



Nomogram Based on Preoperative Absolute Lymphocyte Count to Predict Local Recurrence in Patients with Non-Small Cell Lung Cancer After Microwave Ablation

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Purpose: This study aims to investigate the prognostic value of preoperative absolute lymphocyte count (preALC) for non-small cell lung cancer (NSCLC) after microwave ablation (MWA) and build a combined nomograph with clinical features to predict the local recurrence.

Patients and Methods: A total of 118 NSCLC patients who underwent microwave ablation were enrolled in this study. The median local recurrence-free survival (LRFS) was 35.5 months. Independent prognostic factors obtained by multivariate analysis were included in the prediction model. The prognostic value of the model was assessed by the area under the time-dependent receiver operating characteristic curve (T-AUC).

Results: Histological subtype and preALC were independent risk factors for local relapse-free survival. According to the time-dependent receiver operating characteristic curve (T-ROC), the optimal cut-off value of preALC was $1.965 \times 10^9/L$, the sensitivity was 0.837, and the specificity was 0.594. The area under the T-ROC curve (AUC) of preALC was 0.703. To establish a nomogram to predict the local recurrence rate of NSCLC after MWA based on the prognostic factors revealed by Cox regression.

Conclusion: Preoperative lymphocyte count reduction is associated with poor prognosis of NSCLC. The nomogram model combined with preALC can provide a good individualized prediction of local recurrence after microwave ablation.

Keywords: non-small cell lung cancer, microwave ablation, nomogram, preoperative absolute lymphocyte count

Introduction

Lung cancer is the most common cause of cancer mortality globally.¹ Surgical resection is the standard treatment for patients with early NSCLC.² However, it is estimated that 25% of patients with non-small cell lung cancer (NSCLC) are not suitable for curative resection because of medical comorbidities,³ who need an alternative local treatment, such as stereotactic body radiation therapy (SBRT), radiofrequency ablation (RFA), or microwave ablation (MWA). MWA with higher convection and lower heat deposition effect in the lung can maximize the preservation of normal lung tissue,⁴ which is suitable for patients with chronic obstructive pulmonary disease and pulmonary fibrosis.⁵ Prediction of early local recurrence after MWA is very important to improve the prognosis of NSCLC patients. The latest guidelines recommend using a 1 cm frosted glass shadow around the lesion after thermal ablation to determine whether the lesion is

completely ablated.⁶ However, this subjective evaluation method is difficult to make a consistent result due to the impact of bleeding or exudation.

The occurrence and development of inflammation played an important role in determining the clinical course and outcome in some solid malignancies and could be used to predict the prognosis of patients with a variety of malignant tumors.^{7,8} Lymphocytes are the main immune cell and play an important role in host anticancer defense mechanisms.⁹ Preoperative lymphocytopenia was associated with poor prognosis.^{10–12} Absolute lymphocyte count (ALC) had been used to evaluate the prognosis of lung cancer.^{13–15} However, these studies investigated the evaluation of ALC in lung cancer patients who underwent resection¹⁵ or chemoradiotherapy.^{13,14} In addition, numerous studies in recent years have demonstrated that tumor ablation can induce anti-tumor immune responses, primarily by causing tumor cell necrosis, further antigen release, and then antigen presenting cells (APC) to present tumor antigens to effector cells that migrate to other parts of the disease and enhance the immune response.¹⁶ This may also be a factor in the influence of pre-ablation lymphocyte count on the recurrence of lung cancer after ablation. As far as we know, there are no study to evaluate the prognostic value of preoperative absolute lymphocyte count (preALC) in lung cancer with MWA therapy.

The study was to explore the predictive value of preALC for local recurrence of lung cancer after MWA and establish a combined nomograph prediction model with clinical information to predict the local recurrence of NSCLC after microwave ablation (MWA) therapy.

Method

Patient Selection

This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Biomedical Research Ethic Committee of Shandong Provincial Hospital (ethics number: 2022–582), informed consent was waived due to the retrospective nature of this study. All personal identification data were anonymized and deidentified before analysis. We retrospectively analyzed 404 patients with confirmed or suspected lung cancer who were treated with MWA in our hospital from January 2010 to June 2018. The patients were screened according to the inclusion and exclusion criteria. The inclusion criteria were as follows: (1) pathological diagnosis as primary non-small cell lung cancer; (2) chest CT scan were performed before MWA within 1 week, and the cTNM stage was classified as T1~2N0M0 based on CT/MRI imaging; (3) no anticancer therapy before MWA treatment; (4) hematology examination was evaluated within 1 week before MWA (including lymphocytes, white blood cells, neutrophils, monocytes and so on); (5) no infection during peripheral blood collection. The exclusion criteria were as follows: (1) pathological diagnosis: small cell lung cancer or other carcinoma; (2) concomitant other malignancy before MWA; (3) lymph node metastases or distant metastases were present in CT/MRI imaging; (4) incomplete clinical pathological data; (4) patients lost information on follow-up (Figure 1).

Imaging Analysis

NSCLC tumor staging was determined by the clinical TNM staging system of the International Union for Cancer Control (8th edition).¹⁷ All NSCLC patients underwent chest CT (Discovery, GE Healthcare, Chicago, IL) prior to MWA surgery, and all CT imaging was reviewed by two radiologists with more than 5 years of experience in chest radiology to assess tumor location, size, density, presence of lymph nodes, and distant metastases. All laboratory tests were performed within one week prior to MWA.

Patient's Follow Up

Patients with NSCLC were reexamined with chest enhanced CT 4–6 weeks after MWA and considered as baseline. The follow-up strategy: every 3 months within 2 years and every 6 months after 2 years by chest CT. The primary endpoint was local recurrence-free survival (LRFS), which was defined as the time from MWA surgery to the first occurrence of LR or patient death. When there had no follow-up information on the date of last follow-up, it was considered as lost follow-up. However, lost follow-up patients who met the 1-, 2-, and 3-year LRFS follow-up criteria were included in the study to increase sample size and improve the study results. Local response was assessed by the modified response evaluation criteria in solid tumors (mRECIST 1.1).¹⁸

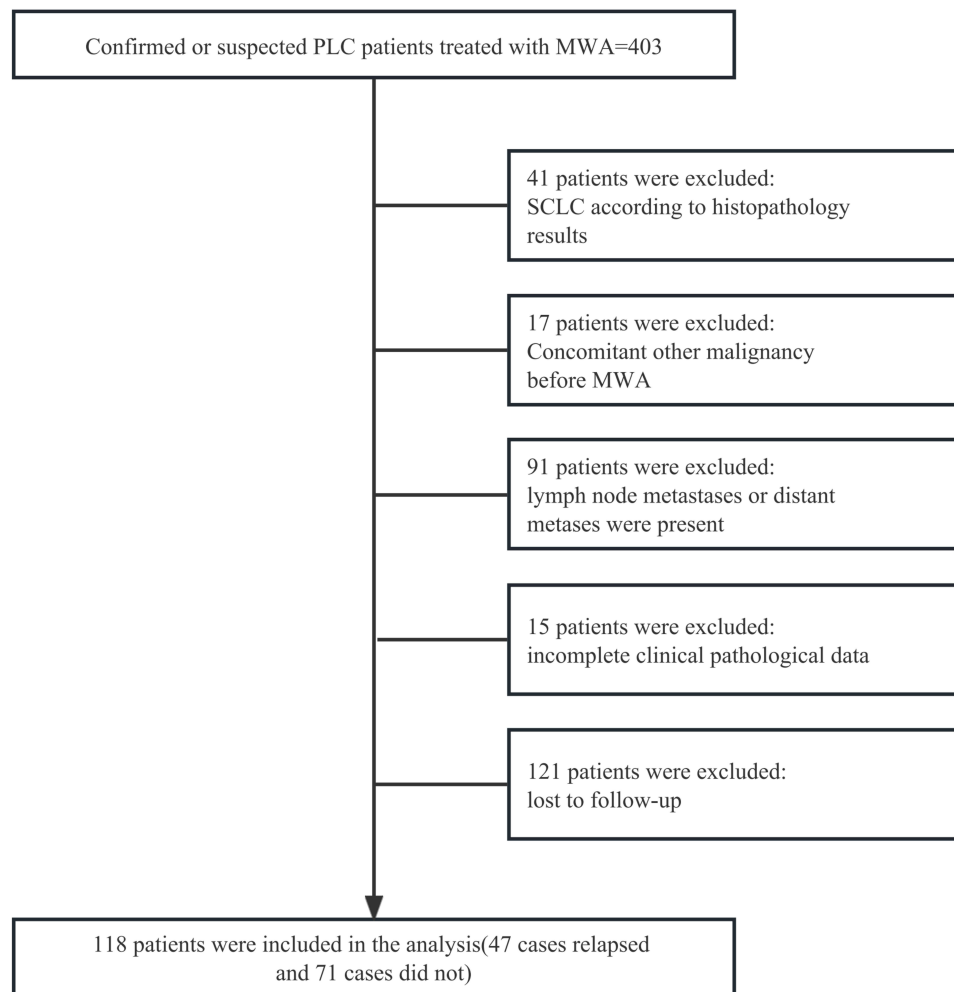


Figure 1 Patient selection flowchart.

Abbreviations: PLC, primary lung cancer; MWA, microwave ablation; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

MWA Procedure

All MWA procedures were performed by two radiologists with more than 5 years of experience in CT-guided interventional procedures. The microwave system used (Nanjing Eigao Microwave Research Institute, Nanjing, China) consists of a microwave generator and a hollow water-cooled shaft antenna, a flexible coaxial cable and a microwave generator. The operating frequency is 2450 ± 50 MHz, the maximum output power is 70W. In this study, 18G (diameter) \times 180 mm (effective length) water-cooled microwave needle was used to puncture tumors under CT guidance. Preoperative CT was performed to inform the treatment plan, determine the appropriate body position, puncture site location, optimal puncture trajectory, and number of MWA needles. The patient was placed in the supine or oblique position depending on the tumor location. 0.2 g of 2% lidocaine and 37.5 mg bupivacaine were diluted to 50 mL with normal saline, and appropriate amounts were taken for local infiltration anesthesia. The needle was introduced to the planned site, and the location was confirmed by CT. Subsequently, tumor MWA was performed, and the power and duration were adjusted as needed. The procedure was terminated when the ablation zone presented a 5–10 mm edge beyond the lesion boundary. A chest CT scan was performed immediately after ablation to assess the ablation area and detect possible complications. Simultaneous coaxial cannula biopsy was performed in all patients.

Statistical Analysis

The optimal cutoff values for preALC were calculated based on the maximum Youden index (sensitivity+specificity-1) point on the time-dependent receiver operating characteristic curve (t-ROC) for the prediction of LRFS. Survival curves

were plotted using Kaplan-Meier method and compared using logarithmic rank test. Cox's regression model was used for univariable and multivariable analyses. In the univariate analysis, P values <0.05 was entered into the multivariate Cox regression analysis as a candidate variable. The nomogram was constructed according to the result of the univariate and multivariate analysis. The concordance index (C-index) was applied to measure the discrimination of the model. The identification ability of the model was evaluated by calculating the area under the curve (AUC). Decision curve analysis (DCA) was used to assess the net benefit and clinical performance of the nomogram. The IBM SPSS version 26.0 software (IBM Corp.) and R software version 4.2.1 will be utilized for statistical analyses. All tests of significance were two-tailed, and P values <0.05 were taken to indicate significant differences.

Results

Baseline Characteristics

A total of 118 NSCLC patients (69 males and 49 females) were enrolled, of which 47 patients showed local recurrence and 71 patients did not show local recurrence, with an overall local recurrence rate of 39.8% and the median LRFS was 35.5 months. 94 patients (79.7%) had adenocarcinoma; 52 patients (44.1%) had smoking history; 13 patients (11.0%) had preoperative CEA ≥ 10 ng/mL. Detailed baseline characteristics are shown in Table 1.

The Cutoff Values of Absolute Lymphocyte Count (preALC)

According to the t-ROC curve, the optimal cutoff values of the preALC were $1.965 \times 10^9/L$, with sensitivity of 0.837 and specificity of 0.594, respectively (Figure 2). The AUCs of the t-ROC curves for the preALC were 0.703. Survival analysis indicated that the difference in LRFS between the high and low preALC groups was statistically significant (Figure 3).

Table 1 Baseline Characteristics of the 118 Patients in This Study

Variable	Cohort (n = 118)
Gender (male)	69 (58.5%)
Age (>60 years)	91 (77.2%)
Histological subtype	
ACC	94 (79.7%)
SCC	24 (20.3%)
COPD (present)	36 (30.5%)
Tumor location	
The left lung upper lobe	33 (28.0%)
The left lung lower lobe	23 (19.5%)
The right lung upper lobe	33 (28.0%)
The right lung middle lobes	7 (5.9%)
The right lung lower lobe	22 (18.6%)
CEA (≥ 10 ng/mL)	13 (11.0%)
Nodular type	
Solid nodule	93 (78.8%)
Non-solid nodule	25 (21.2%)
Tumor size (>3cm)	29 (24.6%)
Smoking history (yes)	52 (44.1%)
preALC	
$\leq 1.965 \times 10^9/L$	69 (58.5%)
$> 1.965 \times 10^9/L$	49 (41.5%)

Abbreviations: COPD, chronic obstructive pulmonary disease; CEA, carcinoembryonic antigen. preALC, preoperative Absolute lymphocyte count; smoking status, a history or current history of smoking, regardless of the amount of smoking.

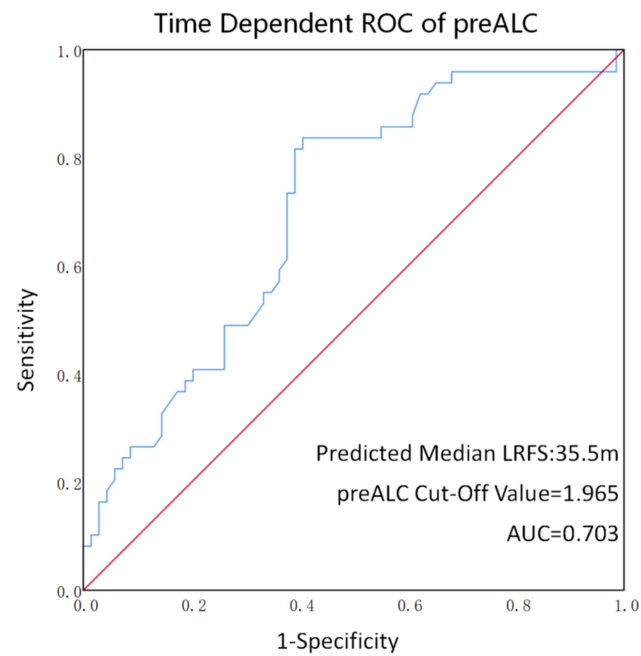


Figure 2 Time-dependent ROC of preALC.

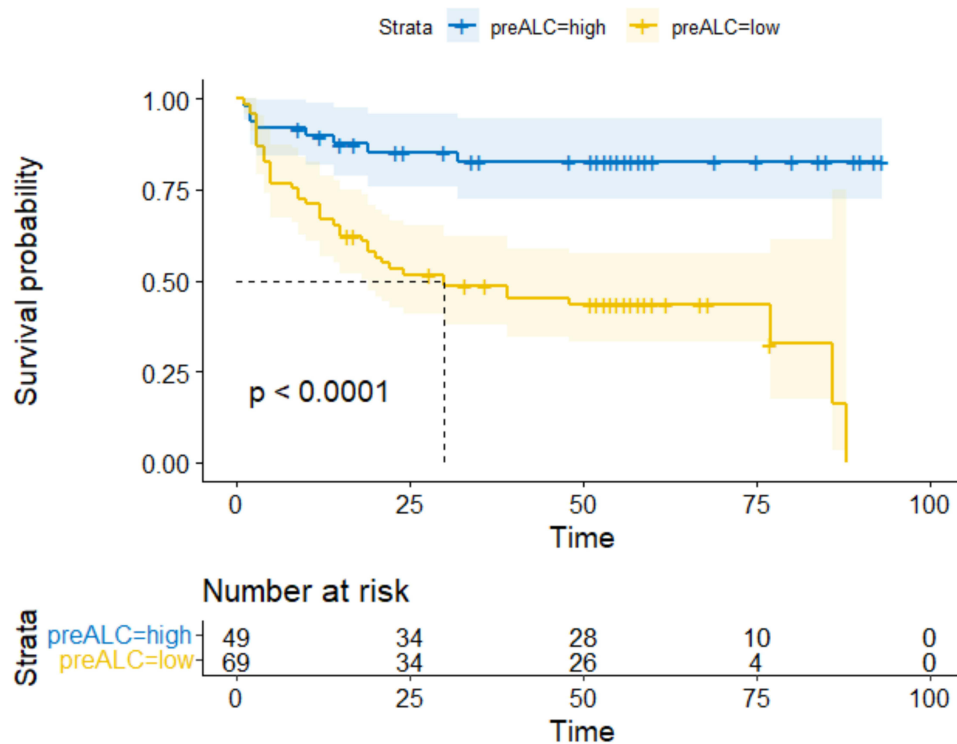


Figure 3 Kaplan-Meier survival curve.

Construction of the Nomogram for LRFS

Univariate analysis showed that histological subtype, CEA level, and preALC were risk factors for poor LRFS in NSCLC patients receiving MWA ($p < 0.05$). Histological subtype and preALC were included in multivariate analysis to construct

Table 2 Analysis of Prognostic Factors for LRFS

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Gender (male)	1.766	0.955–3.268	0.070			
Age (>60 years)	0.892	0.464–1.714	0.732			
Histological subtype	2.666	1.452–4.896	0.002	2.595	1.412–4.768	0.002
ACC						
SCC						
COPD (present)	1.678	0.946–2.979	0.077			
Tumor location	0.980	0.795–1.207	0.848			
The left lung upper lobe						
The left lung lower lobe						
The right lung upper lobe						
The right lung middle lobes						
The right lung lower lobe						
CEA (≥ 10 ng/mL)	2.261	1.089–4.694	0.029	1.807	0.862–3.788	0.117
Nodular type	0.507	0.227–1.134	0.098			
Solid nodule						
Non-solid nodule						
Tumor size (>3cm)	0.900	0.782–1.323	0.900			
Smoking history (yes)	1.664	0.935–2.962	0.083			
preALC	0.203	0.094–0.439	<0.001	0.221	0.101–0.482	<0.001
$\leq 1.95 \times 10^9/L$						
$> 1.95 \times 10^9/L$						

a nomogram. Histological subtype (HR = 2.595, 95% CI = 1.412–4.768, $P = 0.002$), and preALC (HR = 0.221, 95% CI = 0.101–0.482, $P \leq 0.001$) were independent prognostic factors of LRFS (Table 2). These indicators were further included in the construction of the nomogram prediction model (Figure 4).

Calibration, Validation and Decision Curve Analysis of the Nomogram

The prediction ability of the model was evaluated by calculating the C index, which was 0.693, indicating that the nomogram had good prediction accuracy. The correction curve showed that the prediction of 1-year, 2-year, and 3-year local recurrence rates with MWA treated NSCLC patients based on pre-ALC and histological subtypes, especially the results within 1 year, were in good agreement with the actual observed results (Figure 4).

The time-dependent ROC curve was used to evaluate the prognostic effect of independent prognostic factors in predicting local recurrence. We found that the model had the best predictive performance at 1 year (AUC of 0.688), which was better than that at 2 and 3 years (AUC of 0.606 and 0.612) (Figure 5).

The DCA shows the satisfactory benefit of a line graph under threshold probabilities (Figure 6).

Discussion

Local tumor recurrence is a key problem after MWA of NSCLC. Early identification of risk factors for local recurrence and adjustment of treatment plan can improve the prognosis of NSCLC patients. In this study, the findings showed that early-stage NSCLC patients with reduced absolute lymphocyte value before MWA treatment were more likely to have local recurrence.

Previous studies have shown that the occurrence and progression of most cancers is related to chronic inflammation,¹⁹ and ALC was associated with the prognosis of patients with a variety of malignant tumors.^{10–12} Inflammatory factors have been used to predict the prognosis of some malignant tumors. Different inflammatory cells have both pro-tumor and anti-tumor properties. Rabold's study proposed that T lymphocytopenia was associated with a poor prognosis in patients with advanced thyroid cancer.²⁰ Teck Seo's study reported that chemotherapy-related lymphocytopenia was an

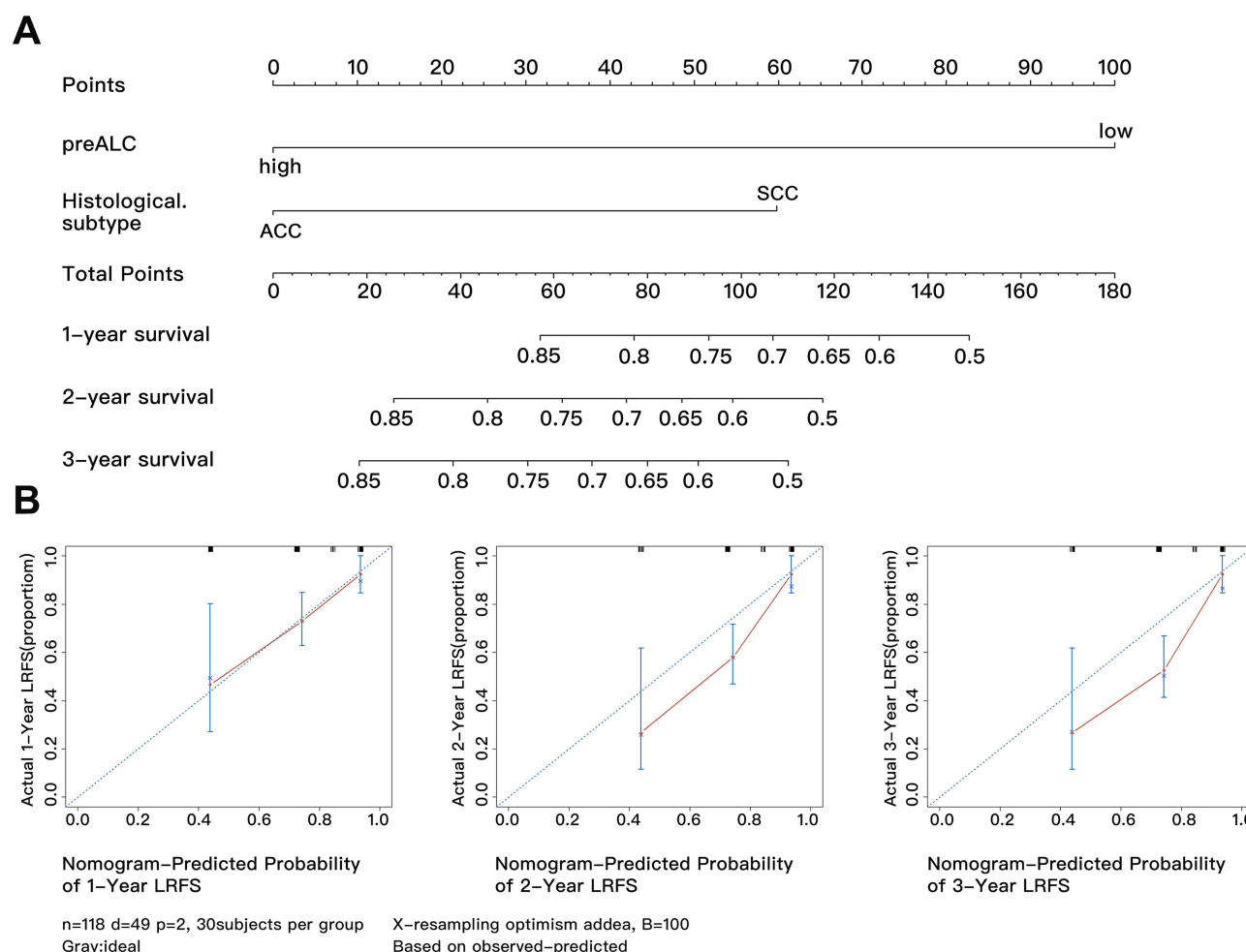


Figure 4 Nomogram and correction curve. **(A)** Nomogram for predicting based on preALC. **(B)** LRFS calibration curves used to predict 1, 2, and 3 years in NSCLC patients after ablation.

independent prognostic factor for adjuvant chemotherapy after potentially curative surgery in colorectal cancer patients.²¹ In our study, multivariate analysis revealed that preoperative ALC and histological subtype were predictive markers of LRFS in NSCLC. Patients with preoperative lymphocytopenia were more likely to have local recurrence than those who exhibited relatively high preoperative ALC. This result suggests that the reduction of peripheral blood lymphocyte count is one of the reasons for the poor prognosis of NSCLC patients, which was consistent with the previous findings.¹³ However, most previous studies have evaluated the impact of lymphocyte count on distant progression and overall survival of lung cancer patients, few studies have studied the impact on the outcome of simple local recurrence. In this study, combined with preoperative ALC, early local recurrence after early NSCLC MWA was predicted. The diagnosis of simple local recurrence is very important for local recurrence case because MWA ablation can be repeated at the same site,²² which is meaningful to guide the clinical determination of the next treatment plan.

At present, the exact mechanism of the prognostic value of peripheral blood lymphocyte count in cancer patients remains unclear. Several theories could explain this connection. T lymphocytes mediate cellular immunity and play an important role in anti-tumor immune response. T cells can generally be divided into CD4⁺ T cells, CD8⁺ T cells, memory T cells and natural killer T cells.²³ CD8⁺ T cells are the core participants of anti-tumor immunity, and their cytotoxic activity against tumor cells can destroy tumor cells. CD4⁺ T cells, especially Th1 subsets, control cell-mediated antitumor immunity and can assist CD8⁺ T cells to participate in cellular immune killing or exert direct antitumor activity independent of CD8⁺ T cells. CD4⁺ T cells and CD8⁺ T cells can induce apoptosis of tumor cells through their interaction.²⁴ Low lymphocyte counts are often associated with poorer clinical outcomes, possibly due to a reduced

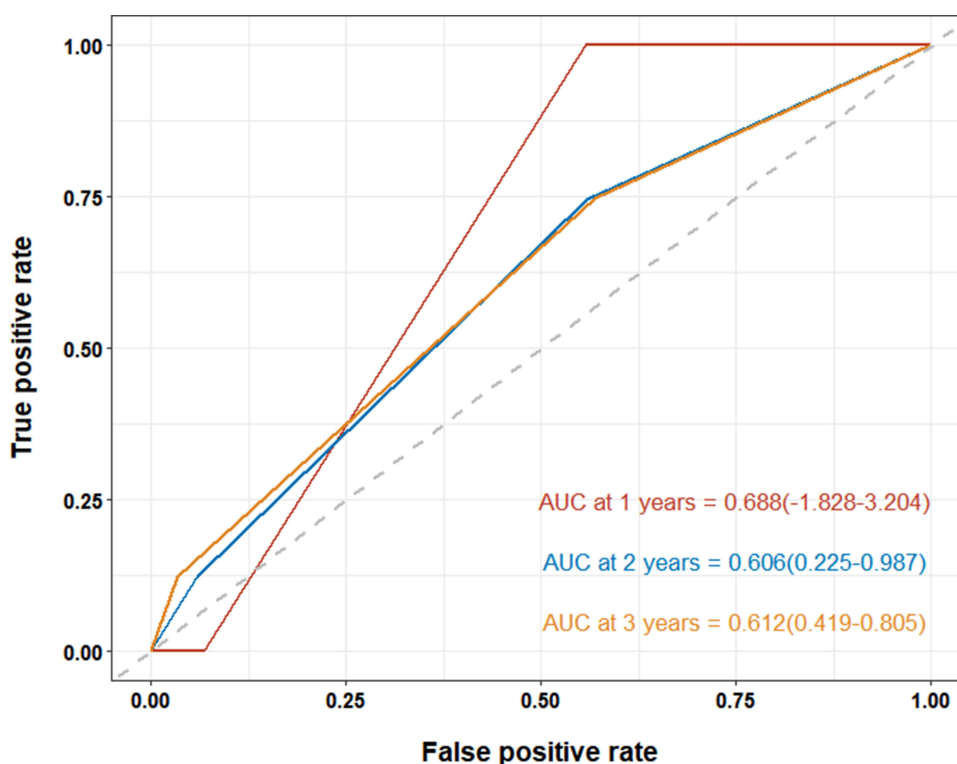


Figure 5 Time dependent ROC of nomogram.

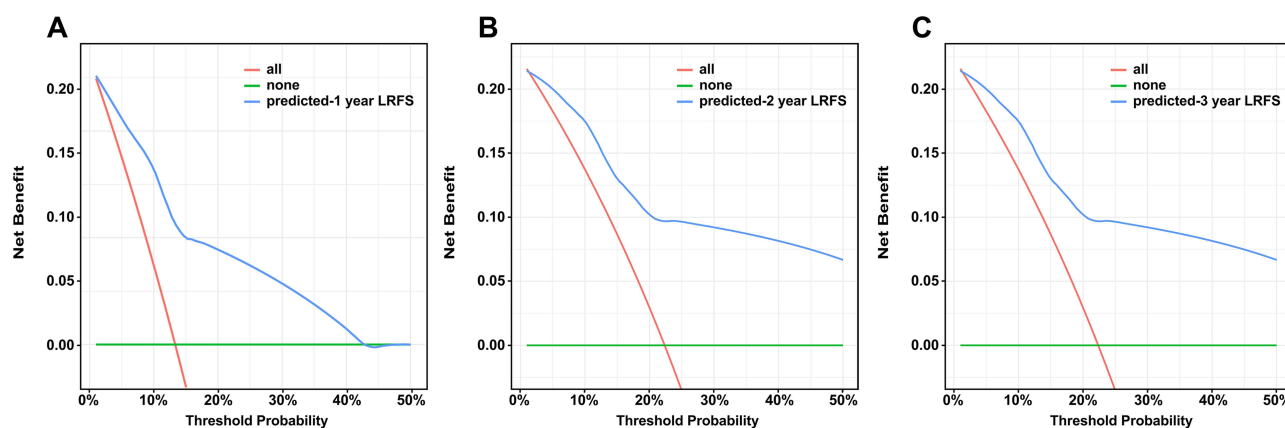


Figure 6 DCA of the nomogram for (A) 1 years, (B) 2 years and (C) 3 years.

lymphocyte-mediated immune response to the tumor. Meanwhile, previous studies have evaluated the immunogenic changes of thermal ablation in a variety of malignancies, especially liver cancer and breast cancer.^{25,26} Some studies²⁷ have reported that cold ablation of NSCLC has a strong anti-cancer immune response and distancing effect. We believe that the pre-ablation lymphocyte count of NSCLC may have an impact on the anti-cancer immune response triggered by ablation, and the specific mechanism needs to be further explored.

In addition, previous studies have reported the prognostic role of histological subtypes in lung adenocarcinoma.²² In this study, we found that patients with adenocarcinoma had a lower risk of local recurrence after ablation than those with squamous cell carcinoma, which was consistent with the results of previous relevant studies.

A nomogram is a simple visual statistical model that has been widely used in cancer prognosis.²⁸ Based on the independent prognostic variables identified in Cox regression analyses, we developed and validated a combination nomogram to assess the risk of local recurrence after MWA of NSCLC. The model had the best identification ability in predicting 1-year LRFS, with an AUC of 0.688, while the AUC values of the second and third year decreased. The following reason may explain this trend: 1) most of NSCLC patients received follow-up examination in our hospital within 1 year after surgery, but a few of patients underwent the follow-up examination in local hospitals; 2) NSCLC patients received different adjuvant treatments after MWA. In the study, the calibration plot showed good prediction accuracy and can predict good agreement. We believe that nomogram can provide personalized prediction of local recurrence after MWA of NSCLC and be helpful for patients and clinicians in the treatment decision-making process.

The study has some limitations. First of all, the study was a retrospective analysis, which may introduce some bias. Secondly, the number of patients included in this study was small; a large prospective study is needed to confirm our results. In recent years, it has been reported that artificial intelligence has been used to predict the recurrence of other tumors after ablation, and satisfactory results have been obtained. In the next study, we are working on combining artificial intelligence to predict local recurrence after MWA for NSCLC.

In conclusion, preoperative lymphocyte count reduction is associated with poor prognosis of NSCLC. The nomogram model combined with preALC can provide a good individualized prediction of local recurrence after MWA.

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Disclosure

The authors report no conflicts of interest in this work.

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