



A survival nomogram model for patients with resectable non-small cell lung cancer and lymph node metastasis (N1 or N2) based on the Surveillance, Epidemiology, and End Results Database and single-center data

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Background: The ability to predict survival in patients with lymph node metastasis has long been elusive. After surgery, the basis for decision-making on the combination treatment of patients is not clear. The purpose of this study was thus to build a survival nomogram model to effectively predict the overall survival (OS) of patients with non-small cell lung cancer (NSCLC) and lymph node metastasis. The number of dissected lymph nodes (NDLN), number of positive lymph nodes (NPLN), lymph node ratio (LNR), and log odds of positive lymph nodes (LODDS) were included in this study to determine the risk factors in patients with advanced NSCLC.

Methods: The data of 5,132 patients with NSCLC and lymph node metastasis (N1 or N2) were extracted from the Surveillance, Epidemiology, and End Results (SEER) database according to inclusion and exclusion criteria and used as the training cohort. We enrolled 117 patients from the First Affiliated Hospital, Zhejiang University School of Medicine as the external validation cohort. Receiver operating characteristic (ROC) analyses were performed to determine the best cutoff values for predicting the prognosis of patients with NSCLC. Based on the risk factors affecting prognosis, a nomogram was constructed using univariate and multivariate Cox proportional hazard regression models. The discrimination ability of the nomogram was evaluated with the concordance index (C-index) and calibration curves. For the independent risk factors, survival curves were drawn using Kaplan-Meier analysis.

Results: ROC curve analysis showed that the optimal NPLN cut-off value was 4, LNR was 0.26, and LODDS was -0.25 , respectively. However, LNR was nonsignificant in multivariate analysis, with a P value of 0.274. The novel survival nomogram model included seven independent risk factors, among which were NPLN, LODDS, and chemotherapy. Model 4, which included N stage, NPLN, and LODDS, had a higher likelihood ratio (LR) and C-index than did the other models. The C-index was 0.648 [95% confidence interval (CI): 0.636–0.659] in the training cohort and 0.807 (95% CI: 0.751–0.863) in the external validation cohort, showing good prognostic accuracy and discrimination ability. According to the median risk score,

the patients in the training cohort and external validation cohort were divided into high-risk and low-risk groups, between which significant differences in OS were found. In the training cohort, age, sex, T stage, N stage, NPLN, LODDS, and chemotherapy were significantly associated with OS ($P < 0.001$). In the external validation cohort, T stage, NPLN, LODDS, and chemotherapy were found to be correlated with OS.

Conclusions: The NPLN and LODDS nomogram is an accurate survival prediction tool for patients with N1 or N2 NSCLC. Patients with lymph node metastasis can benefit from chemotherapy, but no evidence shows that radiotherapy is necessary for patients with resectable NSCLC.

Keywords: Lymph node metastasis; log odds of positive lymph nodes (LODDS); non-small cell lung cancer (NSCLC); Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Lung cancer is the leading cause of cancer-specific death in men and women. The prevalence of cancer screening contributes to improving the proportion of patients who receive localized diagnoses (1). Most patients with non-small cell lung cancer (NSCLC) are at an advanced stage when they are diagnosed, only a few patients with stage III NSCLC undergo surgery, and most patients are treated

with chemotherapy and/or radiation. Some patients who receive targeted and immunotherapy drugs for advanced NSCLC can receive benefit, but the 5-year overall survival (OS) of patients with NSCLC remains at approximately 20% (2). We hypothesize that the high mortality in NSCLC is due to the high recurrence rate, the absence of specific genetic mutations, and a lack of high programmed death-ligand 1 (PD-L1) expression among patients. Despite numerous studies showing that postoperative cisplatin-based chemotherapy significantly improves survival in patients with NSCLC (3,4), there is insufficient evidence to predict prognosis and guide postoperative chemotherapy after surgery in those with NSCLC and lymph node (LN) metastasis (N1 and N2). The role of radiation therapy in patients with resectable LN-positive NSCLC is also controversial. Some researchers believe chemoradiotherapy has advantages for patients with stage III NSCLC (5). However, many patients cannot be treated with radiation due to the risks associated with higher age or those posed by multiple comorbidities, and the necessity of radiation therapy in patients with operable stage III NSCLC has not been adequately discussed. Another viewpoint is that radiotherapy with sequential adjuvant chemotherapy does not improve the survival of patients with N2 lung cancer (6).

Due to the above-described uncertainties, we established a nomogram for predicting the long-term survival outcomes of patients with NSCLC and LN metastasis (N1 or N2) based on data from the Surveillance, Epidemiology, and End Results (SEER) database (<https://seer.cancer.gov/>). This novel survival model was verified through external single-center data. Log odds of positive lymph nodes (LODDS), a novel and promising ratio-based LN staging system, was

Highlight box

Key findings

- A novel survival nomogram model was developed for predicting the long-term survival of patients with resectable non-small cell lung cancer (NSCLC) and positive lymph node (LN) metastasis (N1 or N2).

What is known and what is new?

- Chemotherapy is the main postoperative comprehensive treatment strategy for patients with LN metastasis of NSCLC. The necessity of radiotherapy in this particular group of patients is subject to debate, and no accurate model exists for predicting the prognosis of patients with LN metastasis.
- Our study compared the LN stage (N), number of positive lymph nodes (NPLN), lymph node ratio (LNR), and log odds of positive lymph nodes (LODDS). The nomogram containing the NPLN and LODDS could accurately predict the survival of patients with N1 or N2 NSCLC.

What is the implication, and what should change now?

- The nomogram containing NPLN and LODDS is an accurate survival prediction tool for patients with N1 or N2 NSCLC. Patients with LN metastasis can benefit from chemotherapy, but there is no evidence supporting the necessity of radiotherapy for patients with resectable NSCLC.

also applied in the nomogram model and compared with the N stage and number of positive lymph nodes (NPLN). We present this article in accordance with the TRIPOD reporting checklist (available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-24-119/rc>).

Methods

Training cohort data collection and selection criteria

The data of patients with resectable NSCLC and LN metastasis (N1 or N2) were extracted from the SEER database using the SEER*Stat program (v. 8.3.9.2). The database name was Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying), and the SEER Program permission number was 19642-Nov2020. The patients with NSCLC were diagnosed between 2010 and 2015. The selection formula was as follows: {Site and Morphology. TNM 7/CS v0204+ Schema} = “Lung” AND {Stage - 7th edition. Derived AJCC N, 7th ed (2010-2015)} = ‘N1’, ‘N1a’, ‘N1b’, ‘N1c’, ‘N1mi’, ‘N1NOS’, ‘N2’, ‘N2a’, ‘N2b’, ‘N2c’, ‘N2NOS’ AND {Race, Sex, Year Dx, Registry, County. Year of diagnosis} = ‘2010’, ‘2011’, ‘2012’, ‘2013’, ‘2014’, ‘2015’. Variables extracted from the SEER database included patient ID, age at diagnosis, sex, race recode, marital status at diagnosis, year of diagnosis, primary site, grade, laterality, International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology and behavior, derived American Joint Committee on Cancer (AJCC) T stage, derived AJCC N stage, derived AJCC M stage, Rx summary (surgery at primary site), radiation sequence with surgery, chemotherapy recode, regional nodes examined, regional nodes positive, survival months, SEER cause-specific death classification, SEER other cause of death classification, and vital status recode. The T stage and N stage mentioned above were pathological tumor, node, metastasis (TNM). Patients who met the following inclusion criteria were included: (I) age ≥ 18 years; (II) histological pathology: confirmed NSCLC including codes 8010, 8012, 8013, 8014, 8015, 8020, 8021, 8022, 8031, 8032, 8046, 8050–8052, 8070–8078, 8140–8147, 8250–8255, 8260, 8310, 8323, 8430, 8480, 8481, 8482, 8490, 8560, and 8570–8575 based on the ICD-O-3 histology and behavior malignant code (7); (III) radical surgery (R0 resection) and systematic LN dissection of verified N1 or N2 stage disease; (IV) information on chemotherapy use available; and (V) complete record of sequence radiotherapy

information (patients who received postoperative adjuvant radiotherapy or did not receive radiotherapy). The exclusion criteria were as follows: (I) age < 18 years or > 80 years; (II) pathological diagnosis of N0 or N3; (III) other malignant tumors; (IV) confirmed distant metastasis (M1); (V) preoperative radiotherapy; (VI) no radical surgery or systematic lymphadenectomy; and (VII) missing TNM staging system or survival time data. Tumor staging was performed according to the seventh edition of the AJCC.

External validation cohort and selection criteria

An external validation cohort of patients treated from June 2015 to December 2016 in the Department of Thoracic Surgery of the First Affiliated Hospital, Zhejiang University School of Medicine, was used to validate the developed nomogram reliably. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 2023-0012) and individual consent for this retrospective analysis was waived.

The validation cohort included 117 patients with postoperative N1 or N2 NSCLC. The inclusion and exclusion criteria were the same as those in the training cohort from the SEER database. The last follow-up for the cohort was in December 2022, and the primary outcome was OS.

Data processing of the number of dissected lymph nodes (NDLN), NPLN, lymph node ratio (LNR), and LODDS systems

The LNR was defined as the ratio of positive LNs divided by the total NDLN and was calculated using the following formula: $NPLN/NDLN$. LODDS was calculated as follows: $LODDS = \log(NPLN + 0.50)/(NDLN - NPLN + 0.50)$. 0.50 was added to the numerator and denominator (8) to avoid an infinite number.

Establishing a nomogram model for survival

The relationship between potential clinical risk factors and OS were estimated using Cox proportional hazards regression models, and the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated. Based on the results of univariate and multivariate Cox regression conducted via R version 4.2.2

software (The R Foundation of Statistical Computing), we included the applicable independent risk factors in the nomogram to predict the 1-, 3- and 5-year OS probabilities of patients with N1 or N2 NSCLC who underwent radical surgery using.

Prediction accuracy of the nomogram model

The discrimination ability of the nomogram model was determined via the concordance index (C-index) (9). The closer the C-index is to 1, the better the prediction ability of the nomogram model. Moreover, we used the corresponding area under the curves (AUCs) generated by the 1-, 3- and 5-year OS receiver operating characteristic (ROC) curves to estimate the predictive accuracy of the nomogram (10). The calibration curve is a diagram reflecting the association between the observed outcome frequencies and the predicted probabilities. A predicted calibration curve closer to the standard curve indicates that the predictive ability of the nomogram model is more efficient.

Predictive performance of different nodal staging systems

The four different multivariable Cox regression models included model 1 (N stage), model 2 (N stage + NPLN), model 3 (N stage + LODDS), and model 4 (N stage + NPLN + LODDS). Other potential predictors in the univariate analysis were simultaneously entered into the Cox regression model. Homogeneity and discrimination ability were evaluated with the likelihood ratio (LR) test and C-index, respectively.

Statistical methods

Statistical tests were performed with R version 4.2.2 and SPSS 22.0 (IBM Corp.). HRs were determined through univariate and multivariate Cox proportional hazards models. OS was defined as the number of months from diagnosis to death or the last follow-up (December 22, 2022) for censored observations. The median risk score was used to determine the high-risk and low-risk groups and was calculated with the “survival” R package. Kaplan-Meier survival analysis of different independent risk factors included in the nomogram model was performed, and the statistical difference was analyzed using the log-rank test.

Results

Study cohort

Data from 5,132 patients diagnosed with NSCLC in 2010–2015 and with LN metastasis (N1 or N2) were extracted from the SEER database. A total of 117 patients diagnosed in 2015–2016 were enrolled as the external validation cohort. In the training cohort, 1,302 (25.4%) patients were aged <60 years, and 2,458 (47.9%) were female. A total of 3,546 (69.1%) patients received chemotherapy, and 1,276 (24.9%) patients received postoperative adjuvant radiotherapy. In the external validation cohort, 68 (58.1%) patients were aged <60 years, and 56 (47.9%) patients were female. Among these patients, 53 (45.3%) received adjuvant chemotherapy, and 21 (17.9%) received radiation after surgery. The baseline characteristics of the patients in the training and external validation cohorts are presented in *Table 1*.

Independent risk factors in the training cohort

Age, sex, T stage, N stage, chemotherapy, radiation sequence with surgery, regional nodes examined, NPLN, LNR, and LODDS were significantly associated with OS in the univariate analysis (P value <0.01). According to univariate analysis, 14 independent risk factors were selected for inclusion in the multivariate analysis using Cox regression. The seven following factors were found to be significant: age (age \geq 60 years: HR =1.341, 95% CI: 1.288–1.394; P<0.001), sex (male: HR =1.367, 95% CI: 1.323–1.411; P<0.001), T stage (T2: HR =1.191, 95% CI: 1.134–1.248, P=0.002; T3: HR =1.821, 95% CI: 1.755–1.887, P<0.001; T4: HR =1.754, 95% CI: 1.712–1.848, P<0.001), N stage (N2: HR =1.293, 95% CI: 1.244–1.342; P<0.001), chemotherapy (yes: HR =0.604, 95% CI: 0.557–0.651; P<0.001), NPLN (\geq 4: HR =1.212, 95% CI: 1.151–1.273; P=0.002), and LODDS (\geq -0.25: HR =1.378, 95% CI: 1.298–1.458; P<0.001). In contrast, primary site, grade, ICD-O-3 histology and behavior, Radiation sequence with surgery, regional nodes examined, surgery primary site, and LNR were not statistically significant. The results of the univariate and multivariate analyses are presented in *Table 2*.

The nomogram model for predicting OS

The nomogram (*Figure 1*) for predicting OS was constructed based on the following seven independent risk

Table 1 Baseline characteristics of the patients in the training and external validation cohorts

Variables	Training cohort		Validation cohort	
	N	%	N	%
Age (years)				
<60	1,302	25.4	68	58.1
≥60	3,830	74.6	49	41.9
Race				
White	4,165	81.2	N/A	
Black	504	9.8	N/A	
Other	463	9.0	N/A	
Marital status				
Single	651	12.7	N/A	
Married	3,137	61.1	N/A	
Other	1,344	26.2	N/A	
Sex				
Female	2,458	47.9	56	47.9
Male	2,674	52.1	61	52.1
Primary site				
Lower lobe	1,826	35.6	31	26.5
Middle lobe	256	5.0	8	6.8
Upper lobe	2,863	55.8	65	55.6
Overlapping lesion	114	2.2	7	6.0
Main bronchus	73	1.4	6	5.1
Grade				
Grade I	286	5.6	1	0.9
Grade II	2,336	45.5	27	23.1
Grade III	2,415	47.1	89	76.1
Grade IV	95	1.9	0	0
Laterality				
Left-origin of primary	2,392	46.6	53	45.3
Right-origin of primary	2,740	53.4	64	54.7
ICD-O-3 Histology and Behavior				
Squamous cell carcinoma	1,462	28.5	36	30.8
Adenocarcinoma	3,168	61.7	75	64.1
Adenosquamous carcinoma	199	3.9	4	3.4
Large-cell carcinoma	101	2.0	0	0
Others	124	2.4	2	1.7
Pathological T stage				
T1	1,261	24.6	53	45.3
T2	2,583	50.3	58	49.6
T3	981	19.1	3	2.6
T4	307	6.0	3	2.6

Table 1 (continued)

Table 1 (continued)

Variables	Training cohort		Validation cohort	
	N	%	N	%
Pathological N stage				
N1	2972	57.9	59	50.4
N2	2160	42.1	58	49.6
Primary surgical site				
Pneumonectomy	602	11.7	6	5.1
Lobectomy or extended bilobectomy	216	4.2	0	0
Lobectomy with mediastinal lymph node resection	3,478	67.8	96	82.1
Resection of lobe or bilobectomy	554	10.8	9	7.7
Excision of less than one lobe	282	5.5	6	5.1
Radiation sequence with surgery				
No radiation	3,856	75.1	96	82.1
Radiation after surgery	1,276	24.9	21	17.9
Chemotherapy				
No/unknown	1,586	30.9	64	54.7
Yes	3,546	69.1	53	45.3
NDLN				
<10	3,067	59.8	11	9.4
≥10	2,065	40.2	106	90.6
NPLN				
<4	3,824	74.5	71	60.7
≥4	1,308	25.5	46	39.3
LNR				
<0.26	3,223	62.8	84	71.8
≥0.26	1,909	37.2	33	28.2
LODDS				
<-0.25	3,704	72.2	99	84.6
≥-0.25	1,428	27.8	18	15.4

Grade I, well differentiated; grade II, moderately differentiated; grade III, poorly differentiated; grade IV, undifferentiated/anaplastic. ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; NDLN, number of dissected lymph nodes; NPLN, number of positive lymph nodes; LNR, lymph node ratio; LODDS, log odds of positive lymph nodes; N/A, not available.

Table 2 The results of univariate and multivariate analysis of factors for OS according to the SEER database

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)				
<60	Reference		Reference	
≥60	1.398 (1.264–1.546)	<0.001	1.341 (1.288–1.394)	<0.001
Race				
White	Reference		N/A	
Black	1.183 (1.017–1.375)	0.029	N/A	
Other	0.956 (0.781–1.169)	0.659	N/A	
Marital status				
Single	Reference		N/A	
Married	1.011 (0.879–1.163)	0.878	N/A	
Other	0.923 (0.839–1.016)	0.104	N/A	
Sex				
Female	Reference		Reference	
Male	0.732 (0.673–0.796)	<0.001	1.367 (1.323–1.411)	<0.001
Primary site				
Lower lobe	Reference		Reference	
Middle lobe	0.817 (0.576–1.157)	0.254	0.810 (0.702–0.918)	0.050
Upper lobe	0.623 (0.420–0.924)	0.019	0.948 (0.902–0.994)	0.248
Overlapping lesion	0.762 (0.539–1.076)	0.123	1.291 (1.157–1.425)	0.056
Main bronchus	1.142 (0.750–1.738)	0.535	1.107 (0.920–1.294)	0.587
Grade				
Grade I	Reference		Reference	
Grade II	0.744 (0.526–1.052)	0.095	1.022 (0.923–1.121)	0.828
Grade III	0.748 (0.553–1.011)	0.059	1.240 (1.140–1.340)	0.030
Grade IV	0.945 (0.699–1.277)	0.711	1.120 (0.932–1.308)	0.548
Laterality				
Left origin of primary site	Reference		N/A	
Right origin of primary site	0.967 (0.890–1.051)	0.435	N/A	
ICD-O-3 histology and behavior				
Squamous cell carcinoma	Reference		Reference	
Adenocarcinoma	1.028 (0.783–1.350)	0.844	0.934 (0.882–0.986)	0.186
Adenosquamous carcinoma	0.890 (0.681–1.163)	0.392	1.108 (0.999–1.217)	0.347
Large-cell carcinoma	0.914 (0.609–1.372)	0.665	1.439 (1.289–1.589)	0.015
Others	1.409 (0.973–2.041)	0.069	0.956 (0.815–1.097)	0.752

Table 2 (continued)

Table 2 (continued)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Pathological T stage				
T1		Reference		Reference
T2	0.538 (0.450–0.643)	<0.001	1.191 (1.134–1.248)	0.002
T3	0.665 (0.565–0.784)	<0.001	1.821 (1.755–1.887)	<0.001
T4	1.017 (0.854–1.211)	0.848	1.754 (1.712–1.848)	<0.001
Pathological N stage				
N1		Reference		Reference
N2	0.750 (0.691–0.815)	<0.001	1.293 (1.244–1.342)	<0.001
Primary surgical site				
Pneumonectomy		Reference		Reference
Lobectomy or extended bilobectomy	1.012 (0.824–1.243)	0.906	1.152 (1.039–1.265)	0.210
Lobectomy with mediastinal lymph node resection	1.164 (0.906–1.495)	0.236	0.929 (0.857–1.001)	0.306
Resection of lobe or bilobectomy	0.799 (0.668–0.955)	0.014	1.032 (0.939–1.125)	0.734
Excision of less than one lobe	0.897 (0.726–1.107)	0.309	0.963 (0.848–1.078)	0.743
Radiation sequence with surgery				
No radiation		Reference		Reference
Radiation after surgery	0.877 (0.799–0.963)	0.006	1.085 (1.031–1.139)	0.130
Chemotherapy				
No/unknown		Reference		Reference
Yes	1.528 (1.402–1.665)	<0.001	0.604 (0.557–0.651)	<0.001
NDLN				
<10	1.131 (1.041–1.230)	0.004		Reference
≥10		Reference	1.101 (1.049–1.153)	0.065
NPLN				
<4		Reference		Reference
≥4	1.447 (1.323–1.583)	<0.001	1.212 (1.151–1.273)	0.002
LNR				
<0.26		Reference		Reference
≥0.26	0.662 (0.609–0.719)	<0.001	1.057 (0.978–1.136)	0.477
LODDS				
<–0.25		Reference		Reference
≥–0.25	0.629 (0.577–0.686)	<0.001	1.378 (1.298–1.458)	<0.001

Grade I, well differentiated; grade II, moderately differentiated; grade III, poorly differentiated; grade IV, undifferentiated/anaplastic. OS, overall survival; SEER, Surveillance, Epidemiology, and End Results; HR, hazard ratio; CI, confidence interval; N/A, not available; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; NDLN, number of dissected lymph nodes; NPLN, number of positive lymph nodes; LNR, lymph node ratio; LODDS, log odds of positive lymph nodes.

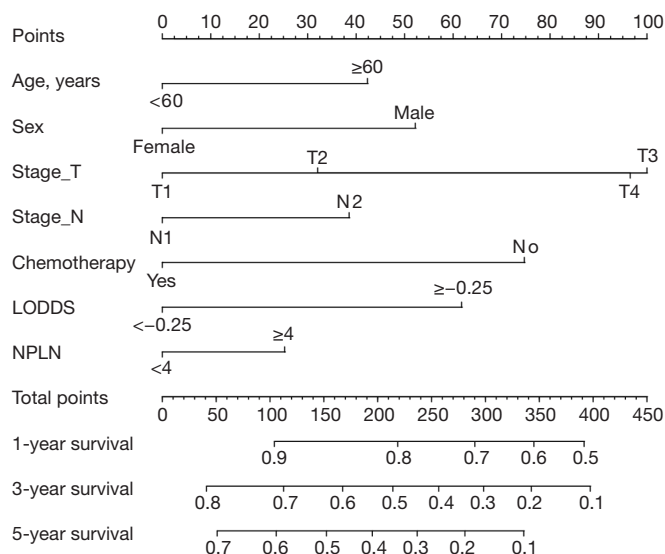


Figure 1 Prognostic nomograms for predicting 1-, 3-, and 5-year survival. LODDS, log odds of positive lymph nodes; NPLN, number of positive lymph nodes.

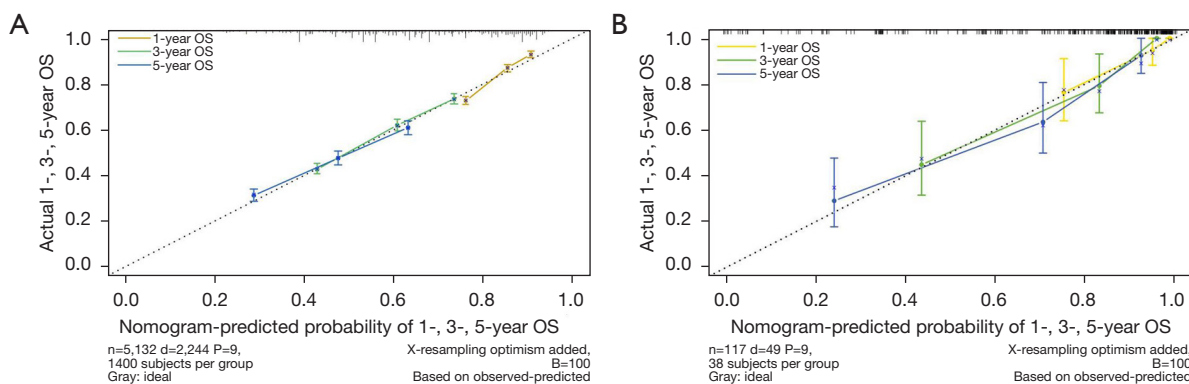


Figure 2 Calibration curves predicting the 1-, 3-, and 5-year OS of patients in the training cohort (A) and the external validation cohort (B). The X-axis and Y-axis indicate the predicted survival probability and actual survival probability, respectively. The black dotted gray line indicates the accordance of the prediction with the actual situation. OS, overall survival.

factors: age (<60 or ≥60 years), sex (male or female), T stage (T1, T2, T3, or T4), N stage (N1 or N2), chemotherapy (yes or no), LODDS (<-0.25 or ≥-0.25), and NPLN (<4 or ≥4). Each independent risk factor corresponded to a distinct score, and the total score compared to 1-, 3-, and 5-year OS.

Discrimination accuracy of the nomogram model

In the training and external validation cohorts, we found favorable consistency between the nomogram predictions

and the actual observed outcomes of the 1-, 3-, and 5-year OS according to the calibration curves (Figure 2). We evaluated the discrimination ability of the nomogram using C-index values, which were 0.648 (95% CI: 0.636–0.659) in the training cohort and 0.807 (95% CI: 0.751–0.863) in the external validation cohort. The AUCs generated by the 1-, 3-, and 5-year OS ROC curves were 0.7, 0.663, and 0.6476 in the training cohort, respectively, while the AUCs in the external validation cohort were 0.8, 0.834, and 0.84571, respectively (Figure 3).

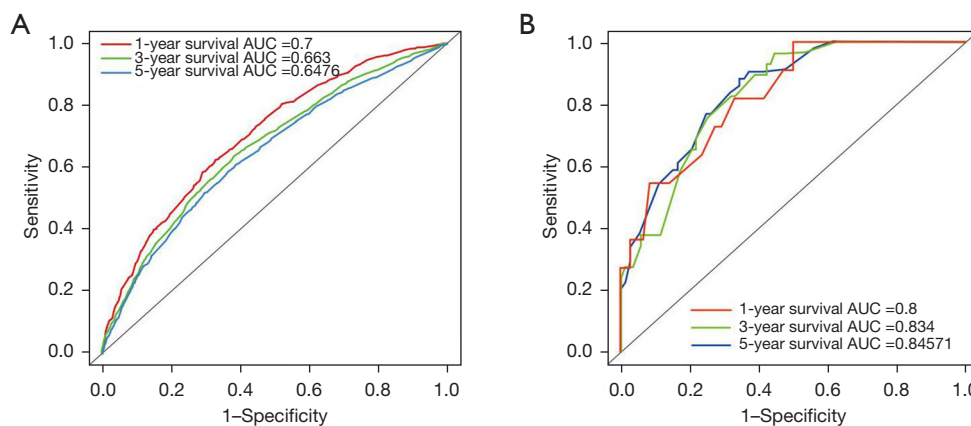


Figure 3 Prognostic accuracy of the nomogram represented via ROC curves and AUC values for survival at 1, 3, and 5 years in the training cohort (A) and the external validation cohort (B). AUC, area under the curve; ROC, receiver operating characteristic.

Table 3 Comparison of the predictive performance of overall survival between different nodal staging systems

Measures	LR test	C-index
Model 1 (N)	380.23	0.635
Model 2 (N + NPLN)	422.43	0.641
Model 3 (N + LODDS)	477.65	0.647
Model4 (N + NPLN + LODDS)	487.69	0.648

LR, likelihood ratio; C-index, concordance index; N, N stage; NPLN, number of positive lymph nodes; LODDS, log odds of positive lymph nodes.

Comparison of different nodal staging systems

The four different multivariable Cox regression models included model 1 (N stage), model 2 (N stage + NPLN), model 3 (N stage + LODDS), and model 4 (N stage + NPLN + LODDS). The predictive performance values were as follows: model 1, LR test 380.23 and C-index 0.635; model 2, LR test 422.43 and C-index 0.641; model 3, LR test 477.65 and C-index 0.647; and model 4, LR test 487.69 and C-index 0.648. Based on these results (Table 3), we selected model 4 to assess LNs.

OS of patients with different risk factors

As shown in Figure 4, we observed that those in the low-risk group, aged <60 years, female, with T stage 1, with N stage 1, with NPLN <4, with LODDS <-0.25, and treated with chemotherapy had a significantly longer OS. In our external validation cohort, T stage, NPLN, LODDS, and

chemotherapy also exhibited excellent discriminatory power in stratifying prognoses (Figure 5).

Discussion

According to the National Comprehensive Cancer Network (NCCN) guidelines, adjuvant chemotherapy is recommended for patients with stage II and IIIA NSCLC following radical surgery (9,10). For patients with stage IIIB resectable NSCLC, the recommended adjuvant therapy is chemotherapy or radiotherapy. Therefore, the necessity of radiotherapy remains controversial, and with accessibility to targeted therapy and immunotherapy, selecting a therapeutic strategy is also a challenge. Metastasis to ipsilateral peribronchial nodes, hilar nodes, or intrapulmonary nodes is considered to indicate pathological N stage 1; meanwhile, metastasis to ipsilateral mediastinal and/or subcarinal nodes is supposed to indicate pathological N stage 2 (11,12). The TNM system is a simple way to distinguish the LN situation of patients but is not a good predictor of prognosis. Hence, it is urgent to develop a new LN evaluation system. Complete LN dissection is not only associated with the quality of the surgery but also means achieving a sufficient number of resected positive LNs. The ratio-based LN evaluation systems of LODDS and LNR include NDLN and NPLN. To some extent, the LODDS can overcome the limitation of LNR because $LNR = NPLN/NDLN$ could be used to obtain the same result with different NPLN and NDLN values. Different NPLN values are consistently associated with different prognoses, and the resulting clinical decisions may also vary

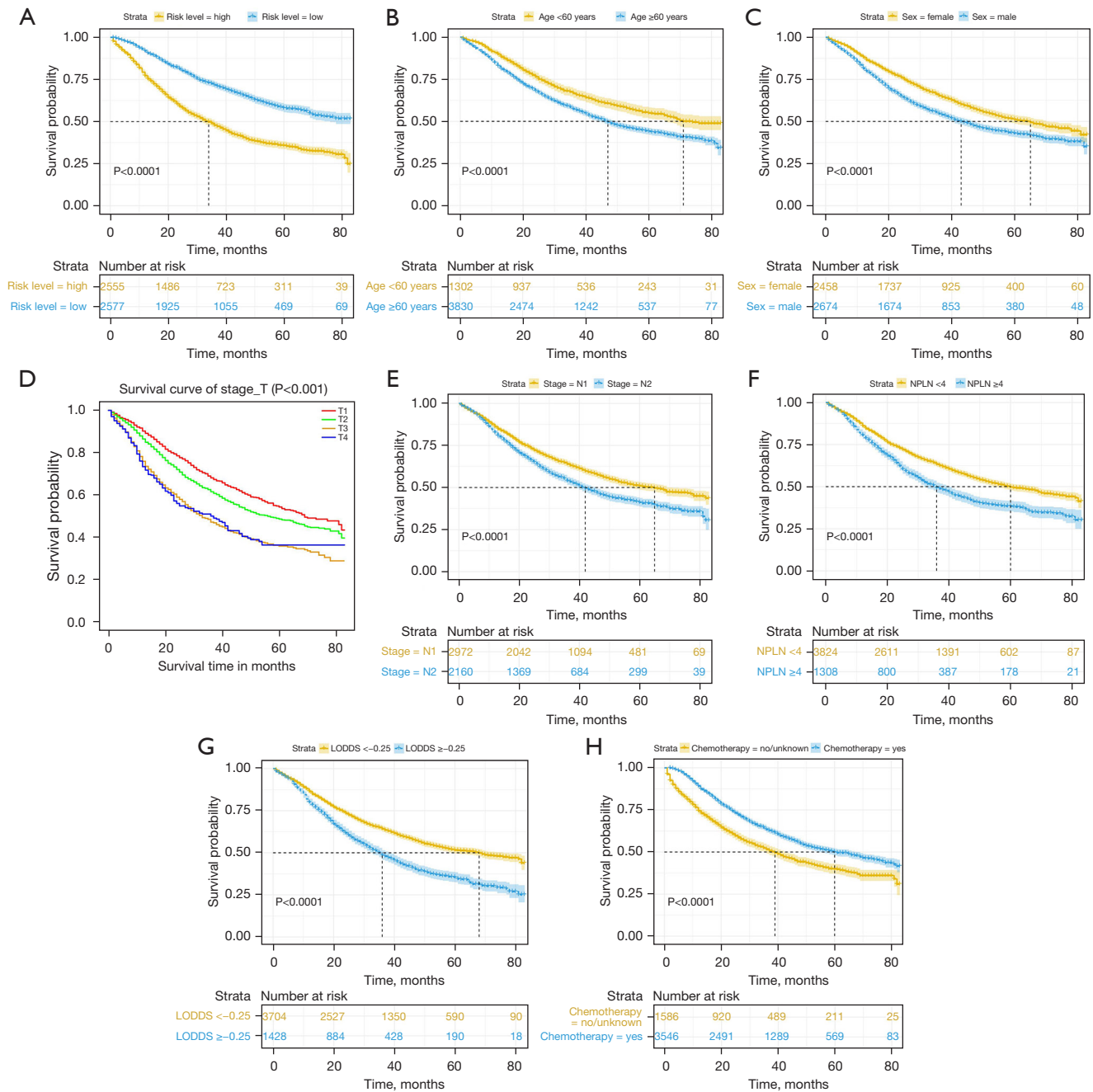


Figure 4 Kaplan-Meier estimates of overall survival for patients with N1/N2 NSCLC after surgery according to risk level (A), age (B), sex (C), T stage (D), N stage (E), NPLN (F), LODDS (G), and chemotherapy (H) in the training cohort. NPLN, number of positive lymph nodes; LODDS, log odds of positive lymph nodes; NSCLC, non-small cell lung cancer.

considerably.

In our study, the data of patients with N1 or N2 resectable NSCLC were obtained from the SEER database, and the external validation cohort data were collected from the Department of Thoracic Surgery, the

First Affiliated Hospital, Zhejiang University School of Medicine. The enrolled validation cohort had good universality and representativeness for Chinese patients with N1 or N2 resectable NSCLC. By performing univariate and multivariate analyses, we identified seven

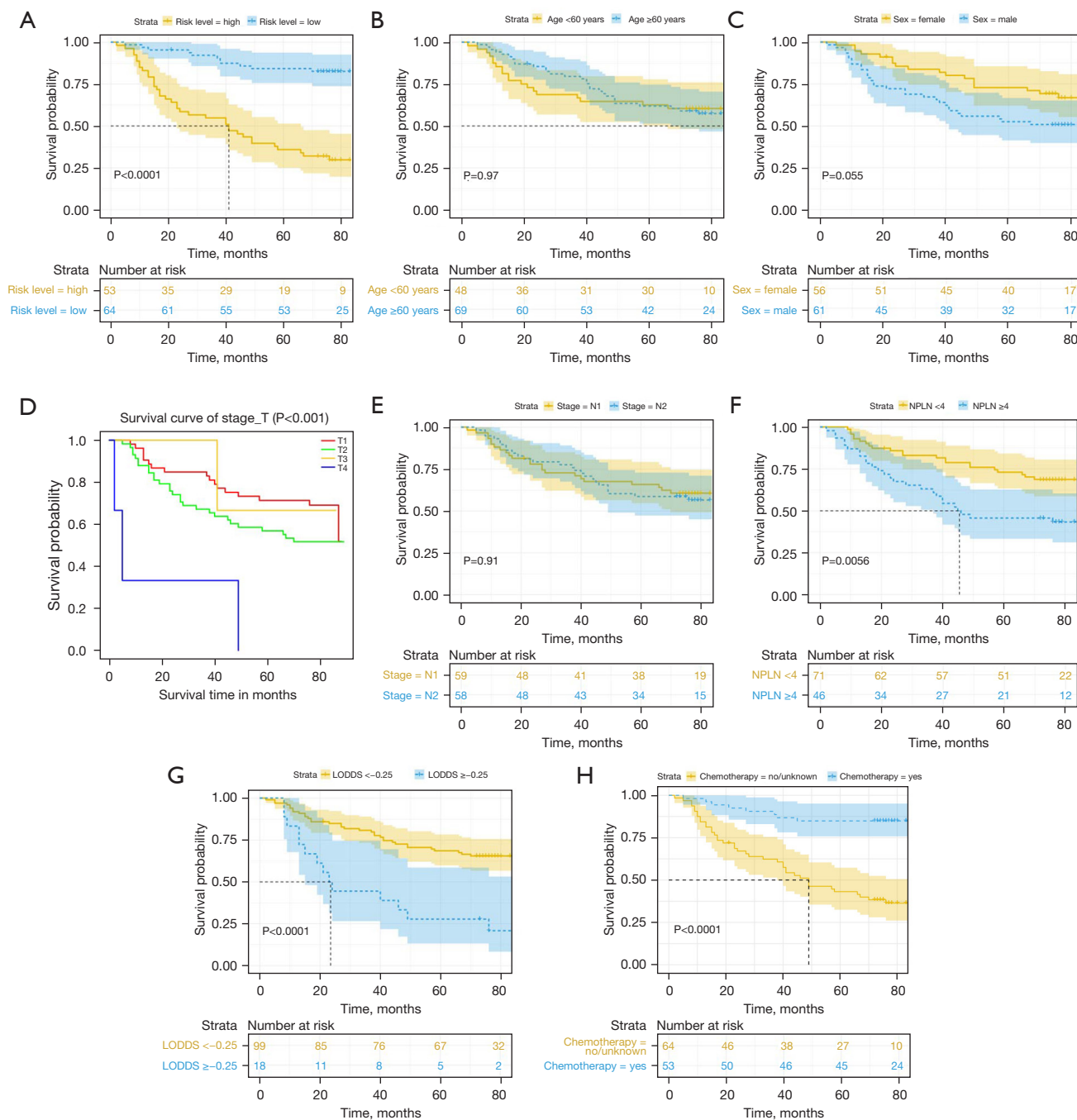


Figure 5 Kaplan-Meier estimates of overall survival for patients with N1/N2 NSCLC after surgery according to risk level (A), age (B), sex (C), T stage (D), N stage (E), NPLN (F), LODDS (G), and chemotherapy (H) in the validation cohort. NPLN, number of positive lymph nodes; LODDS, log odds of positive lymph nodes; NSCLC, non-small cell lung cancer.

independent risk factors, including age, sex, T stage, N stage, NPLN, LODDS, and chemotherapy. The cutoff values for classification were obtained via ROC curves. A recent study reported that skip N2 might be a favorable

factor for patients with N2 lung cancer (13). Therefore, these patients cannot simply be classified as stage N2. In lung adenocarcinoma, Wang *et al.* found that LNR showed a slightly better prediction performance than did LODDS (14).

At the same time, Yu *et al.* demonstrated that LODDS had a better predictive performance among patients with node-positive lung squamous cell carcinoma after surgery than N, NPLN, and LNR (15). In other tumors, Cao *et al.* reported that among patients undergoing resection of esophageal cancer, LODDS predicted survival more accurately than did either LNM or LNR (16). Another study reported that the NPLN was superior to LNR and LODDS for predicting the prognosis of pancreatic neuroendocrine neoplasms (17). LODDS has also been applied to predict the survival of patients with NSCLC receiving neoadjuvant therapy (18).

In our study, although LNR showed statistical significance in the univariate analysis, it was not significant in the multivariate analysis, with a P value of 0.274. Therefore, LNR was not included in our nomogram model. As shown in *Table 2*, model 4, including N stage, NPLN, and LODDS, exhibited the most powerful prognostic predictive ability. According to this model, patients with a higher age, a higher T or N stage, no chemotherapy, more NPLNs, and a larger LODDS had worse OS. Thus, according to this model, we suggest more aggressive therapeutic strategies and close follow-up for patients with lower scores. The novel survival nomogram model we built combining N stage, NPLN, and LODDS could better predict postoperative long-term OS for patients with N1 or N2 NSCLC. Previous articles have compared the predictive power and accuracy of N stage, LNR, and LODDS (19,20). We incorporated N stage, NPLN, LODDS, and chemotherapy into a prognostic model. In a sense, we altered the traditional evaluation of TNM classification, and by taking full advantage of the pathological information retrieved from surgery, we could develop better adjuvant treatment strategies. The role of postoperative radiotherapy (PORT) in patients with completely resected NSCLC remains debatable. From the univariate Cox analysis results, we did not discover survival benefits consistent with those reported in previous studies (21,22). Chien *et al.* reported that PORT prolongs disease-free survival (DFS) and OS in selected patients, such as those with epidermal growth factor receptor (*EGFR*) mutation. Still, the sample size was only 82 patients (23). Hui *et al.* demonstrated that in patients with pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy, PORT did not improve DFS (24). According to a meta-analysis, PORT should not be considered routine treatment of patients with completely resected NSCLC (25). The Lung ART trial found that PORT was not associated with a better DFS than no PORT (26).

There are some limitations to our study. First, selection

bias was unavoidable due to the retrospective nature of the study design. Second, some essential detailed data were missing, such as visceral pleural invasion, lymphovascular invasion, nerve invasion, bronchogenic spread, cancer thrombus occurrence, types of gene mutations, targeted therapy, and the usage of immune checkpoint inhibitors. These missing data might be important for predicting the prognosis of patients with NSCLC. The SEER database has some limits that it lacks any details about chemotherapeutic regimens and details about recurrence [DFS and progression-free survival (PFS)]. DFS and PFS were other significant parameters related to patients' adjuvant therapy and quality of life.

There were some strengths to our study as well. Our study included the LODDS system and further compared it with NPLN and LNR. We confirmed the superiority of LODDS in evaluating the survival prognosis of patients with N1 or N2 NSCLC. LODDS was also applied in the construction of the nomogram model. This study was based on large-scale population data from the SEER database that were used to establish a nomogram model, and the reliability of our nomogram model was validated through internal and external samples. Moreover, our model could accurately predict the OS due to the adequate follow-up time and comparatively complete survival data, which provided sufficient power to assess the nomogram model.

Conclusions

Our novel survival nomogram model confirmed the prognostic value of LODDS for predicting long-term OS in patients with N1 or N2 NSCLC after undergoing surgical intervention. In addition, the LODDS system might have better prognostic effectiveness than the AJCC N classification or the NPLN and LNR systems. Adjuvant chemotherapy confers a significant survival benefit for patients with N1 or N2 NSCLC. In terms of radiation therapy, we did not find that it provided any survival benefits. Thus, we believe that radiotherapy might not be necessary for those with N1 or N2 resectable NSCLC. Radiotherapy might be advantageous in patients with unresectable NSCLC lesions. The treatment strategy of targeted drugs and immune checkpoint inhibitors as neoadjuvant therapy is becoming more mainstream. Therefore, matching strategy in patients considering surgery is emerging as an important issue. Prospective studies are needed in the future to identify the optimal therapeutic regimen.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at <https://tclr.amegroups.com/article/view/10.21037/tlcr-24-119/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tclr.amegroups.com/article/view/10.21037/tlcr-24-119/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (No. 2023-0012) and individual consent for this retrospective analysis was waived.

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