

Complications of CT-guided pulmonary nodule biopsy, Post-TNAB (Transthoracic needle aspiration biopsy) under CT Guidance

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ABSTRACT

► Original article

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Received: August 2024

Final revised: December 2024

Accepted: January 2025

Int. J. Radiat. Res., April 2025;
23(2): 441-446

DOI: 10.61186/ijrr.23.2.25

Keywords: Lung puncture, pneumothorax, risk prediction model, forest plot, nomogram.

Background: To investigate the independent risk factors of pneumothorax after CT-guided pulmonary puncture, and to construct a nomogram model to predict the occurrence of pneumothorax. **Materials and Methods** The relevant factors of 257 patients with pulmonary nodule puncture in the lung tumor ward of a tertiary hospital from 2021 to 2023 were collected, and the logistic regression analysis method of backward elimination was used to obtain independent predictors. Finally, the multivariate logistic regression results were used. By drawing forest charts, exploring independent risk factors for pulmonary puncture complicated by pneumothorax, risk prediction models were established and general nomograms and develop more intuitive multivariate dynamic nomograms were constructed to evaluate the model by calculating the AUC value of the area under the curve through the ROC curve performance; and to use Bootstrap's internal resampling method to perform internal validation of the model. **Results** Multivariate logistic regression analysis showed that lung nodule size (every 1 mm increase) (OR=0.82), education (OR=2.73) and age (OR=1.08) were independent risk factors for pneumothorax after lung puncture. **Conclusion** The nomogram constructed in this study can effectively predict the occurrence of postoperative pneumothorax in patients undergoing CT-guided pulmonary puncture. The model has a good degree of discrimination and consistency, and clinical medical staff can accurately and quickly predict the nomogram through pulmonary puncture complicated with pneumothorax, quickly identify patients with high risk of pulmonary puncture complicated with pneumothorax, and provide a reference for the development of targeted intervention measures.

INTRODUCTION

Small, focal growths in the lungs, known as pulmonary nodules, often detected through digital imaging, affect up to 27% of imaging studies, with males showing a slightly higher incidence rate. Advancing age and tobacco use are consistently identified as key risk factors ⁽¹⁾. In clinical radiology, pulmonary nodules are tissue shadows surrounded by aerated lung tissue with a diameter of 5-10 mm. They are typically round and can exist singularly or multiply. Nodules can be benign or malignant; benign nodules are usually caused by inflammation, tuberculosis, bleeding, etc., while malignant nodules result from primary lung cancer or metastatic malignant tumors ⁽²⁾. Transthoracic needle aspiration biopsy (TNAB) under CT guidance using a coaxial needle is the golden standard method to distinguish benign and malignant nodules in clinical practice ⁽³⁾. This procedure allows for the acquisition of effective pathological tissue under real-time monitoring, and it is known for its high confirmation rate, convenient operation, fewer complications, and wide clinical

application, especially for peripheral lesions. Despite the continuous improvement of this technique, pneumothorax remains the most common complication of TNAB, with reported incidences around 20-30% ^(4, 5). It can be classified into three categories: Primary Spontaneous Pneumothorax (PSP), Secondary Spontaneous Pneumothorax (SSP), and Traumatic Pneumothorax. Timely diagnosis can improve patient prognosis ⁽⁶⁾. Pneumothorax associated with TNAB relies mainly on nodule size, puncture angle, age, lung function, and patient cooperation during the operation ⁽⁷⁾. It may prolong hospital stays, increase additional medical expenses, and extend the treatment plan if not promptly addressed. Current research primarily focuses on risk factors associated with the development of pneumothorax following CT-guided lung biopsy. Some research has shown that saline injection can prevent pneumothorax ⁽⁸⁾.

The prediction of pneumothorax in lung biopsies is a crucial aspect of minimizing complications in computed tomography (CT)-guided percutaneous lung biopsies. A multicenter study by Chuang *et al.*

(2022) identified age, emphysema, and operation time as significant risk factors for pneumothorax, with an area under the curve (AUC) of 0.749 for their predictive model ⁽⁹⁾. Similarly, a systematic review and meta-analysis by Huo *et al.* (2020) examined 36 studies and identified several risk factors for pneumothorax, including patient positioning, needle size, and lesion characteristics, finding that positioning patients in a lateral decubitus position with the biopsied lung dependent, using smaller caliber needles, and a coaxial technique decreased the risk of pneumothorax ⁽¹⁰⁾. A study by Lamfichekh *et al.* (2023) proposed a predictive score for pneumothorax occurrence based on clinical and radiologic factors, including chronic obstructive pulmonary disease, number of pleural passages, and skin-to-pleura distance, finding that a negative score predicted a low probability of pneumothorax occurrence and suggested a reduced length of hospital stay ⁽¹¹⁾. A retrospective study by Rong *et al.* (2021) found that smaller lesion size and longer intrapulmonary needle traversal increased the risk of pneumothorax, while previous ipsilateral lung surgery and longer needle traversal through subcutaneous tissue were protective of pneumothorax ⁽¹²⁾. Furthermore, a study by Maalouf *et al.* (2022) found that an angle between the needle and pleura of less than 90 degrees increased the risk of pneumothorax, highlighting the importance of careful needle placement ⁽¹³⁾. However, pneumothorax still occurs to varying degrees, and the risk of pneumothorax is unpredictable. Therefore, early identification of high-risk populations and constructing a risk prediction model for pneumothorax can provide a basis for targeted and effective preventative nursing measures to minimize patient discomfort. Alignment chart, also known as Nomogram, is a visual method for displaying the results of a predictive model, which involves adding the scores of each independent risk factor to obtain the predicted probability of risk. The dynamic Alignment Chart is simpler and more convenient and eliminates the need for calculation. It is especially suitable for busy nursing staff. At present, no reports concerning the construction of an alignment chart for the risk prediction of pneumothorax in TNAB have been found. In this study, we retrospectively analyzed 257 cases who had undergone lung biopsies under CT guidance between 2021 and 2023. By identifying the influential factors of pneumothorax, we constructed a risk prediction model and alignment chart to provide a reference for puncture path design and for predicting complications.

MATERIALS AND METHODS

Study subjects

We collected data from 257 patients who underwent lung biopsy under CT guidance from

January 2021 to January 2023, with complete case information. Inclusion criteria: ① Patients who were selected for investigation due to lung occupancy, had normal lung function and no other underlying diseases; ② Those who underwent TNAB examination under CT guidance during hospitalization and underwent CT reexamination after the operation; ③ Patients whose medical records contain enhanced CT within a week before TNAB. Exclusion criteria: ① Patients with missing imaging data or unclear descriptions; ② Those with failed TNAB operation or TNAB operation terminated due to other reasons; ③ Patients discharged or transferred after the TNAB operation. This study includes 7 risk factors, and according to the requirement of the modeling sample size calculation formula, each independent variable required 5 to 10 lung biopsy patients. The postoperative pneumothorax complication rate was 30%, therefore the required sample size for this research was $7 \times 10 / 0.3 = 233$.

Methods

Ethical consideration

This study was approved by the Ethics Committee of The Second Affiliated Hospital of Anhui Medical University. Informed consent was obtained from all patients before undergoing CT-guided pulmonary nodule biopsy. The study was conducted in accordance with the principles of the Declaration of Helsinki.(2021AMUH-4563)

Biopsy

According to the predetermined puncture plan, the patient performed CT scanning in an appropriate position, body surface marking was done with a metal bar, and the puncture path and puncture point were determined. The operation was performed by doctors with or above intermediate titles. After routine disinfection and local anesthesia, the patient was told to hold their breath and the needle was inserted into the lung tissue at a predetermined angle and depth. CT scanning was performed again to check the angle of needle insertion until the tip of the puncture needle was at the edge of the nodule. The needle core was then removed, and an 18G matching biopsy gun was used to take a sample while the patient held their breath ⁽¹⁴⁾. A snapshot of process is shown in figure 1.

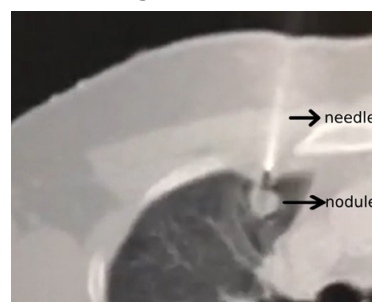


Figure 1. Snapshot showing biopsy needle pointing a pulmonary nodule

Postoperative CT was rechecked to see if pneumothorax occurred in the surgical area and to preliminarily determine the amount of pneumothorax, promptly suck out the accumulated gas in the surgical area with a syringe to alleviate the symptoms of pneumothorax.

Data collection

Patients' general information and detailed descriptions in lung puncture procedure records were retrospectively collected. The size and position of the patient's nodules were based on CT reports within a week of enhancement, the puncture angle, and patient position were recorded in the patient's detailed TNAB operation records, whether there was pneumothorax or not was based on the surgical records on the same day and within three days after the TNAB operation, gender, and age information were collected from the patients' general information.

Statistical methods

R3.6.3 was used for statistical analysis. Categorical variables were processed into binary classifications and assigned values. Measurement data obeying a normal distribution were described using mean, while nonnormally distributed measurement data were described using median and quartile; counting data were described using frequency and percentage. The independent risk factors for pneumothorax were screened out through backward stepwise regression, and the screened independent variables were incorporated into the binary multivariate Logistic analysis to construct a risk prediction model. The rms package was used to construct a nomogram for visual display. The prediction effect of the model was tested by the area under the ROC curve (AUC) to evaluate the predictive performance.

RESULTS

General information about study participants

A total of 257 patients were included in this study, of which 178 were male (69.3%) and 79 were female (30.7%). The average age was 67 (66.63±12.95) years. In this study, 69 (26.8%) patients developed pneumothorax.

Univariate analysis of pneumothorax in patients

The study subjects were divided into groups with and without pneumothorax. Using backward stepwise regression analysis with R, we analyzed the risk factors related to patients with and without pneumothorax. All independent variables were included in the model, with one variable removed at each step. Finally, based on the minimum Akaike Information Criterion (AIC) ^(12, 13), age, nodule size, direction of puncture, presence or absence of cough, and education level were left as influential factors for

the occurrence of pneumothorax post-TNAB, and they were statistically significant ($P<0.05$). More details can be found in table 1.

Table 1. Comparison of risk factor situations within the group with or without pneumothorax post-TNAB.

| | Overall | No | Yes | <i>p</i> |
|---|----------------------|----------------------|----------------------|----------|
| n | 257 | 188 | 69 | |
| Age [mean (SD)] | 66.63 (12.95) | 63.95 (12.82) | 73.93 (10.25) | <0.001 |
| Age [median (IQR)] | 67.00 [58.00, 77.00] | 65.00 [56.00, 73.00] | 73.00 [67.00, 82.00] | <0.001 |
| Nodule size [mean (SD)] | 4.30 (2.46) | 4.55 (2.57) | 3.64 (2.01) | 0.008 |
| Nodule size [median (IQR)] | 4.05 [2.70, 5.43] | 4.30 [2.90, 5.88] | 3.56 [2.30, 4.70] | 0.006 |
| Age (Percentage of males) | 178 (69.3) | 134 (71.3) | 44 (63.8) | 0.316 |
| Orientation of puncture (Percentage of oblique insertion) | 104 (40.5) | 68 (36.2) | 36 (52.2) | 0.03 |
| Cough [Yes (%)] | 157 (61.1) | 106 (56.4) | 51 (73.9) | 0.016 |
| Education [Primary school or above (%)] | 98 (38.1) | 84 (44.7) | 14 (20.3) | 0.001 |
| Nodule location [lower lobe (%)] | 118 (45.9) | 83 (44.1) | 35 (50.7) | 0.426 |
| Puncture position (%) | | | | 0.227 |
| Lateral position | 46 (17.9) | 29 (15.4) | 17 (24.6) | |
| Prone position | 131 (51.0) | 98 (52.1) | 33 (47.8) | |
| Supine position | 80 (31.1) | 61 (32.4) | 19 (27.5) | |

Multivariate analysis of pneumothorax in patients

The risk factors from the univariate analysis that proved to be statistically significant (age, nodule size, direction of puncture, presence or absence of cough, and education level) served as independent variables, and the instance of pneumothorax in patients as the dependent variable, were incorporated into a binary logistic regression equation. The analysis indicated that nodule size, age, and education level are independent risk factors for developing pneumothorax after TNAB. Specifically, the risk of post-TNAB pneumothorax possibly increases by 0.82 times ($P<0.05$) for each decrease in nodule size by 1mm, by 1.08 times ($P<0.05$) for each increase in age by one year, and for patients with education of primary school or below, the risk of pneumothorax post-TNAB is 2.73 times ($P<0.05$) that of patients with education level above primary school. The results of this regression analysis were visualized using the 'forestplot' package in R (table 2).

Table 2. Results of multivariate Logistic regression analysis of pneumothorax post-TNAB.

| Group | <i>P</i> | OR (95%CI) | Forest |
|-------------------------|----------|-----------------|--------|
| Nodule size | <0.01 | 0.82(0.69-0.95) | |
| Age | <0.01 | 1.08(1.05-1.11) | |
| Education | <0.01 | 2.73(1.36-5.76) | |
| Cough | 0.116 | 1.73(0.88-3.47) | |
| Orientation of puncture | 0.124 | 1.64(0.87-3.11) | 1.6 |

Construction and prediction effect of pneumothorax risk prediction model after TNAB

Independent risk factors for post-TNAB pneumothorax, including nodule size, age, and education level were included in the Logistic model, and a risk prediction nomogram for the occurrence of post-TNAB pneumothorax was drawn using R software, as shown in figure 2. Each risk factor can fetch the corresponding scores according to the scale in the first row, the total score is the sum of all existing risk factors' scores ⁽¹⁴⁾, and the corresponding possibility of pneumothorax occurrence can be found from the total score. Based on the theory of the dynamic Nomogram model, it is shown through an online software with a complex calculation formula in R (website: <http://127.0.0.1:6096>). On this software, the model quickly calculates the patient's probability of pneumothorax by selecting the numerical values corresponding to the hospitalized patients ⁽¹⁵⁾, as shown in Figure 3. Just slide the module to select different patients' age, nodule size, and education and directly output the risk of pneumothorax and look up detailed data information.

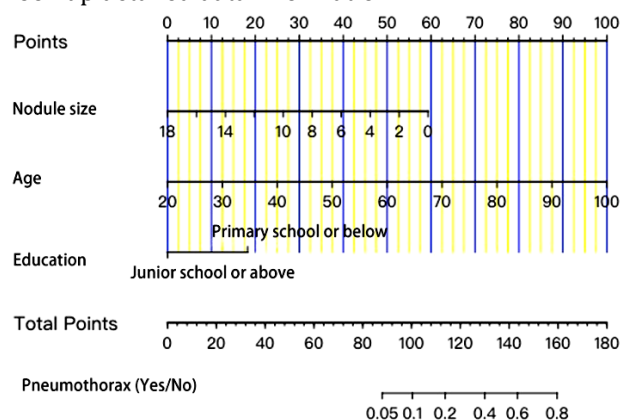


Figure 2. Nomogram for predicting risk of pneumothorax occurrence post-TNAB.

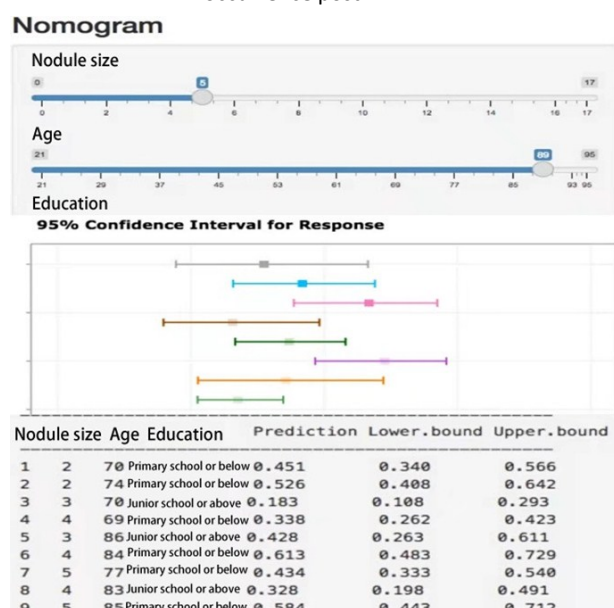


Figure 3. Dynamic nomogram for predicting pneumothorax occurrence post-TNAB.

Verification of pneumothorax risk prediction model after TNAB

The ROC curve of the post-TNAB pneumothorax risk prediction model was drawn using the R software package pROC, with an AUC value of 0.788, indicating good differentiation of the model, as shown in figure 4. This study used the Bootstrapping algorithm to evaluate the predictive performance of the risk of pneumothorax occurrence post-TNAB. After 1000 rounds of internal resampling, the results, as shown in figure 5, indicate good fit of the calibration curve, showing the predicted probability of post-TNAB pneumothorax occurrence is close to the actual occurrence probability ⁽¹⁶⁾.

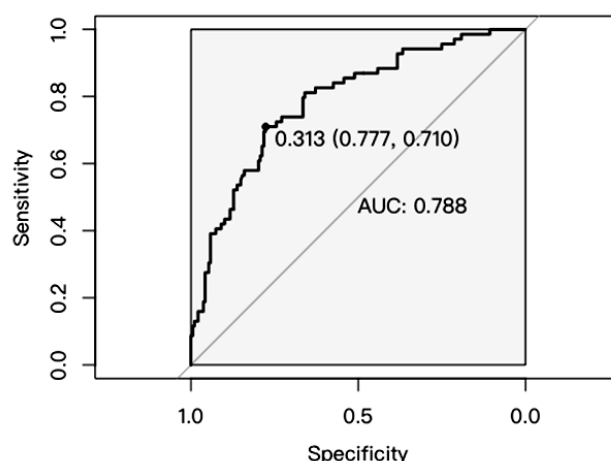


Figure 3. ROC curve of post-TNAB pneumothorax risk prediction model.

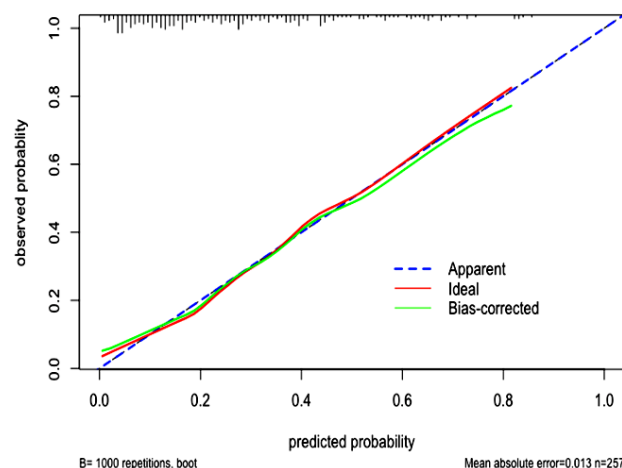


Figure 4. Calibration curve of post-TNAB pneumothorax risk prediction model.

DISCUSSION

The present study's findings on the risk factors for pneumothorax after TNAB are consistent with recent research in the field. Our study identified nodule size, age, and education level as independent risk factors for developing pneumothorax after TNAB, with a predictive model showing good differentiation (AUC=0.788). These findings are consistent with previous studies that have identified age as a

significant risk factor for pneumothorax in lung biopsies^(9, 12, 13). However, our study diverges from others in identifying education level as a risk factor, which may be related to patient compliance with post-procedure instructions. In contrast to Chuang *et al.* (2022), we did not find emphysema to be a significant risk factor, possibly due to differences in patient populations or study design⁽⁹⁾. Our results also differ from Huo *et al.* (2020) in that we did not find patient positioning or needle size to be significant risk factors⁽¹⁰⁾. Furthermore, our predictive model did not include factors such as chronic obstructive pulmonary disease, number of pleural passages, or skin-to-pleura distance, which were identified as important by Lamfichekh *et al.* (2023)⁽¹¹⁾. A recent study by Zhang *et al.* (2024) also investigated the risk factors for pneumothorax in CT-guided lung biopsy, although they focused on a different patient population and used a retrospective logistic regression analysis⁽¹⁵⁾. Both studies identified smaller lesion size as a significant risk factor for pneumothorax, with an odds ratio of 0.82 per 1mm decrease in nodule size in our study and an odds ratio of 0.724 per unit decrease in lesion size in Zhang *et al.*'s study. However, our study found that age and education level were also independent risk factors for pneumothorax, which was not reported in Zhang *et al.*'s study. Additionally, our study used a multivariate logistic regression analysis and developed a risk prediction nomogram to predict the probability of pneumothorax, which was not done in Zhang *et al.*'s study. The AUC values for our risk prediction model were 0.788, indicating good differentiation, whereas Zhang *et al.*'s study reported AUC values of 0.749, 0.812, and 0.850 for maximum diameter, needle tract length, and L/D ratio, respectively⁽¹⁵⁾.

A study by Huang *et al.* (2024) also investigated the risk factors for pneumothorax in CT-guided core needle biopsy, using a combination of clinical variables and radiomics features⁽¹⁶⁾. Both studies identified age as a significant risk factor for pneumothorax, although Huang *et al.*'s study found that patients with emphysema were also at higher risk. In contrast, our study found that education level was an independent risk factor for pneumothorax, which was not reported in Huang *et al.*'s study⁽¹⁶⁾. Additionally, Huang *et al.*'s study used a more advanced approach, incorporating radiomics features extracted from the subpleural lung parenchyma, which showed promise in predicting moderate pneumothorax⁽¹⁶⁾. The area under the ROC curve (AUC) values for Huang *et al.*'s combined clinical-radiomics model was 0.78 in the training cohort and 0.86 in the external test cohort, indicating good to excellent performance⁽¹⁶⁾. In comparison, our study's risk prediction model achieved an AUC value of 0.788.

A study by Weon *et al.* (2021) also investigated

the risk factors for pneumothorax and intercostal catheter insertion (ICC) after CT-guided lung biopsy, using a similar retrospective approach⁽¹⁷⁾. Both studies identified smaller lesion size as a significant risk factor for pneumothorax, although Weon *et al.*'s study⁽¹⁷⁾ found that lesions not in contact with pleura, shorter skin-to-pleura distance, and needle crossing a fissure were also independent risk factors. In contrast, our study found that age and education level were significant risk factors for pneumothorax, which were not reported in Weon *et al.*'s study⁽¹⁷⁾. Additionally, these authors developed risk prediction models for both pneumothorax and ICC insertion, with area under the ROC curve (AUC) values of 0.800 and 0.859, respectively, which is comparable to our study's AUC value of 0.788⁽¹⁷⁾. However, Weon *et al.*'s study used a more comprehensive approach, incorporating multiple variables and internally validating their models using split-sample methods.

A study by Kolu *et al.* (2020) also investigated the risk factors for pneumothorax after CT-guided TTFNAB, and found that the number of pleural transitions, emphysematous lungs, and lesions unrelated to the pleura were significant risk factors⁽¹⁸⁾. Our study's findings on pneumothorax risk factors after TNAB are consistent with Yang *et al.*'s (2020) nationwide study, which identified older age, male sex, and COPD as significant risk factors⁽¹⁹⁾. Unlike our study, Herout *et al.* (2019) found that transbronchial biopsy from the left upper pulmonary lobe, not age or education, was associated with increased risk of pneumothorax⁽²⁰⁾. Unlike our study, Sargent *et al.* (2022) found that emphysema in the needle biopsy path, not age or education, was the strongest predictors⁽²¹⁾, as well as Li *et al.* (2021) that mentioned obstructive pulmonary dysfunction and emphysema⁽²²⁾. These studies reported different results compared to our study due to various factors, including differences in study populations, with each study having a unique demographic profile, such as age, sex, and underlying health conditions. The biopsy techniques used in each study also varied, with Sargent *et al.* using CT-guided core needle biopsy⁽²¹⁾, Herout *et al.* using transbronchial biopsy⁽²⁰⁾, and Li *et al.* using CT-guided percutaneous core needle biopsy⁽²²⁾. Additionally, the variables analyzed as potential risk factors for pneumothorax differed across the studies, with Sargent *et al.* examining the role of emphysema in the needle biopsy path⁽²¹⁾, while Li *et al.* looked at obstructive pulmonary dysfunction⁽²²⁾, and our study focused on age, education level, and other factors. The study designs also differed, with Sargent *et al.*⁽²¹⁾ and Li *et al.* using retrospective designs⁽²²⁾, while Herout *et al.* used a prospective design⁽²⁰⁾. The sample sizes of the studies varied, with our study having a relatively small sample size compared to the other studies. Furthermore, the statistical analyses used in each study differed, with Sargent *et al.* using multivariable

logistic regression, while Li *et al.* used univariate and multivariate logistic regression ⁽²²⁾.

Innovation and limitations of this study

This study is possibly the first to construct a pneumothorax risk prediction model post-TNAB under CT guidance, showing results directly in the form of a dynamic forest plot. The limitation of this study lies in the relatively small number of research samples, and the research has only been conducted in one hospital's Respiratory Department. Consequent research needs further validation of these conclusions.

CONCLUSION

A forest plot of pneumothorax risk prediction post-TNAB under CT guidance was developed in this study. For patients undergoing TNAB under CT guidance, factors such as lung nodule size, patients' education level, and age can be assessed in advance, thereby accurately making preoperative pneumothorax predications and increasing the healthcare workers' recognition efficacy for post-TNAB pneumothorax. The model also demonstrates good predictive performance.

Funding: This study was not funded by any external sources.

Conflicts of interests: The authors declare that they have no conflicts of interest.

Ethical consideration: This study was approved by the Ethics Committee of The Second Affiliated Hospital of Anhui Medical University. Informed consent was obtained from all patients before undergoing CT-guided pulmonary nodule biopsy. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Author contribution: X.W.: Conceptualization, methodology, writing-original draft, writing-review & editing; H.W. and M.C.: Data curation, formal analysis, investigation; J.B.: Supervision, writing-review & editing.

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