married	Reference		Reference	
Unmarried	1.194 (1.078-1.324)	<0.001	1.417 (1.272-1.578)	<0.001
Seperated/Divorced/Widowed	1.064 (0.981-1.155)	0.135	1.163 (1.067-1.269)	<0.001
Laterality				
Right	Reference			
Left	1.002 (0.935-1.073)	0.961		
Primary site				
Main bronchus	Reference		Reference	
Upper lobe	1.068 (0.833-1.370)	0.603	1.109 (0.857-1.434)	0.432
Middle lobe	1.130 (0.842-1.516)	0.416	1.265 (0.934-1.714)	0.128
Lower lobe	1.293 (1.002-1.668)	0.048	1.373 (1.056-1.785)	0.018

Overlapping lesion of lung	1.498 (1.079-2.078)	0.016	1.233 (0.885-1.719)	0.216
Histologic type				
Adenocarcinoma	Reference		Reference	
Squamous cell	1.111 (1.031-1.197)	0.006	1.022 (0.942-1.109)	0.598
Other	0.982 (0.893-1.081)	0.716	0.911 (0.822-1.009)	0.073
Differentiation				
Grade I	Reference		Reference	
Grade II	1.254 (1.015-1.550)	0.036	1.223 (0.986-1.516)	0.067
Grade III	1.361 (1.106-1.674)	0.004	1.258 (1.018-1.554)	0.034
Grade IV	1.153 (0.843-1.577)	0.373	1.289 (0.936-1.776)	0.12
Unknown	1.116 (0.899-1.386)	0.321	1.140 (0.913-1.423)	0.247
T				
T1	Reference		Reference	
T2	1.163 (1.038-1.302)	0.009	1.116 (0.993-1.253)	0.065
T3	1.337 (1.196-1.494)	<0.001	1.337 (1.194-1.497)	<0.001
T4	1.405 (1.253-1.575)	<0.001	1.468 (1.302-1.656)	<0.001
N				
N0	Reference		Reference	
N1	1.356 (1.219-1.508)	<0.001	0.930 (0.829-1.043)	0.216
N2	1.416 (1.299-1.544)	<0.001	1.046 (0.947-1.156)	0.377
N3	1.542 (1.231-1.931)	<0.001	1.062 (0.840-1.342)	0.617
Surgery				
Sublobectomy	Reference		Reference	
Lobectomy	0.819 (0.687-0.977)	0.027	0.913 (0.762-1.093)	0.32
Pneumonectomy	1.028 (0.851-1.241)	0.776	1.156 (0.949-1.408)	0.149
Radiotherapy				
No/Unknown	Reference		Reference	
Yes	1.065 (0.989-1.146)	0.096	1.067 (0.987-1.153)	0.105
Chemotherapy				

No/Unknown	Reference	
Yes	0.936 (0.692-1.266)	0.67

NSCLC, non-small cell lung cancer; IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; LODDS, log odds of positive lymph nodes.

TABLE 4 Multivariable Cox regression analysis of subgroups of NSCLC patients underwent neoadjuvant therapy

Subgroups	LODDS<-1.07	-1.07≤LODDS<-0.27		LODDS≥-0.27	
	HR	HR (95%CI)	P	HR (95%CI)	P
Age					
≤60 years old	Reference	1.649 (1.319-2.061)	<0.001	2.587 (1.924-3.477)	<0.001
61-67 years old	Reference	1.302 (0.985-1.721)	0.064	1.709 (1.148-2.544)	0.008
≥68 years old	Reference	1.299 (1.040-1.623)	0.021	2.018 (1.477-2.756)	<0.001
Gender					
Female	Reference	1.197 (0.967-1.482)	0.098	1.893 (1.449-2.472)	<0.001
Male	Reference	1.503 (1.261-1.791)	<0.001	2.252 (1.739-2.917)	<0.001
Laterality					
Right	Reference	1.260 (1.060-1.498)	0.009	1.832 (1.456-2.305)	<0.001
Left	Reference	1.638 (1.320-2.033)	<0.001	2.646 (1.936-3.617)	<0.001
Primary site					
Main bronchus	Reference	1.207 (0.351-4.149)	0.766	5.019 (0.974-25.856)	0.054
Upper lobe	Reference	1.415 (1.202-1.667)	<0.001	2.305 (1.829-2.905)	<0.001
Middle lobe	Reference	1.853 (0.734-4.676)	0.192	1.741 (0.600-5.053)	0.308
Lower lobe	Reference	1.375 (1.037-1.822)	0.027	1.813 (1.244-2.642)	0.002
Overlapping lesion of lung	Reference	1.684 (0.562-5.046)	0.352	0.745 (0.126-4.396)	0.746
Differentiation					
Grade I	Reference	1.723 (0.680-4.362)	0.251	1.940 (0.538-6.998)	0.311
Grade II	Reference	1.361 (1.030-1.800)	0.030	2.259 (1.592-3.205)	<0.001
Grade III	Reference	1.301 (1.077-1.571)	0.006	1.971 (1.521-2.554)	<0.001

Grade IV	Reference	0.764 (0.338-1.728)	0.518	0.245 (0.018-3.310)	0.290
Unknown	Reference	2.298 (1.630-3.239)	<0.001	2.923 (1.795-4.761)	<0.001
T					
T1	Reference	1.302 (0.855-1.981)	0.219	1.821 (1.071-3.096)	0.027
T2	Reference	1.582 (1.193-2.098)	0.001	2.003 (1.444-2.778)	<0.001
T3	Reference	1.468 (1.165-1.850)	0.001	2.115 (1.482-3.017)	<0.001
T4	Reference	1.184 (0.924-1.516)	0.182	2.291 (1.510-3.476)	<0.001
N					
N0	Reference	0.987 (0.778-1.251)	0.911	NA	NA
N1	Reference	1.393 (0.993-1.953)	0.055	1.939 (1.221-3.078)	0.005
N2	Reference	1.786 (1.444-2.209)	<0.001	2.523 (1.983-3.211)	<0.001
N3	Reference	5.538 (1.011-30.326)	0.049	3.885 (0.377-40.074)	0.254
Radiotherapy					
No/Unknown	Reference	1.532 (1.190-1.972)	0.001	2.901 (2.052-4.101)	<0.001
Yes	Reference	1.348 (1.149-1.582)	<0.001	1.884 (1.513-2.346)	<0.001

HRs of multivariable analysis of subgroups were adjusted by age, gender, laterality, primary site, differentiation, T, N, and radiotherapy except for the subgroup variable itself. LODDS, log odds of positive lymph nodes; NSCLC, non-small cell lung cancer; HR: hazard ratio; CI: confidence interval.

TABLE 5 Comparison of predictive performance between LODDS and other models

Model	IDI (95%CI)	P	NRI (95%CI)	P
1-year OS				
LODDS	Reference		Reference	
N classification	-0.007 (-0.014 to -0.002)	0.007	-0.060 (-0.122 to 0.002)	0.060
Multivariable model	0.020 (0.012 to 0.031)	<0.001	0.184 (0.114 to 0.250)	<0.001
3-year OS				
LODDS	Reference		Reference	
N classification	-0.018 (-0.030 to -0.007)	<0.001	-0.049 (-0.157 to -0.001)	0.047
Multivariable model	0.029 (0.017 to 0.045)	<0.001	0.136 (0.096 to 0.196)	<0.001
5-year OS				
LODDS	Reference		Reference	
N classification	-0.025 (-0.040 to -0.012)	<0.001	-0.074 (-0.183 to -0.025)	0.007
Multivariable model	0.036 (0.024 to 0.057)	<0.001	0.171 (0.126 to 0.224)	<0.001
10-year OS				
LODDS	Reference		Reference	
N classification	-0.030 (-0.050 to -0.010)	<0.001	-0.200 (-0.290 to -0.006)	0.027
Multivariable model	0.056 (0.034 to 0.086)	<0.001	0.258 (0.168 to 0.348)	<0.001

Multivariable model includes LODDS, age, gender, T, and radiotherapy. LODDS, log odds of positive lymph nodes; OS, overall survival; IDI, integrated discrimination improvement; NRI, net reclassification improvement; CI, confidence interval.

Figures

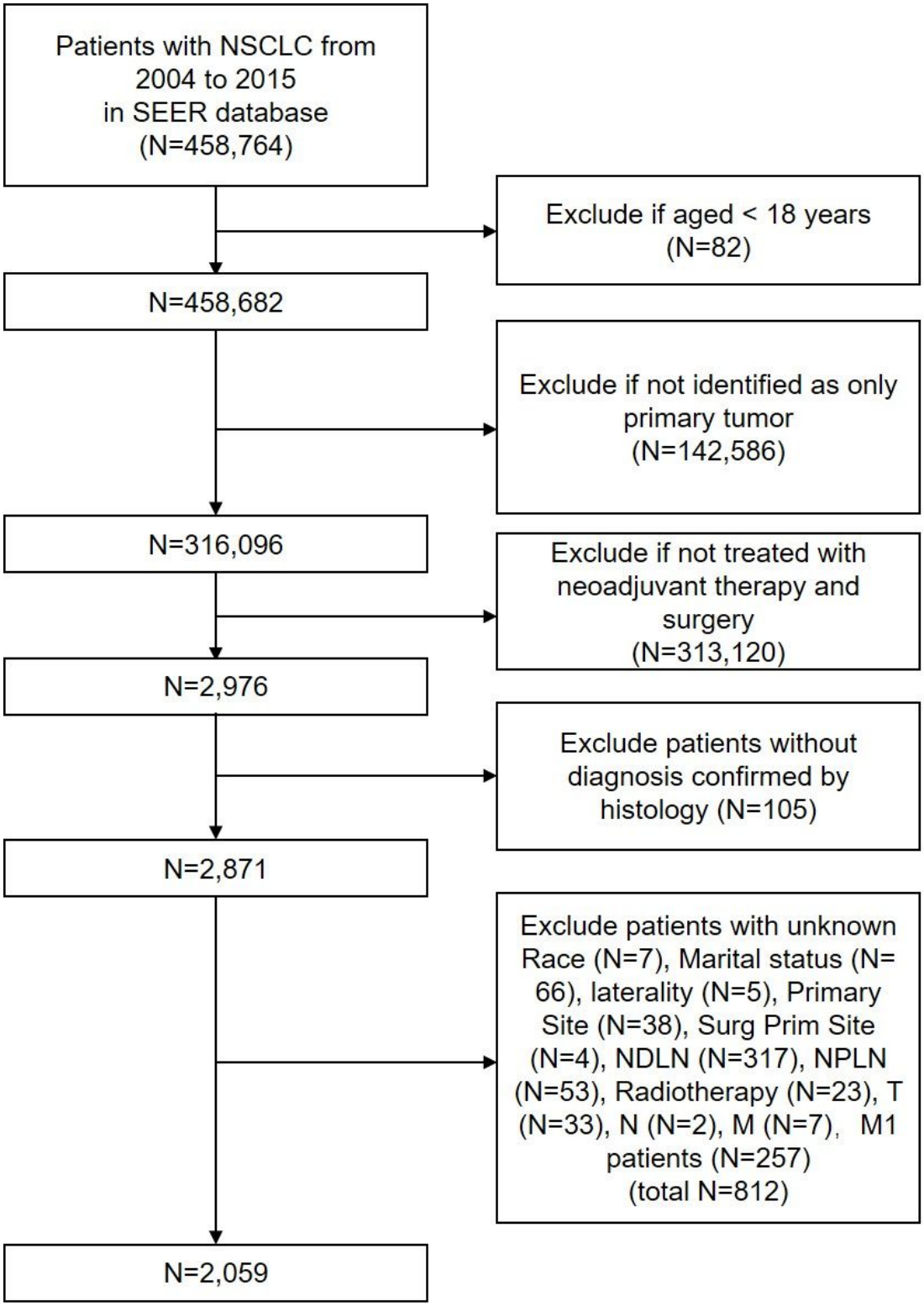

Figure 1

Flowchart of the patient selection

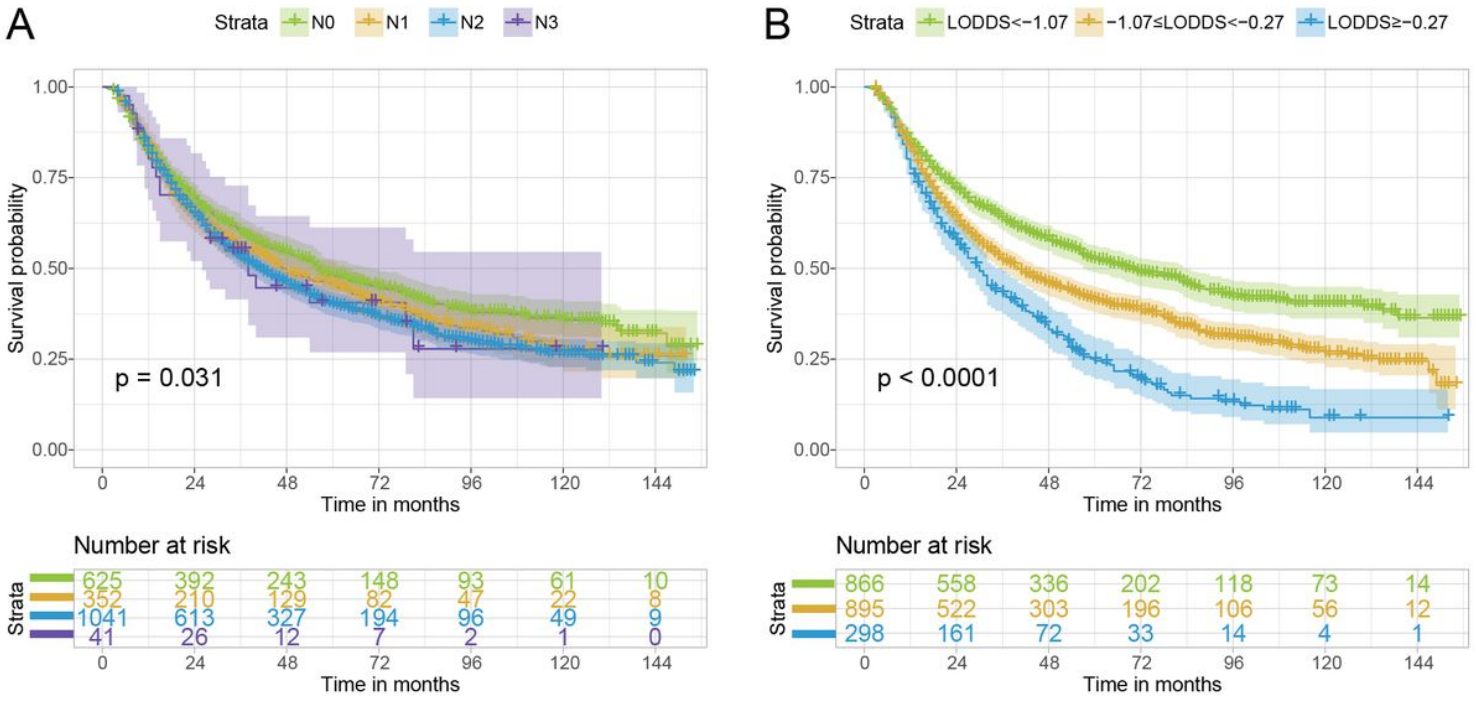

Figure 2

Kaplan-Meier estimates of OS for NSCLC patients who underwent neoadjuvant therapy stratified by N classification (A) and LODDS (B) before IPTW. OS, overall survival; NSCLC, non-small cell lung cancer; LODDS, log odds of positive lymph node; IPTW, inverse probability of treatment weighting.

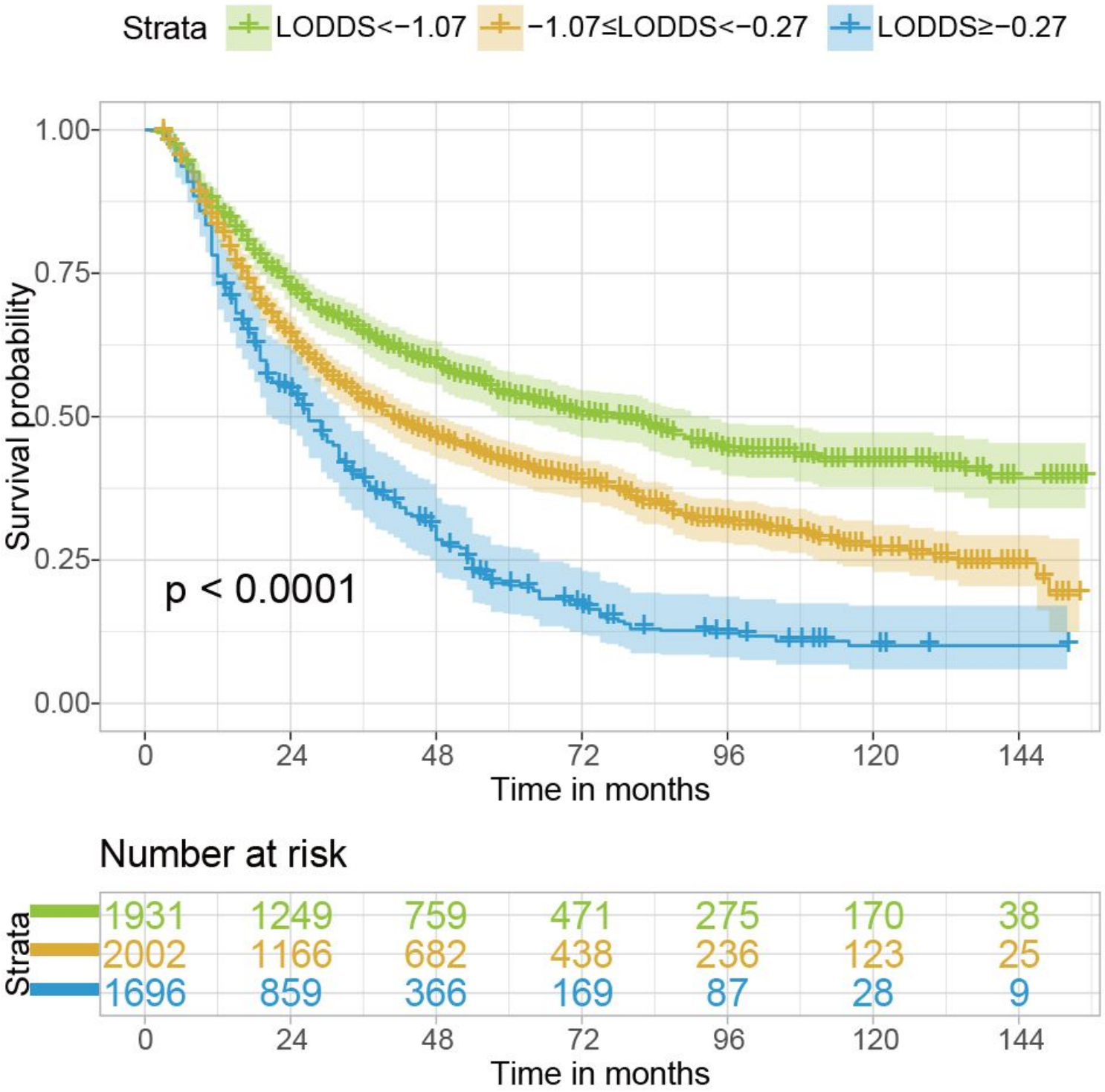

Figure 3

Kaplan-Meier estimates of OS for NSCLC patients who underwent neoadjuvant therapy stratified by LODDS after IPTW. OS, overall survival; NSCLC, non-small cell lung cancer; LODDS, log odds of positive lymph node; IPTW, inverse probability of treatment weighting.

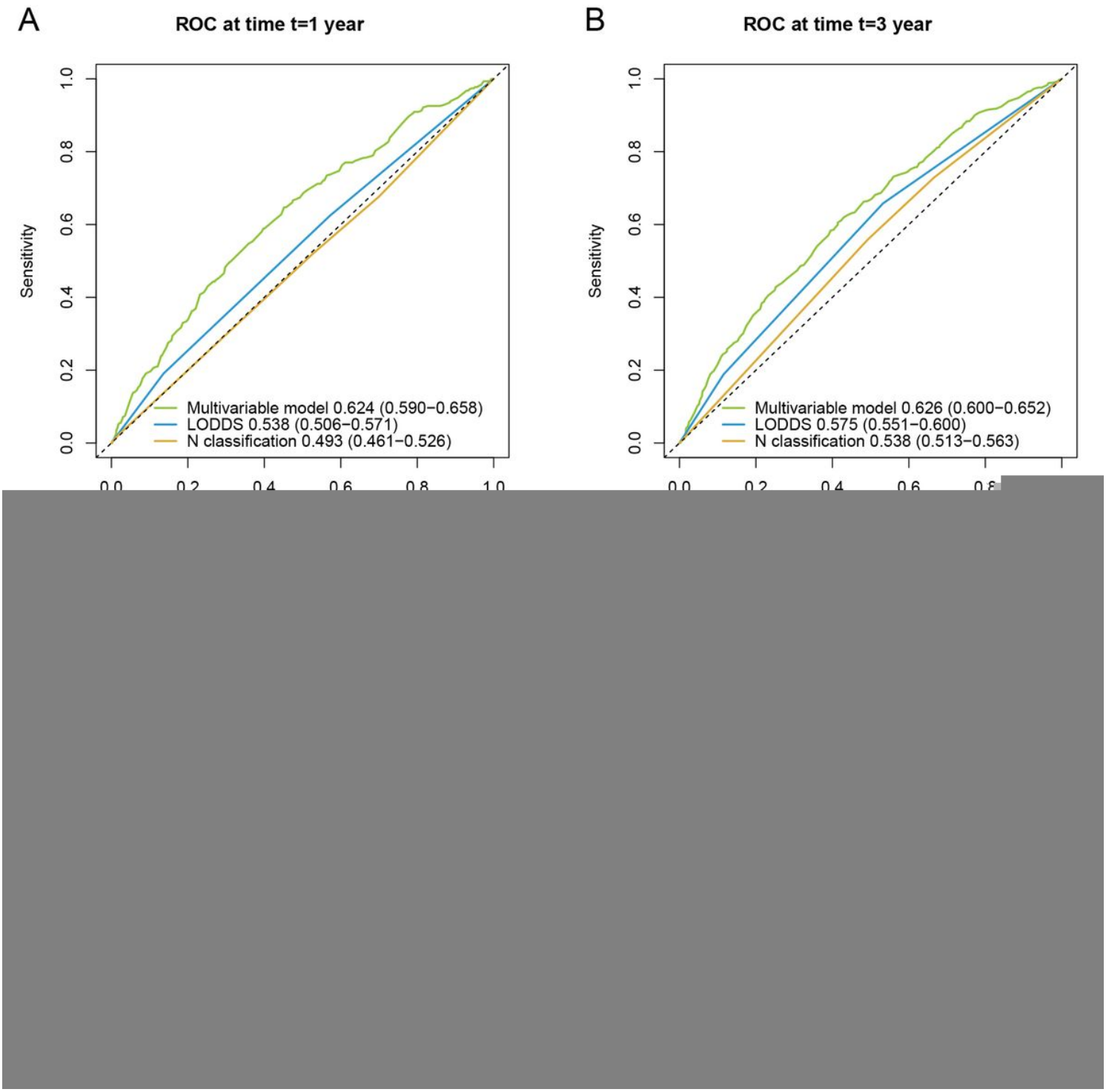

Figure 4

ROC curves for multivariable model (including LODDS, age, gender, T stage, and radiotherapy), LODDS, and N classification predicting 1-year(A), 3-year (B), 5-year (C), 10-year (D) OS of NSCLC patients underwent neoadjuvant therapy. ROC, receiver operating characteristic; LODDS, log odds of positive lymph node; OS, overall survival; NSCLC, non-small cell lung cancer.

Supplementary Files

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- SupplementaryfileS1.docx