Development and Validation of a Novel Nomogram to Predict Lymph Node Involvement in T1 Stage Lung Adenocarcinoma.

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Research article

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Abstract

A total of 326 patients with T1 lung adenocarcinoma from March 2012 to April 2016 in our center were included. The relationship between LNI and different risk factors were accessed by univariate and multivariate logistic regression analyses. Four significant risk factors identified by multivariate logistic regression were tumor diameter (OR = 2.175, 95%CI:1.277–3.072, p = 0.0045), lymph node swelling exist preoperative (OR = 6.144, 95%CI:6.947–14.059, p = 0.003), platelet to lymphocyte ratio (OR = 3.149, 95%CI:1.546–6.673, p = 0.003), CEA (OR = 4.375, 95%CI: 2.613–7.537, p = 0.00694). A nomogram was constructed by combing risk factors and validated with an internal set. The C-index of this nomogram was 0.875, which was validated by bootstrap method. At last we concluded that the novel nomogram showed the potential value of LNI prediction for lung adenocarcinoma.

Background:

Lung cancer is still the predominant cause of cancer-associated deaths around the world, accounting for nearly 228,820 new cases and 135,720 deaths according to the global cancer statistics published in 2020[1]. Lung adenocarcinoma is the most common pathological type of lung cancer and the incidence of lung adenocarcinoma has risen steadily over the past decades[2]. More than 70% of resected cases are finally diagnosed as lung adenocarcinoma every year[3]. Lung adenocarcinoma has been confirmed to have a high risk of lymph node invasion[4], so that the lymph node dissection play an important role in the surgical treatment. Lung lobectomy and systemic lymph node dissection is still the standard procedure for early lung cancer[5], however, the scope of lymph node dissection especially for lung cancer under T1 is still controversial. Recently, an increasing number of early stage lung cancers were detected by radiology examination, the accurate prediction of lymph node involvement (LNI) before surgery became crucial. Although radiology technology and radiology with artificial intelligence development these years have made great advances in distinguishing the lymph node invasion from lymph node swelling[6], it is of great benefit to establish a brief and direct tool to predict the probability of LNI preoperative. Therefore, we developed and validated a novel nomogram that included laboratory blood examinations, radiology results and pathological findings during the operation. We believe that this nomogram could be applied into the clinical decision-making for the surgical treatment in lung adenocarcinoma.

Patients And Methods:

Patients:

A total of 326 lung adenocarcinoma patients without distal metastasis admitted to our center from March 2012 to April 2016 were enrolled. All patients have sighed the written consent forms. The study was approved by the Institutional Ethics Board of Henan Provincial People's Hospital. The inclusion criteria were adenocarcinoma subtype of non-small cell lung cancer(NSCLC), tumor size less than 3 cm, no distal metastasis detected by PET/CT scan and have not been diagnosed with other cancer. The

exclusion criteria were clinical information incomplete, non-primary tumor, have adopted chemical or radiation therapy before surgery and no systematic lymph node dissection performed.

The preoperative evaluations included physical examination, chest CT, PET/CT, blood routine test, blood biochemistry test and relative tumor makers test less than 1 week prior to surgery. The tumor diameter was defined as the longest diameter through the tumor. LNI was defined as more than 1 lymph node positive were detected in the postoperative histopathological test. The CT results were assessed by two dependent radiologists. All patients underwent lobectomy with systematic lymphadenectomy or lymph nodes sampling.

Methods:

The result were presented as mean and STD for continuous variables and n and percent for categorical variables. Student t test or chi square test were conducted to compare the data between two sets. In order to identify the potential risk factors to build the nomogram, univariate logistic regression analysis and multivariate logistic regression analysis were conducted stepwise. In the univariate logistic regression analysis, the pathological result of lymph node examination was taken as dependent variable and all the preoperative information were regarded as independent variables. These independent variables were patient age, gender, body mass index (BMI), tumor position, tumor diameter, weather the lymph node swelling exist, lymphocyte to monocyte count (LMR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lactate dehydrogenase (LDH), SCC (squamous cell carcinoma) antigen carcino-embryonic antigen (CEA), neurone specific enolase (NSE) and CA125. To simplify the clinical practice, all the continuous variables were changed to ordered categorial variables. 3.0 was considered as the cut-off value for LMR and NLR, while 132 was set as the cut-off value of PLR. The cut-off value of SCC antigen, CEA, NSE, CA125 was 1.5 μg/L, 5.0 ng/ml, 16.8 ng/ml and 35.0 μ/ml. After univariate logistic regression analysis, potential risk factors were imported into multivariate regression analysis to establish the prediction model. OR and p-value was calculated and 95% confidence interval was selected. The nomogram were developed with the final risk factors. Each risk factors were assigned a model value according to its contribution to the LNI probability. Then the nomogram was validated internally and C-index of the nomogram was evaluated. All statistical analyses were performed in the R software environment (3.6.3 version; http://r-project.org/) and $p < 0.05$ was considered significant in all statistical analyses.

Results:

The clinical characteristics of the patients were showed in Table 1. Among the 326 patients, 21.78% (71/326) were found have more than one lymph node involved (LNI), and 78.22%(255/326) were confirmed have no lymph node involved (nLNI). The Mean ± STD age of the patients was 53.58 ± 13.17 years and the lymph node involvement group was a little older than lymph node negative group ($p = 0.0191$). The Mean ± STD of tumor diameter was 2.01 ± 0.78 and the LNI group was larger than nLNI group. About 41.1% cases were right upper lobe tumor. 73.24% patients in LNI group have lymph node

swelling detected by CT before surgery. LMR, PLT, LDH, CEA and CA125 showed significant different between these two groups.

Table 1
Demographic and clinical information

Factors	All patients	LNI group	no-LNI group	p value
Age	53.58 ± 13.17	54.34 ± 15.04	53.36 ± 12.62	0.0191
Gender: female/male	150/176 (46.01%/53.99%)	27/44 (38.03%/61.97%)	123/132 (48.23%/51.76%)	0.1277
BMI	24.8 ± 3.46	24.1 ± 3.61	24.99 ± 3.4	0.0562
History of smoking	110(33.74%)	28(39.44%)	82(32.16%)	0.2526
Position	82(25.15%)	20(28.17%)	62(24.31%)	0.6758
left upper	44(13.50%)	7(9.86%)	37(14.51%)	
left lower	134(41.10%)	26(36.62%)	107(41.96%)	
right upper	31(9.51%)	8(11.27%)	23(9.02%)	
right middle	34(10.43%)	10(14.08%)	25(9.80%)	
right lower				
Diameter	2.01 ± 0.78	2.23 ± 0.56	1.75 ± 0.43	< 0.0001
Lymph node swelling	72(22.09%)	52 (73.24%)	20(7.84%)	< 0.0001
LMR	4.49 ± 2.36	3.72 ± 1.82	4.71 ± 2.45	0.0027
NLR	2.64 ± 0.56	2.58 ± 0.7	2.65 ± 0.52	0.3230
PLR	137.28 ± 41.91	150.02 ± 40.23	133.73 ± 41.76	0.0036
LDH	167.51 ± 130.66	202.59 ± 250.08	157.75 ± 64.56	0.0103
SCC	0.98 ± 0.25	1.02 ± 0.19	0.97 ± 0.27	0.1255
CEA	3.32 ± 3.14	4.52 ± 6.41	3 ± 0.95	< 0.0001
NSE	16.3 ± 6.35	16.15 ± 6.79	16.34 ± 6.23	0.9209
CA125	22.2 ± 13.45	43.52 ± 13.99	16.27 ± 3.88	< 0.0001

After univariate logistic regression analysis (Table 2), tumor diameter, lymph node swelling exist, LMR, PLR, CEA show potential predictive value with ORs and 95% CI were 1.948(1.496–2.571), 12.158(6.401–

16.267), 0.785(0.671–0.906), 0.955(0.556–1.624), 11.871(6.425–22.492), respectively. To further screen the risk factors, multivariate logistic regression analysis revealed that tumor diameter, lymph node swelling, PLR and CEA were independent factors (Table 3). The ORs and 95%CI were: 2.175(1.277–3.072), 6.144(3.947–14.059), 3.149(1.546–6.673), 4.375(2.613–7.537) respectively. Then the four factors were selected to build the final nomogram. The nomogram was presented in Fig. 1. We can obtain the LNI probability by locating the patient's different parameter on each axis, drawing a vertical line to the "Points", calculating the sum of points to have the "Total points" and the LNI probability was just under that. We validated and calculated the nomogram with bootstrap method (1000 times)(Fig. 2).

Table 2
The results of univariate logistic regression analysis

Factor	OR(95%CI)	p value
Age	1.006(0.986–1.027)	0.581
Gender	1.519(0.891–2.625)	0.128
BMI	1.231(0.745–2.032)	0.416
History of smoking	0.728(0.424–1.262)	0.252
Position	0.955(0.769–1.182)	0.675
Diameter	1.948(1.496–2.571)	1.28E-06
Lymph node swelling	12.158(6.401–16.267)	2E-08
LMR	0.785(0.671–0.906)	0.00156
NLR	0.756(0.411–1.246)	0.324
PLR	0.955(0.556–1.624)	0.0324
LDH	1.003(1.001–1.007)	0.0704
SCC	1.976(0.765–5.157)	0.143
CEA	11.871(6.425–22.492)	8.38E-15
NSE	0.974(0.575–1.650)	0.921
CA125	1.460(0.860–2.505)	0.164

Table 3
The results of multivariate logistic regression analysis

Factor	OR(95%CI)	P value
Diameter	2.175(1.277–3.072)	0.0045
Lymph node swelling	6.144(3.947–14.059)	0.003
PLT	3.149(1.546–6.673)	0.002
CEA	4.375(2.613–7.537)	0.00694

Discussion:

Lymph nodes and vessels are important spread way of lung adenocarcinoma metastasis. In clinical, systemic lymph node dissection is still dominant in lung adenocarcinoma surgery to clarify the tumor stage and predict the prognosis[7]. However, the scope of lymph node dissection is controversial, especially for early stage lung cancer[8–10]. Although imageology have a great improvement in these days, lymph nodes status could be evaluated by PET/CT, there still some cases would be found LNI unexpectedly after surgery. What's more, to perform the systematic lymph node dissection in all early stage cases would increase complications and damage health tissue. Recently, many lymph node dissection methods have been recommended, like selective lymph node dissection, lpbespecific lymph node dissection, lymph node sampling. For the early stage NSCLC patients, the methods of lymph node dissection seemed not imfluence the disease free survival and overall survival[11,12]. Considering this, to develop a prediction tool to improve the accurate of LNI evaluation is meaningful.

In 2016, Yu et al identified 2268 operable lung adenocarcinoma patients with tumor size less than 3 cm to clarify the risk factors for lymph node involvement and they found that the subtype of lung adenocarcinoma played the most important roles[13]. In 2017, Haruki et al have retrospectively reviewed 225 lung adenocarcinoma patients to demonstrate the clinicopathological characteristics for lung adenocarcinoma with unexpected lymph node metastasis[14]. They found younger age, left side tumor, larger tumor size and micropapillary component were significant associated with LNI by multivariate analysis. However, some of these factors reported in these articles could not be obtained preoperative which restricted the application the model. Lye et al reported the result of FDG PET/CT in predicting lymph node metastasis for T1a lung adenocarcinoma. The the sensitivity and specificity for predicting occult lymph node metastasis were 90.0% and 61.7%, with the C-index was 0.761[15].. Zhao et al constructed a 3D deep learning model for accurate lymph node metastasis prediction in T1 lung adenocarcinoma[16]. They enrolled 501 patients and trained with 401 cases among them. The model achieved an C-index of 0.926, which was impressive high and seemed to have a bright future. But the methods required doctors have the knowledge of computer radiomics which could not be put into use in short time.

In this study, we developed a novel nomogram that could predict the risk of having the lymph node involvement based on 326 patients' clinicopathological parameter. Finally four routine preoperative factors were included: tumor diameter, the presence of lymph node swelling, PLR and CEA. Multivariate logistic regression analysis help us selected the strongest factors and simplify the model as much as we can. The finally discriminative ability of this nomogram was examined and the 0.875 as C-index was high than former simple model. Tumor diameter could influence the LNI probability was accordance with our knowledge before. Wu et al revealed that tumor size parameters based on CT scan were significantly correlated with tumor invasiveness, and the evaluation of m-CT value was most useful musurement in predicting more invasive lung cancer[17]. Role of preoperative CT scan still is the most common method to stage the NSCLC, even the radiomics have acquired more and more importance. Platelets has been recognized as an increasingly functional factors in the pathogenesis of different cancer[18]. PLR was a parameter depends on platelet and lymphocyte counts, is a representative index of systemic inflammation. Its prognostic and prediction value in many types of malignance have been demonstrated[19–21]. The potential prognostic role of PLR in lung adenocarcinoma have also been revealed[22,23]. CEA is a classic oncofetal protein attached to epithelial-cell apical membrane via its c-terminal glycosylphosphatidylinositolanchor[24]. High CEA level was also reported have association with NSCLC[25,26]. High CEA always indict a bad prognostic. In a retrospective study conducted by Wang et al, they found that CEA and PLR were independent risk factors for brain metastasis of lung adenocarcinoma and could be used as predictors for brain metastasis predictability[27].However, in a prospective study conducted by Reinmuth et al, CEA showed no prognostic impart for NSCLC[28]. In our study,

The limitations of this study included its retrospective and single center design. Although we have collected 326 cases, the sample size was still too small. Lack of the information of tumor subtype is another weakness as biopsy preoperative is quite rare and we could not accurate diagnose this without pathology. So as pleural and duct invasion and other pathological feathers.

As far as we know, this is first nomogram for predicting the lymph node metastasis in lung adenocarcinoma with preoperative information. We hope this model could be used and validated by other medical centers around the world.

Conclusion

Tumor diameter, whether lymph node swelling exist, PLT and CEA level were independent risk factors for LNI in lung adenocarcinoma. The C-index of the nomogram was 0.875 and have been validated internally.

Declarations

Conflict of Interest Statement

All authors have declared no conflicts of interest.

Acknowledgement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Methodology: Quan Zhang,Zeheng Ma

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Resources Jiwei Li

Software: Jianjun Wang, Jiwei Li

Supervision:Li Wei

Validation: Li Wei

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Writing – review & editing: Li Wei

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Figures

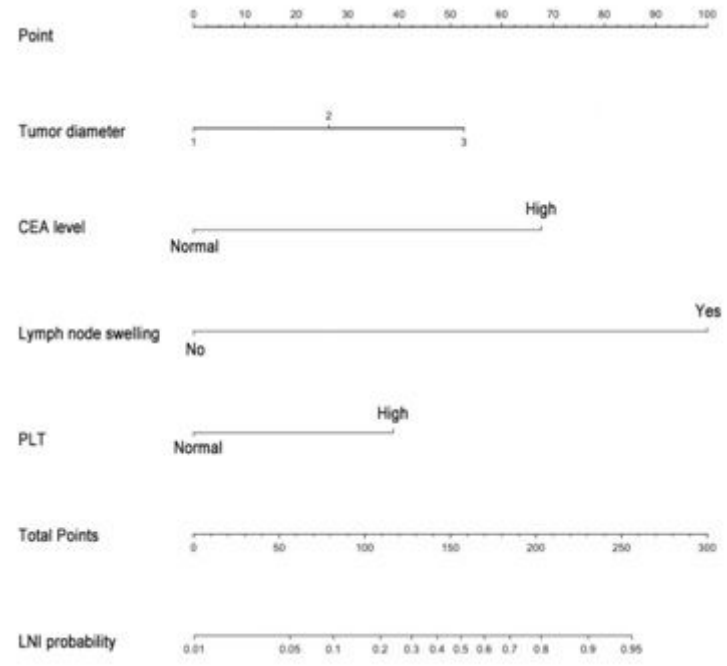

Figure 1

The LNI probability prediction nomogram

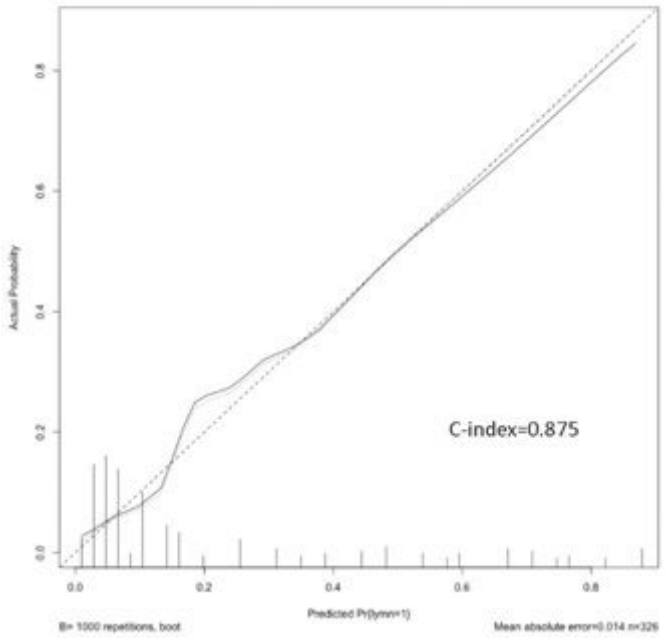

Figure 2

Calibration plot of the predicted and actual probabilities.