Nonspecific benign pathological results on computed tomography-guided lung biopsy: A predictive model of true negatives

ABSTRACT

Objective: The aim of this study is to develop a predictive model for identifying true negatives among nonspecific benign results on computed tomography-guided lung biopsy.

Materials and Methods: This was a single-center retrospective study. Between December 2013 and May 2016, a total of 126 patients with nonspecific benign biopsy results were used as the training group to create a predictive model of true-negative findings. Between June 2016 and June 2017, additional 56 patients were used as the validation group to test the constructed model.

Results: In the training group, a total of 126 lesions from 126 patients were biopsied. Biopsies from 106 patients were true negatives and 20 were false-negatives. Univariate and multivariate logistic regression analyses were identified a biopsy result of "chronic inflammation with fibroplasia" as a predictor of true-negative results ($P = 0.013$). Abnormal neuron-specific enolase (NSE) level ($P = 0.012$) and pneumothorax during the lung biopsy ($P = 0.021$) were identified as predictors of false-negative results. A predictive model was developed as follows: Risk score = $-0.437 + 2.637 \times$ NSE level $+ 1.687 \times$ pneumothorax $- 1.82 \times$ biopsy result of "chronic inflammation with fibroplasia." The area under the receiver operator characteristic (ROC) curve was 0.78 ($P < 0.001$). To maximize sensitivity and specificity, we selected a cutoff risk score of $-0.029$. When the model was used on the validation group, the area under the ROC curve was 0.766 ($P = 0.005$).

Conclusions: Our predictive model showed good predictive ability for identifying true negatives among nonspecific benign lung biopsy results.

KEYWORDS: False-negative, lung biopsy, nonspecific benign, true-negative

INTRODUCTION

Computed tomography (CT)-guided lung biopsy is a safe, accurate, and minimally invasive approach for determining the benign or malignant nature of lung masses or nodules. The overall diagnostic accuracy of a CT-guided lung biopsy ranges from 90% to 94%. A malignant diagnosis obtained from a lung biopsy facilitates direct clinical decision-making because of an extremely low rate of false-positives (0%–0.2%). A specific benign diagnosis (e.g., tuberculosis, fungal infection, or hamartoma) from lung biopsy can also be accepted as a final diagnosis, enabling patients with suspicious lung lesions to avoid unnecessary surgery. However, a nonspecific benign diagnosis (e.g., chronic inflammation) from a lung biopsy is challenging to manage because of a high rate of false-negatives, with reports indicating a range of 7.1%–16.4%. Furthermore, a nonspecific benign biopsy result does not preclude further assessment with more invasive diagnostic methods and treatments.

A previous study by Kim et al. identified several predictors of false-negative findings from nonspecific benign lung biopsy results. However, this study did not combine predictors into an integrated predictive model. The purpose of our study was to develop a predictive model for identifying true negatives among nonspecific benign results from a CT-guided lung biopsy.

MATERIALS AND METHODS

This retrospective study was approved by the Local Institutional Review Board, and the requirement of written informed consent was waived.

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Study design
A total of 716 patients underwent CT-guided lung biopsy at our hospital between December 2013 and May 2016. All patients had lung lesions that were suspicious for malignancies. The indication for lung biopsy was determined from a multidisciplinary discussion between oncologists, respiratory physicians, and interventional radiologists. Among the 716 patients, we included 126 patients with nonspecific benign biopsy results as the training group to create a predictive model of true-negative findings among nonspecific benign lung biopsy results. The exclusion criteria were as follows: (a) lesions without a final diagnosis, (b) chronic granulomatous inflammation on lung biopsy results (because several studies had found that biopsy result of granulomatous inflammation was a robust indicator of true negatives,[10,11]), and (c) patients with distant metastases. A study diagram of the training group is shown in Figure 1. Baseline data of these patients included age, gender, patients’ history, imaging examination, details of biopsy, and laboratory examination.

Clinical data were also collected from an additional 73 patients with nonspecific benign biopsy results between June 2016 and June 2017. Among the 73 patients, 17 patients were excluded because they were missing a final diagnosis (n = 12) or presented with distant metastases (n = 5). Therefore, 56 patients were included in a validation group that tested the constructed model.

Biopsy needles
Biopsy needles were 18G semi-automatic cutting needles (Precisa, Roma, Italy, or Wego, Weihai, China). All needles were 100 or 150 mm long, and consisted of an outer needle and an inner stylet. The stylet contains a 20 mm sample notch. The end of the needle is a trigger, which allowed the outer needle to advance. The outer needle was used to localize the lesion, and the stylet was used to obtain the samples.

Lung biopsy procedure
All procedures were performed by an interventional radiologist with 10 years of experience. Lung biopsy was guided by a 16-detector CT (Philips, Cleveland, Ohio, USA). The tube voltage and current were 120 kV and 150 mA/s, respectively.

Patients were placed in the prone, supine, or lateral position in accordance with the location of the target lesion. The needle pathway was evaluated by a preoperative chest CT using a routine section thickness of 5 mm. A section thickness of 2 mm was used if an appropriate pathway could not be determined based on a section thickness of 5 mm. The needle pathway was selected with the intention of avoiding bone, visible vessels, bullae, and fissures. The puncture site was selected by CT gantry laser lights and landmarks using a radiopaque grid on the patient’s skin.

The coaxial system was not used during the procedure. After administering 5 ml of 2% lidocaine as a local anesthetic, an 18G cutting needle was used to puncture the lung and additional CT scanning was performed to evaluate the needle puncture site. A specimen was obtained with the needle tip in superficial contact with the lesion. If the lesion diameter was larger than 20 mm, the required sample length was 10–20 mm. If the lesion diameter was <20 mm, the required sample length was 5–10 mm. Samples were placed into 10% formaldehyde until pathological examination.

Definitions
Technical success of a lung biopsy was defined as obtaining an adequate tissue sample upon visual inspection.[6] Pathological results of lung biopsies were classified into 1 of 4 groups: (a) malignancy or suspected malignancy; (b) specific benign; (c) nonspecific benign; or (d) invalid diagnosis (necrotic tissue or alveolar tissue). Diagnoses of malignancy and suspected malignancy were considered positive results; diagnoses of specific and nonspecific benign were considered negative results. An invalid diagnosis was neither positive nor negative.[7]

Specific benign results were defined as benign tumors (e.g., hamartoma and leiomyoma) or infectious diseases with identified pathogens (e.g., fungal, bacterial, and mycobacterial infections).[11] Nonspecific benign results were defined as the presence of benign pathological features such as inflammatory cells or fibrosis that was insufficient to render a specific diagnosis.[11]

Nonspecific benign results on lung biopsy were considered to be true negatives if the lesions were benign on final diagnosis. A final benign diagnosis could be made in 1 of the 3 ways: (a) surgical resection; (b) determination of a specific benign lesion upon pathological analysis of the lung biopsy
Statistical analysis
The statistical analysis was performed using the SPSS 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as the mean or median. Numeric data were analyzed using the Chi-squared tests or Fisher’s exact probability tests. Predictors of true-negative findings were identified using univariate and multivariate logistic regression analyses. The covariates incorporated into the multivariate analysis were variables with $P < 0.05$ in the univariate analysis. Receiver operator characteristic (ROC) curves were created and areas under the curves were calculated. A value of $P < 0.05$ was considered as statistically significant.

RESULTS

Training group
A total of 126 patients with 126 nonspecific benign biopsy results were included in training group. Biopsy results for 106 patients were true-negative and 20 were false-negative [Table 1]. The negative predictive value (NPV) of the nonspecific benign biopsy was 84.1% (106/126).

Complications
Among the 126 patients, 36 patients (28.6%) experienced procedure-related complications (hemoptysis: 19; pneumothorax: 16; hemoptysis with pneumothorax: 1). According to the Society of Interventional Radiology classification,[12,13] 27 patients experienced major complication and 9 patients experienced minor complication. All patients with hemoptysis were successfully treated by appropriate hemostasis. The pneumothorax was managed by chest tube insertion in 8 patients and the remaining 9 patients did not undergo special treatment.

During the lung biopsy procedure, 79, 40, and 7 patients were placed in prone, supine, and lateral positions, respectively. There were no significant differences in hemoptysis (prone: 11/79; supine: 9/40; lateral: 0/7, $P = 0.239$) and pneumothorax (prone: 10/79; supine: 5/40; lateral: 2/7, $P = 0.486$) between patients with different positions.

True negatives
Among the 106 true-negative lesions, 78 had their final diagnosis confirmed by clinical follow-up, and 28 were not confirmed.

| Table 1: Comparison of baseline data between true-and false-negative lesions in training group |
|---------------------------------|-----------------|-----------------|---|
|                                | True-negative ($n=106$) | False-negative ($n=20$) | $P$ |
| Age (years)                    | 58.2±11.4        | 63.3±6.1        | 0.006 |
| Gender                         |                 |                 |     |
| Male                           | 63               | 14              | 0.374 |
| Female                         | 43               | 6               |     |
| Smoking history                | 51               | 13              | 0.166 |
| Tumor history                  | 2                | 0               | 1.00 |
| Imaging features               |                 |                 |     |
| Diameter (mm)                  | 31.8±19.2        | 38.8±26.9       | 0.28 |
| Side                           |                 |                 |     |
| Left                           | 46               | 11              | 0.339 |
| Right                          | 60               | 9               |     |
| Lobe                           |                 |                 |     |
| Upper                          | 47               | 12              | 0.198 |
| Nonupper                       | 59               | 8               |     |
| Nature                         |                 |                 |     |
| Solid                          | 105              | 18              | 0.065 |
| Sub-solid                      | 1                | 2               |     |
| Location                       |                 |                 |     |
| Hilar                          | 23               | 9               | 0.071 |
| Peripheral                     | 83               | 11              |     |
| Tumor markers                  |                 |                 |     |
| Abnormal CEA (range: 0-5 ng/ml)| 7                | 4               | 0.13 |
| Abnormal Cyfra211 (range: 0-3.3 ng/ml) | 12       | 6               | 0.066 |
| Abnormal SCC (range: 0-2.5 ng/ml) | 3               | 4               | 0.011 |
| Abnormal NSE (range: 0-16.3 ng/ml) | 4             | 5               | 0.005 |
| Details of biopsy procedure    |                 |                 |     |
| Lesion-pleura distance (mm)    | 14.3±15.2        | 18.2±14.6       | 0.303 |
| Needle-pleura angle (°)        | 67.3±17.1        | 65.7±20.7       | 0.71 |
| Number of samples              | 1.60±0.7         | 1.3±0.5         | 0.051 |
| Pneumothorax                   | 11               | 6               | 0.046 |
| Hemoptysis                     | 14               | 6               | 0.121 |
| Pathological features from biopsy |             |                 |     |
| Chronic inflammation with fibroplasia | 58             | 5               | 0.015 |
| Chronic inflammation with alveolar epithelial hyperplasia | 17 | 5 | 0.317 |

CEA=Carcinoembryonic antigen, SCC=Squamous cell carcinoma antigen, NSE=Neuron-specific enolase
confirmed by surgery. Among the 28 cases whose diagnoses were confirmed by surgery. Among the 28 cases who were confirmed by surgery, 23 cases were confirmed as chronic inflammation, 2 cases were confirmed as hamartoma, 1 case was confirmed as fungus, 1 case was confirmed as tuberculosis, and 1 case was confirmed as a bronchial cyst.

**False-negatives**

Among 20 false-negative lesions, 12 had their final diagnoses confirmed by surgery, 7 were confirmed by repeat lung biopsy, and 1 was confirmed by bronchoscopy. The final diagnoses of the 20 lesions included adenocarcinoma (n = 12), squamous cells carcinoma (n = 5), and small-cell lung cancer (n = 3).

**Predictors**

Table 2 summarizes the predictors of true-negative and false-negative results. Univariate and multivariate logistic regression analyses revealed that a biopsy result of “chronic inflammation with fibroplasia” was a predictor of true negatives (P = 0.013, hazard ratio (HR) = 0.2, 95% confidential interval (CI) = 0.0–0.7), while abnormal NSE (normal range: 0–16.3 ng/ml) level (P = 0.012, HR = 14.0, 95% CI = 1.8–108.4), and pneumothorax during the lung biopsy (P = 0.021, HR = 5.4. 95% CI = 1.3–22.6) were predictors of false-negatives. The number of samples was not associated with true-negative results (P = 0.055, HR = 0.3, 95% CI = 0.1–1.1).

Risk scores were calculated for individual patients by combining the above-mentioned three prognostic values as follows: −0.437 + 2.637 × NSE level (0: NSE ≤ 16.3; 1: NSE > 16.3) + 1.687 × pneumothorax (0: no pneumothorax; 1: pneumothorax present) - 1.82 × biopsy result of “chronic inflammation with fibroplasia” (0: no present; 1: present).

An ROC curve was used to determine the predictive value of this risk score for true-negative results. The area under the ROC curve was 0.78 [95% CI = 0.65–0.91, P < 0.001, Figure 2a]. To maximize sensitivity and specificity, we selected a cutoff risk score of −0.029 (sensitivity = 50%, specificity = 97.2%). If the score was ≥−0.029, the biopsy result was considered to be true-negative. If the score was <−0.029, the biopsy result was considered to be true-negative.

### Table 2: Predictors of true negatives

| Variables                              | Univariate analysis | Multivariate analysis |
|----------------------------------------|---------------------|-----------------------|
|                                        | Hazard ratio        | 95% CI                | P        | Hazard ratio | 95% CI | P        |
| Hilar lesion                           | 3.1                 | 1.2-8.5               | 0.025    | 2.5         | 0.7-8.8 | 0.163    |
| Abnormal Cyfra211                      | 3.4                 | 1.1-10.4             | 0.036    | 1.9         | 0.4-8.7 | 0.396    |
| Abnormal SCC                           | 8.6                 | 1.8-42.0            | 0.008    | 4.5         | 0.6-34.4 | 0.15     |
| Abnormal NSE                           | 8.5                 | 2.1-35.2             | 0.003    | 14.0        | 1.8-108.4 | 0.012 |
| Number of specimen                     | 0.4                 | 0.1-1.0              | 0.049    | 0.3         | 0.1-1.0 | 0.055    |
| Pneumothorax                           | 4.1                 | 1.3-13.1             | 0.017    | 5.4         | 1.3-22.8 | 0.021    |
| Chronic inflammation with fibroplasia | 0.3                 | 0.1-0.8              | 0.020    | 0.2         | 0.0-0.7 | 0.013    |

Cl=Confident interval, SCC=Squamous cell carcinoma antigen, NSE=Neuron-specific enolase

**Validation group**

Clinical data of the patients in the validation group were used to test the accuracy of the predictive model. The baseline data of the validation group are demonstrated in Table 3. A total of 56 patients with 56 nonspecific benign biopsy results were included in the validation group. Biopsy results for 44 patients were true-negative and 12 were false-negative. The NPV of the nonspecific benign biopsy was 78.6% (44/56). When this risk score was used on the validation group, the area under the ROC curve was 0.766 [95% CI = 0.61–0.93, P = 0.005, Figure 2b].

**DISCUSSION**

This study identified two significant predictors of false-negative biopsies and one significant predictor of true-negative biopsies. Furthermore, we developed an integrated risk score that combines these three predictors to identify true negatives. These findings might help in further analyzing lung lesions with nonspecific benign biopsy results.

CT-guided lung biopsy is widely used to diagnose lung lesions, and lung biopsy samples can provide adequate tissues for molecular testing that can guide treatment in lung cancer cases. Previous studies have investigated predictors or factors that influence the overall diagnostic accuracy of lung biopsy; however, a major problem that limits the accuracy of a lung biopsy is differentiating true negatives in cases of a nonspecific benign biopsy result. In fact, there is no consensus regarding a standard or recommended diagnostic approach after an initial lung biopsy yields a nonspecific benign result, although options include repeated biopsy, surgery, and follow-up.

In the present study, the NPV of 84.1% in the training group was comparable to that in previous studies. Abnormal NSE level, and pneumothorax during the biopsy were predictors of a false-negative result. In a previous study, Kim et al. found that a partial-solid lesion on biopsy was a significant predictor of a false-negative result (HR = 3.95, P = 0.022). However, there was only three subsolid lesions in the training group and they did not have the statistical effect. Nonetheless, two (66.7%) of the three sub-solid lesions were false-negative. We still believe that a nonspecific benign result from a partial-solid lesion biopsy should prompt immediate additional evaluation in order to exclude the possibility of a false-negative malignancy.
NSE is a common tumor maker for lung cancer.\(^{[16]}\) The false-negative group had a significantly higher rate of abnormal NSE than the true-negative group (25% vs. 3.8%, respectively; \(P = 0.005\)). Pneumothorax during the lung biopsy was also a predictor of false-negatives in this study. This result may be attributed to that pneumothorax may disturb the biopsy procedure. Although the number of samples was not associated with the true- or false-negatives, pneumothorax
also could reduce the quality of the samples. Gelbman et al. also found that procedure-related pneumothorax was the main factor predicting false-negative biopsy results because it limited needle insertion into the lesion and the number of passes.[17]

In a previous study, the pathological diagnosis of granulomatous inflammation on biopsy was a robust indicator of true negatives.[11] In this study, we excluded the cases with granulomatous inflammation and found that chronic inflammation with fibroplasia was a predictor of true-negative results ($P = 0.013$). The true-negative group had a significantly higher rate of cases with chronic inflammation with fibroplasia than the false-negative group (54.7% vs. 25%, respectively, $P = 0.015$). Similarly, Doxtader et al. found that 1/16 cases (6.3%) with nonspecific chronic inflammation and fibrosis on biopsy was ultimately a false-negative.[18]

Fibrosis is an important component of the inflammatory response and is a dominant clinical feature in many diseases, including proliferative vitreoretinopathy, mucous membrane pemphigoid, cirrhosis, scleroderma, idiopathic pulmonary fibrosis, and retroperitoneal fibrosis.[18-20] A biopsy sample that presents with chronic inflammation with fibroplasia may indicate that the punctured lesion is true-negative.

Finally, we developed an integrated risk score that combined the above three predictors in order to identify true negatives. The area under the ROC curve showed good predictive ability, and a cut-off value of $-0.029$ was obtained by calculating the optimum sensitivity and specificity. This predictive model was well fitted to the independent validation group of 56 patients from April 2016 to June 2017, which demonstrates the accuracy of the model.

The present study had some limitations. First, a retrospective design led to some selection bias. Second, there is no unified criterion for the quantity of a biopsy sample needed for collection. Instead, we collected biopsy samples in accordance with our experience. Although the number of samples was not associated with true-negative results, it may have otherwise biased our findings. Third, 29 and 12 lesions were classified as nondiagnostic lesions in training and validation groups, respectively. Although nondiagnostic lesions have also been reported in previous studies of lung biopsy,[6,11] they surely influenced predictive values in this study. Fourth, there is no PET-CT data in this study. Due to the high cost of PET-CT, only a few patients underwent PET-CT examination.

**CONCLUSIONS**

A biopsy result of “chronic inflammation with fibroplasia” might indicate the true negatives in nonspecific benign biopsy results. Abnormal NSE level and pneumothorax during the lung biopsy might indicate the false-negatives. Using these factors, we generated a combined risk score that had a good predictive ability for identifying true negatives among nonspecific benign lung biopsy results.

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**Conflicts of interest**
There are no conflicts of interest.

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