The role of pulmonary function testing in predicting risk of pneumothorax by CT-guided percutaneous core needle biopsy of the lung

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Research

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Abstract

Background

To determine risk factors for pneumothorax associated with computed tomography (CT)-guided percutaneous core needle biopsy (PCNB) of the lung. Whether the lung function characteristics are related to pneumothorax is unclear. This study was designed to provide a risk assessment of pneumothorax based on pulmonary function analysis, which can predict the risk especially for patients with severe pulmonary dysfunction.

Methods

We retrospectively evaluated 343 patients who received CT-guided pulmonary PCNBs and underwent preoperative pulmonary function testing. Demographical, lesion-related, procedure-related features and histopathological diagnosis, as well as results of pulmonary function test were analyzed for risk factors of pneumothorax

Results

Variables associated with higher rate of pneumothorax were location of lesion, presence of emphysema and dwell time. Furthermore, there was significant difference of pulmonary function parameters between groups with or without pneumothorax as expressed by FEV₁/FVC ratio, FEV₁/FVC ratio (% pred), FEF_{50%} (% pred), FEF_{75%} (% pred), and FEF_{25–75%} (% pred). Obstructive pulmonary function abnormalities were associated with a higher incidence of pneumothorax. However, no correlation was found between the pneumothorax rate and the severity of pulmonary function abnormalities. Multivariate logistic regression analysis showed lower location of lesion sampled and presence of emphysema were independent predictors of pneumothorax.

Conclusions

Patients with obstructive pulmonary dysfunction have a higher risk of pneumothorax. FEV₁/FVC ratio, FEF_{50%}, FEF_{75%} and FEF_{25–75%} has the potential to identify the high-risk population of pneumothorax.

Background

Computed tomography (CT)-guided percutaneous core needle biopsy (PCNB) of the lung has been widely considered as a common and effective procedure, with accurate histology diagnosis. Pooled overall complication rates for PCNB and fine needle aspiration biopsy (FNAB) from 32 articles (8,133 procedures) were 38.8% (95% CI: 34.3–43.5%) and 24.0% (95% CI: 18.2 – 30.8%), respectively [1]. Although overall complication rate was higher for PCNB than FNAB, the trend has been to replace FNAB with PCNB to provide the diagnosis of lung abnormalities with lower false-negative rate (< 10%) [2]. As is well known, the false-negative rate of FNAB in lung lesions is as high as 20% in the diagnosis of malignant tumors. When nonspecific or inadequate tissue is biopsied, it is usually unreliable to exclude malignant diagnosis [3]. PCNB has become an important procedure to obtain enough specimens for further biological identification and molecular spectrum analysis in the individualized target therapy [4].

Pneumothorax is one of the most common complications of PCNB of the lung. Pooled pneumothorax rate for core biopsy was 25.3% (95% CI: 22.2–28.6%) [1]. Previous studies predicted the risk factors for pneumothorax mainly based on the demographical, lesion-related, procedure-related features, such as patient age, emphysema, lesion size, dwell

time, number of needle punctures, and distance of lesion from the pleura [1, 5, 6], whereas the influence of pulmonary function-related factors were seldom reported. The performance of periprocedural pulmonary function analysis is to recognize patients with an increased risk of complications and to best evaluate the risk of the patients. However, there is no clear clinical quantitative index of pulmonary function to estimate the risk of pneumothorax during needle biopsy. This study focused on the role of lung function in predicting the risk of pneumothorax caused by PCNB, as well as the common risk factors.

Methods

Patients and data collection

Three hundred and forty-three patients with pulmonary function testing have been retrospectively evaluated from 1,110 consecutive patients who received CT-guided PCNBs of the lung between January 2018 and December 2019. Pulmonary function testing was performed within 7 days before PCNB. All the patients had received PCNBs for histopathological diagnosis of lung lesions at Qilu Hospital, Cheeloo College of Medicine, Shandong University, under consistent procedure. This single institutional retrospective study was approved by our hospital institutional review board (registration number: KYLL-202008-145) and complied with the Declaration of Helsinki and the ethical standards of the institutional research committee of Qilu Hospital, Cheeloo College of Medicine, Shandong University. Inclusion criteria also consisted of patients with normal electrocardiogram and with adequate hepatic, renal and hematological function. If patients were given aspirin, warfarin or low-molecular-weight heparin, they were required to suspend their medication one week before the procedure and monitor the prothrombin time. Platelet count should be $\geq 50 \times 10^9 / L$ for biopsy.

Patient records were anonymized and de-identified prior to analysis. Collected data included patient demographics (age, gender, smoking, prior surgery, radiotherapy or chemotherapy), characteristics of target lesions (location, the size of the sampled lesions, abut pleura and emphysema), and procedure-related information (patient position, needle puncture site, length of biopsy pathway, dwell time, needle-pleural angle, number of needle redirections and pleural planes traversed, and number of tissue samplings), results of pulmonary function test, procedure-related complications (pneumothorax, chest drainage catheter insertion, and pulmonary hemorrhage), and the histopathological diagnosis in all the cases.

Middle lobe, lingular, and lower lobe lesions were categorized as “lower locations”; upper lobe lesions, as “upper locations” [7]. Lesion size was measured as the largest diameter of the sampled lesion in the previous CT images. The depth of the lesion was gauged as the length of the needle track from the punctured pleura to the edge of the lesion sampled. The needle-pleural angle was calculated on the transverse 3-mm section in the craniocaudal dimension, according to the method suggested by Ko *et al.* [6]. It was defined as the minimum angle formed by a line tangent to the pleura at the puncture point and a line drawn along the needle (**Figure 1**) [6]. Pneumothorax was evaluated by CT scan after biopsy, as the largest separation between the visceral and parietal pleura. Less than or equal to 1 cm was categorized as “minor pneumothorax”; greater than 1 cm but less than or equal to 2 cm, as “intermediate pneumothorax”; greater than 2 cm, symptomatic or chest drainage catheter insertion needed, as “severe pneumothorax” [8].

CT-guided core needle biopsy

PCNBs were performed by one intervention team led by Prof. C. L. (7 years of experience in CT-guided needle biopsy), using only one type of needle, 17-gauge coaxial introducer and 18-gauge automated cutting needle (Biopince, Argon Medical Devices, Frisco, Texas). All the biopsies were carried out according to the standard protocol. All patients

underwent enhanced CT before the biopsy. Averting obvious emphysema or bulla, the safest and shortest route from the chest wall to solid part of the lesion was chosen to determine the supine, prone or lateral position of the patient on the CT table. All patients were given intravenous indwelling needles, allowing for the infusion of rescue drugs if necessary. The patients were instructed to breathe shallowly and avoid moving, coughing, speaking or deep breathing during and 3 hours after the procedure. If the biopsy route needed to be changed, the patient's position could also be changed. After aseptic technique and local anesthesia with 1% lidocaine, the introducer needle was inserted. The needle is inserted rapidly during pleural puncture, and the needle is withdrawn slowly after the biopsy. Rapid insertion at breath-hold can form a precise puncture point, while slow extraction of the guide needle can make the elastic lung tissue seal the pleural hole. Then the position of the coaxial introducer was determined by CT scans. If the introducer was correctly located within the periphery of the lesion, the biopsy was performed to obtain sufficient tissue samples. The representative images of the CT-guided PCNB are shown in **Figure 1**. After slowly removing the needle, CT scans were performed to evaluate the complications. The patient was then asked to rest for 24 hours. Patients with pneumothorax or bleeding were monitored in the inpatient ward. Patients with intermediate or severe pneumothorax had follow-up CT to determine its stability. If patients had pneumothorax with symptoms of respiratory distress or shortness of breath, a thoracic drainage catheter was placed.

Pulmonary function test

All patients were selected who received pulmonary function tests within 7 days before CT-guided PCNBs, in one single center of Qilu Hospital. Patients were mainly classified into normal, small airway dysfunction, obstructive, restrictive and mixed pulmonary function abnormalities, according to pulmonary function test, as well as their illnesses and severity [9]. The judgment processes of pulmonary function abnormalities were referred to [9-11]. Forced expiratory volume in one second (FEV_1) / forced vital capacity (FVC) ratio, FVC and TLC should be considered first [9, 10]. Obstructive abnormality is defined as a fixed ratio of $FEV_1/FVC < 70\%$ [10]. Even if FEV_1 percent predicted ($FEV_1\%$ pred) is more than 80%, it can be judged as obstructive abnormalities. This slowing of expiratory flow is most obviously reflected in a concave shape on the flow-volume curve. $FEF_{25-75\%}$ and MVV can descend at the same time, but FVC and TLC is limited in normal range [9, 11]. Restrictive abnormality is characterized by a normal FEV_1/FVC and a reduction in FVC and TLC. The flow-volume curve may show a convex pattern [10, 11]. A mixed pulmonary function abnormality is characterized by the coexistence of obstruction and restriction. According to ATS/ERS criteria [8], all the obstructive, restrictive and mixed ventilation abnormalities were stratificated into five severity groups based on the $FEV_1\%$ pred.

Conventional ventilation function parameters such as FEV_1 , FEV_1/FVC , FVC and TLC are still in the normal range, but two of these three parameters $FEF_{50\%}$, $FEF_{75\%}$ and $FEF_{25-75\%}$ are lower than 65% of the predicted value, which can be diagnosed as small airway dysfunction [11].

Statistical analysis

Patients were classified into two groups with or without pneumothorax after CT-guided lung biopsy. Clinical variables included demographic, lesion, technique, diagnostic and pulmonary function characteristics. All the quantitative data showed non-normal distribution by the Shapiro-Wilk test. Significant differences between these groups were identified using the chi-square test for categorical variables, the Mann-Whitney U test for quantitative variables with non-normal distribution. Multivariate logistic regression analysis was used to calculate odds ratios with 95% confidence intervals for potential of the hazard of pneumothorax. Logistic regression model only included significant covariates from univariate analysis. P value < 0.05 was defined to be significant different. All statistical tests were performed by SPSS software package, standard Version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Comparison of groups with and without pneumothorax evaluated by univariate analysis

There were 206 (60.06%) male and 137 (39.94%) female patients in this study. Only two patients received prior chemotherapy, one received prior thoracic surgery, and no one received prior thoracic radiotherapy. The baseline characteristics of these 343 patients were summarized in **Table 1**. All the quantitative data showed non-normal distribution, so the median and the lower quartile to the upper quartile were presented here. The median age was 62 years (range, 18 to 82 years) and the median depth from the pleura to the lesion was 11.6 mm (range, 0 to 70.3 mm). The diameter of the lesions punctured varied from 6.8 to 212.1 mm, with a median of 26.7 mm in previous CT images. The median needle-pleural angle was measured to be 65° (range, 0 to 90°). The median dwell time was 200 s (range, 70 to 1200 s). The 248 (72.30%) histopathologically malignant diagnoses mainly included 191 (55.69%) adenocarcinomas, 34 (9.91%) squamous cell carcinomas, 6 (1.75%) small cell carcinomas, and 6 (1.75%) metastases from other tumor sites (**Table 2**). In 80 (23.32%) benign histopathological diagnoses, 71 (20.70%) were assessed as chronic pneumonia. In addition, there were 2 (0.58%) patients with borderline tumor. There were still 13 (3.79%) cases without histopathologic results for inadequate tissue sampling. Thus, primary diagnostic yield of CT-guided PCNB was 96.21%.

The main complications of PCNBs were pneumothorax, chest drainage catheter insertion and pulmonary hemorrhage. Fifty patients (14.58%) had pneumothorax after PCNBs. Among those, only three patients (6.00%) revealed severe pneumothorax on post-biopsy CT scans, which required placement of chest drainage catheter. In the most serious case of pneumothorax, the lung was compressed by 1/3. All patients with mild or moderate pneumothorax were stable without deterioration and any interventional treatment. Of all the 343 patients, 88 (25.66%) had pulmonary hemorrhage, most of which were slight hemorrhage.

The differences in clinical characteristics between groups with and without pneumothorax were evaluated by univariate analysis (**Table 1**). Variables associated with higher rate of pneumothorax were location of lesion ($P = 0.004$), presence of emphysema ($P = 4.929 \times 10^{-8}$), and dwell time ($P = 0.046$), whereas all the other parameters including demographic and diagnostic parameters showed nonsignificant findings. As shown, the proportion of middle lobe, lingular, or lower lobe lesions in pneumothorax group (30/50, 60.00%) is higher than non-pneumothorax group (113/293, 38.57%). The dwell time varied from 70 to 1200 s, with a median of 240 s in patients with pneumothorax and 200 s in patients without pneumothorax. The incidence of emphysema in pneumothorax group was significantly higher than that in non-pneumothorax group (34.00% vs 7.51%). However, other possible risk factors about lesion and technique, previously reported, such as lesion size, abut pleura, length of intrapulmonary needle tract, needle-pleural angle, and number of pleural punctures, showed no statistically significance of pneumothorax in this study.

Differences in pulmonary function between groups with and without pneumothorax evaluated by univariate analysis

On the other hand, the pulmonary function of these 343 patients was also evaluated (**Table 3**). The main pulmonary function parameters (percent predicted, % pred) were as follows: FVC 103.32% (91.97 – 115.53%), FEV₁ 98.02% (81.73 – 109.90%), FEV₁/FVC ratio 96.95% (89.35 – 103.23%), FEF_{25–75%} 58.02% (37.44 – 78.57%), and PEF 104.35% (84.40 – 119.59%).

Furthermore, there was statistically significant difference of pulmonary function parameters between the two groups with or without pneumothorax as expressed by FEV₁/FVC ratio ($P = 0.004$), FEV₁/FVC ratio (% pred) ($P = 0.005$), FEF_{50%} (% pred) ($P = 0.014$), FEF_{75%} (% pred) ($P = 0.037$), and FEF_{25–75%} (% pred) ($P = 0.033$). No difference was found in VC, FVC or PEF between the two groups. And more importantly, as seen in **Table 3**, although FEV₁ was not

significantly different between the two groups of patients, the FEV₁/FVC ratio (% pred) was significantly lower in patients with pneumothorax (median, lower-upper quartile: 94.43, 86.64 – 98.86) than without pneumothorax (97.45, 90.73 – 103.54). Interestingly, as no other research has been studied so far, the small airway function parameters, such as FEF_{50%}, FEF_{75%} and FEF_{25–75%}, showed significant negative correlations with pneumothorax rate. However, PEF and FEF_{25%} which reflect the large airway function were not associated with the risk of pneumothorax.

3.3 Relationship between incidence of pneumothorax and pulmonary function abnormalities

Patients with pneumothorax had significantly reduced FEV₁/FVC ratio compared with those without pneumothorax, as shown above, indicating that patients with obstructive diseases were more likely to have pneumothorax. **Table 4** shows the relationship between pulmonary function abnormalities and pneumothorax. The chi-square test revealed that obstructive pulmonary function abnormalities, as assessed by a decrease in FEV₁/FVC ratio, were associated with a higher incidence of pneumothorax ($P = 0.005$). The incidence of pneumothorax in the obstructive ventilation abnormalities was 24.66%, whereas in the normal group the rate dropped to 10.71%. The restrictive and mixed ventilation function abnormalities were not found to correlate with the pneumothorax rate ($P = 1.000$ and $P = 0.961$, respectively).

All the obstructive, restrictive and mixed ventilation abnormalities were stratified into five severity groups based on FEV₁% pred (**Table 4**). However, no correlation was found between the pneumothorax rate and the severity of all pulmonary function abnormalities ($P = 0.066$). Similarly, in patients with obstructive ventilation abnormalities, the severity of spirometric abnormality was not associated with the incidence of pneumothorax ($P = 0.604$).

In addition, the incidence of pneumothorax was not significantly different between patients with small airway dysfunction and patients with normal ventilation function ($P = 0.413$).

3.4 Logistic regression model estimates roles of pulmonary function parameters on pneumothorax in all patients studied

A logistic regression model was used to evaluate the relationship of FEV₁/FVC, FEF_{50%}, FEF_{75%} and FEF_{25–75%} to pneumothorax (**Table 5**). Decrease in FEV₁/FVC, FEF_{50%}, FEF_{75%} and FEF_{25–75%} were associated with a higher likelihood of pneumothorax (OR, 2.182, 2.366, 2.303, and 1.974, respectively).

Multivariable logistic regression model for predictors of pneumothorax in all patients studied

Multivariate logistic regression analysis was carried out to find the relationship between multiple dependent variables, and to adjust the differences in confounding factors (**Table 6**). Here, the analysis only considered covariables significant by univariate analysis mentioned in **Table 1 and 3**. Since FEF_{50%}, FEF_{75%} and FEF_{25–75%} are clinically related to FEV₁/FVC, only FEV₁/FVC ratio (%) is retained. Lower location of lesion sampled and presence of emphysema were identified to be independent predictors of pneumothorax after CT-guided PCNB ($P = 0.022$ and $P = 1.150 \times 10^{-4}$, respectively). In all patients, risk of pneumothorax was significantly higher in lower location of lesion sampled (odds ratio [OR], 2.128; 95% confidence interval [CI], 1.117 – 4.051) and presence of emphysema (OR, 4.937; 95% CI, 2.193 – 11.115). Although dwell time, FEV₁/FVC ratio were significantly correlated with pneumothorax on univariate analysis, these were not confirmed to be independent risk factors here.

Discussion

The CT-guided pulmonary PCNB can biopsy smaller pulmonary nodules with the progress of technology, but pneumothorax is still one of the most frequent complications. The rate of pneumothorax induced by PCNB was 14.58% in this study, and that of chest tube placement was 0.87%, which were similar to the rates reported in other studies [12–14]. In order to explore the risk factors of pneumothorax, clinical data such as patient demographics, characteristics of target lesions, procedure-related information, the histopathological diagnosis and results of pulmonary function test were all collected here. However, patient-related and diagnosis-related predictors had no influence on the occurrence of pneumothorax. Interestingly, Ko *et al.* [6] reported that pneumothorax was unlikely to occur in patients who had previous thoracic surgery, focal or diffuse pleural disease, or chest wall involvement. However, it may be that few patients in this study had prior thoracic surgery, so this phenomenon was not found.

Concerning lesion characteristics in this study, several predictors influenced the incidence of pneumothorax, such as the location of lesion and the presence of emphysema. No association was found between the incidence of pneumothorax and the depth, the size of the lesion and the invasion of adjacent pleura or chest wall, which were former risk factors for pneumothorax [5, 7, 14–20]. This reflects the progress of biopsy technology. For instance, the lesion size and the depth of the lesion from the pleural surface were known to be an important predictor of the incidence of pneumothorax associated with FNAB [14, 19]. The incidence of pneumothorax increased 2 times (66% vs 32%) when the depth of lesion was larger than 2.0 cm, partly due to the prolongation of dwell time and the increased amount of lung tissues that the needle penetrates [14]. However, other studies on the depth of lesions and pneumothorax were quite opposite. Some studies thought that the lesion abutting the pleura was more prone to pneumothorax. K M Yeow *et al.* [20] reported that when the subpleural lesions were within 2 cm below the pleural surface, the risk of pneumothorax was 7-fold higher than the lesion depth more than 2 cm. They explained that subpleural lesions tend to shift the needle into the pleural cavity, causing air to enter [20]. We did not observe the similar phenomenon, probably because we used oblique needle approach to deal with the lesions abut pleura. Similarly, for smaller lesions, technical success rate of FNAB was significantly lower (74% for ≤ 1.5 cm vs 97% for > 1.5 cm) [19]. Taleb *et al.* [17] believed that achieving sufficient tissue from smaller lesions is technically more demanding, which may lead to increased number of punctures and increased risk of pneumothorax. At present, CT-guided PCNB has been improved to biopsy pulmonary nodules less than 1 cm, and rarely more than twice.

In terms of procedure-related factors, dwell time was significantly correlated with pneumothorax on univariate analysis, but it was not confirmed as an independent predictor in logistic regression model here. The longer time the needle dwelled in the lung, the more likely the respiratory movement would cause the lung to be punctured. Several studies [5, 6] reported that patients with needle-pleural angles less than 80° and, in particular, less than 50° , had a higher risk of pneumothorax. However, we did not observe any impact of needle-pleural angle on complication rate of CT-guided PCNB. The negative correlation between needle-pleural angle and pneumothorax was not only due to the prolongation of intrapulmonary needle tract, but also due to the enlargement of pleural foramen torn by the needle passage [6]. The shape of the pleural aperture increased the amount of air leaking from the lung [6]. Therefore, in clinical practice, we have been willing to sacrifice the risk of changing the needle puncture site or prolonging the intrapulmonary needle tract in order to make the needle as perpendicular to the pleura as possible (median, lower-upper quartile: 65° , 48° – 80°).

Patients with obstructive pulmonary function abnormalities were at greater risk for PCNB-induced pneumothorax, which was consistent with other studies [7]. For patients with severe impairment of pulmonary function, clinicians are usually reluctant to use core needle biopsy for fear of continuous air leakage. In order to derive a quantitative index of risk for pneumothorax, pulmonary function characteristics were evaluated here. FEV₁/FVC ratio was found to be most strongly associated with pneumothorax, which was in accordance to previous reports [6, 13, 14]. FEV₁/FVC ratio has the potential to identify the high risk population of pneumothorax. However, there were some controversies in the

literature about the correlation between the abnormal pulmonary function analysis and the incidence of pneumothorax [12, 13, 15]. Vitulo *et al.* [12] reported in a retrospective analysis of 243 patients that no predictive value for pneumothorax was found in pulmonary function test. Several authors [6, 13–15] revealed a significant relationship between pneumothorax and FEV₁. But our results were contrary to the observations of these studies. No difference was found in FEV₁% pred between the two groups here. Obstructive pulmonary function abnormalities were related to higher risk for pneumothorax, but the severity demonstrated no association with the incidence of pneumothorax, which was probably due to FEV₁% pred. Although FEV₁/FVC ratio is the most important parameter for determining obstructive impairments, the severity of obstruction should be stratified by reduced FEV₁% [9–11]. Pulmonary function examination before biopsy can risk stratify patients with different types of pulmonary dysfunction, but the severity of pulmonary dysfunction does not affect the risk of pneumothorax. Patients with obstructive functional abnormalities had significantly higher incidence of pneumothorax than those with normal or other types of pulmonary abnormalities. The increase in pneumothorax was due to poor lung elasticity, reduced alveolar air retraction, rupture of the expanded alveoli, emphysema along the needle tract and difficulty in holding breath [7, 14]. Similarly, in patients with obstructive ventilation abnormalities, the severity of spirometric abnormality was not associated with the incidence of pneumothorax.

Furthermore, in this study, FEF_{50%}, FEF_{75%} and FEF_{25–75%} are significantly negatively correlated with the incidence of pneumothorax. Other lung function parameters such as VC, FVC, FEF_{25%} and PEF showed no statistical difference. This study is unique because so far, no other research paper has dealt with such detailed lung function predictors for pneumothorax. FEF_{50%}, FEF_{75%} and FEF_{25–75%} are the middle and end expiratory indexes of exertion dependence, which reflect small airway ventilation function. Small airway dysfunction refers to the dysfunction caused by infection, smoking and external environment in the airway with a diameter of less than 2 mm, including both small bronchi and proximal bronchioles. Small airways are known as the major sites of airflow obstruction in chronic obstructive pulmonary diseases (COPDs). Even before the destruction of emphysema, the narrowing and disappearance of small airways can be observed in patients with obstructive functional abnormalities, leading to the increase of peripheral airway resistance [21]. Small airway dysfunction is a common but easily ignored lung dysfunction, long known as the silent zone of the lung. Small airway lesions are characterized by smooth muscle hyperplasia and hypertrophy, inflammatory cells including neutrophils and macrophages increased, goblet cell hyperplasia, mucus hypersecretion and obstruction, airway wall thickening and fibrosis [22]. As a result, the airflow is restricted, the alveoli are overinflated, the alveolar attachment of the small airways is destroyed, the elastic retraction of lung is reduced, and the internal pressure of the alveoli increases, thereby increasing the occurrence of pneumothorax [10, 21]. Interestingly, in this study, small airway function parameters FEF_{50%}, FEF_{75%} and FEF_{25–75%}, showed significant negative correlations with pneumothorax rate (Table 3). However, no significant correlation was found between small airway dysfunction and pneumothorax (Table 4). This was mainly because small airway function indicators were significantly reduced not only in small airway dysfunction group, but also in obstructive functional abnormalities group (**Supplementary Table 1**). Therefore, logistic regression analysis was further employed to evaluate the roles of pulmonary function parameters in the risk of pneumothorax, respectively (Table 5). Since FEF_{50%}, FEF_{75%} and FEF_{25–75%} are clinically related to FEV₁/FVC, only FEV₁/FVC ratio (%) is retained in multivariable logistic regression model for predictors of pneumothorax. Although FEV₁/FVC ratio significantly correlated with pneumothorax on univariate analysis, multivariate logistic regression analysis shows it was not an independent risk factor.

This study had several limitations. CT-guided PCNB studied here were all performed by one intervention team with only one type of needle according to the standard protocol. Some factors demonstrated no statistical significance here, which does not mean that they have nothing to do with pneumothorax. This may be due to the standardization of the procedures. Ko *et al.* [6] indicated that pneumothorax more commonly occurred in patients with lesions adjacent pleura

or invading the chest wall. However, our puncture approach was deliberately avoided the fissure. Hence, no statistical significance of this factor was found. We used only one size of biopsy needle in this study, making it impossible to compare different sizes of the biopsy specimens. Furthermore, the limited reliability of this study on the risk for pneumothorax in restrictive and mixed ventilation abnormalities may be due to the limited number of such patients.

Conclusions

Pneumothorax is still the most common complication following CT-guided PCNB. With the improvement of the technique, some of the previous risk factors have become less important. This is the real purpose of this study. Several factors have been confirmed to be associated with a higher rate of pneumothorax, including location of lesion, presence of emphysema and dwell time, as well as pulmonary function parameters FEV₁/FVC ratio, FEV₁/FVC ratio (% pred), FEF_{50%} (% pred), FEF_{75%} (% pred) and FEF_{25–75%} (% pred). Multivariate logistic regression model showed that presence of emphysema was the most important predictor of pneumothorax, followed by location of lesion. Careful examination of pulmonary function, especially for patients with a history of smoking for several years, can be very helpful in risk stratification and determining observation methods after punctures.

Abbreviations

COPD: chronic obstructive pulmonary disease; CT: computed tomography; FEF_{25–75%}: mean forced expiratory flow between 25% and 75% of FVC; FEF_{X%}: instantaneous forced expiratory flow when X% of the FVC has been expired; FEV₁: forced expiratory volume in one second; FNAB: fine needle aspiration biopsy; FVC: forced vital capacity; LLN: lower limits of normal; MVV: maximum voluntary ventilation; OR: Odds ratio; PEF: peak expiratory flow PCNB: percutaneous core needle biopsy; PTX: pneumothorax; TLC: total lung capacity; VC: vital capacity; % pred: percent predicted.

Declarations

Authors' contributions

CHL and WZ designed the experiments. WZ supervised the study. CHL, DXW, FXY, YS and WZ performed the experiments. XJY, BL and HPJ assisted with the performance of experiments. CHL, WDX and WZ analyzed the data. CHL and WZ wrote the paper. All authors read and approved the final manuscript

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data generated and analyzed during the current study are included in this published article.

Consent for publication

Not applicable.

Ethics approval and consent to participate

All procedures performed were in accordance with the Declaration of Helsinki and the study was approved by The Institutional Ethics and Investigation Committee of Qilu Hospital, Shandong University [approval no. KYLL-202008-

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References

- [1] W.J. Heerink, G.H. de Bock, G.J. de Jonge, H.J. Groen, R. Vliegenthart, M. Oudkerk, Complication rates of CT-guided transthoracic lung biopsy: meta-analysis, *Eur Radiol*, 27 (2017) 138-148.
- [2] D.M. Minot, E.A. Gilman, M.C. Aubry, J.S. Voss, S.G. Van Epps, D.J. Tuve, A.P. Sciallis, M.R. Henry, D.R. Salomao, P. Lee, S.K. Carlson, A.C. Clayton, An investigation into false-negative transthoracic fine needle aspiration and core biopsy specimens, *Diagn Cytopathol*, 42 (2014) 1063-1068.
- [3] Y.J. Hong, J. Hur, H.J. Lee, J.E. Nam, Y.J. Kim, H.S. Kim, H.Y. Kim, S.K. Kim, J. Chang, J.H. Kim, K.Y. Chung, B.W. Choi, K.O. Choe, Analysis of tumor markers in the cytological fluid obtained from computed tomography-guided needle aspiration biopsy for the diagnosis of non-small cell lung cancer, *J Thorac Oncol*, 6 (2011) 1330-1335.
- [4] S.B. Solomon, M.F. Zakowski, W. Pao, R.H. Thornton, M. Ladanyi, M.G. Kris, V.W. Rusch, N.A. Rizvi, Core needle lung biopsy specimens: adequacy for EGFR and KRAS mutational analysis, *AJR Am J Roentgenol*, 194 (2010) 266-269.
- [5] H. Saji, H. Nakamura, T. Tsuchida, M. Tsuboi, N. Kawate, C. Konaka, H. Kato, The incidence and the risk of pneumothorax and chest tube placement after percutaneous CT-guided lung biopsy: the angle of the needle trajectory is a novel predictor, *Chest*, 121 (2002) 1521-1526.
- [6] J.P. Ko, J.O. Shepard, E.A. Drucker, S.L. Aquino, A. Sharma, B. Sabloff, E. Halpern, T.C. McLoud, Factors influencing pneumothorax rate at lung biopsy: are dwell time and angle of pleural puncture contributing factors?, *Radiology*, 218 (2001) 491-496.
- [7] A. Oikonomou, F.R. Matzinger, J.M. Seely, C.J. Dennie, P.J. Macleod, Ultrathin needle (25 G) aspiration lung biopsy: diagnostic accuracy and complication rates, *Eur Radiol*, 14 (2004) 375-382.
- [8] M.Z. Nikolic, L.S. Lok, K. Mattishent, S. Barth, B. Yung, N.M. Cummings, D. Wade, Y. Vali, K. Chong, A. Wilkinson, T. Mikolasch, S. Brij, H.S. Jenkins, A.V. Kamath, M. Pasteur, T.G. Hopkins, J. Wason, S.J. Marciniak, Noninterventional statistical comparison of BTS and CHEST guidelines for size and severity in primary pneumothorax, *Eur Respir J*, 45 (2015) 1731-1734.
- [9] R. Pellegrino, G. Viegi, V. Brusasco, R.O. Crapo, F. Burgos, R. Casaburi, A. Coates, C.P. van der Grinten, P. Gustafsson, J. Hankinson, R. Jensen, D.C. Johnson, N. MacIntyre, R. McKay, M.R. Miller, D. Navajas, O.F. Pedersen, J. Wanger, Interpretative strategies for lung function tests, *Eur Respir J*, 26 (2005) 948-968.
- [10] D.M.G. Halpin, G.J. Criner, A. Papi, D. Singh, A. Anzueto, F.J. Martinez, A.A. Agusti, C.F. Vogelmeier, Global Initiative for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease. The 2020 GOLD Science

Committee Report on COVID-19 and Chronic Obstructive Pulmonary Disease, *Am J Respir Crit Care Med*, 203 (2021) 24-36.

[11] G.L. Ruppel, P.L. Enright, Pulmonary function testing, *Respir Care*, 57 (2012) 165-175.

[12] P. Vitulo, R. Dore, I. Cerveri, C. Tinelli, P. Cremaschi, The role of functional respiratory tests in predicting pneumothorax during lung needle biopsy, *Chest*, 109 (1996) 612-615.

[13] F. Garcia-Rio, J.M. Pino, J. Casadevall, L. Gomez, J.M. Atienza, S. Diaz-Lobato, J. Villamor, Use of spirometry to predict risk of pneumothorax in CT-guided needle biopsy of the lung, *J Comput Assist Tomogr*, 20 (1996) 20-23.

[14] E.A. Kazerooni, F.T. Lim, A. Mikhail, F.J. Martinez, Risk of pneumothorax in CT-guided transthoracic needle aspiration biopsy of the lung, *Radiology*, 198 (1996) 371-375.

[15] C.M. Heyer, S. Reichelt, S.A. Peters, J.W. Walther, K.M. Muller, V. Nicolas, Computed tomography-navigated transthoracic core biopsy of pulmonary lesions: which factors affect diagnostic yield and complication rates?, *Acad Radiol*, 15 (2008) 1017-1026.

[16] S. Otto, B. Mensel, N. Friedrich, S. Schafer, C. Mahlke, W. von Bernstorff, K. Bock, N. Hosten, J.P. Kuhn, Predictors of technical success and rate of complications of image-guided percutaneous transthoracic lung needle biopsy of pulmonary tumors, *PLoS One*, 10 (2015) e0124947.

[17] S. Taleb, H. Jalaeian, N. Frank, J. Golzarian, D. D'Souza, Is a Routine Chest X-ray Necessary in Every Patient After Percutaneous CT-Guided Lung Biopsy? A Retrospective Review of 278 Cases, *Cardiovasc Intervent Radiol*, 40 (2017) 1415-1420.

[18] Y.C. Cheung, J.W. Chang, J.J. Hsieh, G. Lin, Y.H. Tsai, Adequacy and complications of computed tomography-guided core needle biopsy on non-small cell lung cancers for epidermal growth factor receptor mutations demonstration: 18-gauge or 20-gauge biopsy needle, *Lung Cancer*, 67 (2010) 166-169.

[19] H. Li, P.M. Boiselle, J.O. Shepard, B. Trotman-Dickenson, T.C. McCloud, Diagnostic accuracy and safety of CT-guided percutaneous needle aspiration biopsy of the lung: comparison of small and large pulmonary nodules, *AJR Am J Roentgenol*, 167 (1996) 105-109.

[20] K.M. Yeow, L.C. See, K.W. Lui, M.C. Lin, T.C. Tsao, K.F. Ng, H.P. Liu, Risk factors for pneumothorax and bleeding after CT-guided percutaneous coaxial cutting needle biopsy of lung lesions, *J Vasc Interv Radiol*, 12 (2001) 1305-1312.

[21] J.E. McDonough, R. Yuan, M. Suzuki, N. Seyednejad, W.M. Elliott, P.G. Sanchez, A.C. Wright, W.B. Geftter, L. Litzky, H.O. Coxson, P.D. Pare, D.D. Sin, R.A. Pierce, J.C. Woods, A.M. McWilliams, J.R. Mayo, S.C. Lam, J.D. Cooper, J.C. Hogg, Small-airway obstruction and emphysema in chronic obstructive pulmonary disease, *The New England journal of medicine*, 365 (2011) 1567-1575.

[22] K. Day, K. Ostridge, J. Conway, D. Cellura, A. Watson, C.M. Spalluto, K.J. Staples, B. Thompson, T. Wilkinson, Interrelationships Among Small Airways Dysfunction, Neutrophilic Inflammation, and Exacerbation Frequency in COPD, *Chest*, (2020).

Tables

Table 1 Comparison of groups with and without pneumothorax evaluated by univariate analysis

Clinical Characteristics	All Patients Studied		Pneumothorax			
	*N(%) or Median (lower-upper quartile)	Range [‡]	*Yes	*No	χ^2/Z	PValue [†]
No. of Cases Analyzed	343		50 (14.58%)	293 (85.42%)		
Demographic Characteristic						
Age (years)	62 (53~68)	18~82	61 (55~65)	62 (53~68)	-0.558	0.577
Gender					1.539	0.215
Male	206 (60.06%)		34 (9.91%)	172 (50.15%)		
Female	137 (39.94%)		16 (4.66%)	121 (35.28%)		
Pack-years smoking	0 (0~30)	0~200	6 (0~30)	0 (0~30)	-0.752	0.452
Prior thoracic surgery						1.000
Yes	1 (0.29%)		0 (0%)	1 (0.29%)		
No	342 (99.71%)		50 (14.58%)	292 (85.13%)		
Prior thoracic radiotherapy					–	–
Yes	0 (0.00%)		0 (0%)	0 (0%)		
No	343 (100.00%)		50 (14.58%)	293 (85.42%)		
Prior chemotherapy					–	1.000
Yes	2 (0.58%)		0 (0%)	2 (0.58%)		
No	341 (99.42%)		50 (14.58%)	291 (84.84%)		
Lesion Characteristics						
Location of lesion					8.071	0.004
Up	200 (58.31%)		20 (5.83%)	180 (52.48%)		
Low	143 (41.69%)		30 (8.75%)	113 (32.94%)		
Lesion size (mm)	26.7 (17.9~41.1)	6.80~212.10	25.8 (21.4~41.3)	26.8 (17.4~41.1)	-0.505	0.614
Abut pleura or chest wall invasion					0.057	0.812
Yes	211 (61.52%)		30 (8.75%)	181 (52.77%)		

No	132 (38.48%)		20 (5.83%)	112 (32.65%)		
Presence of emphysema					29.744	4.929×10⁻⁸
Yes	39 (11.37%)		17 (4.96%)	22 (6.41%)		
No	304 (88.63%)		33 (9.62%)	271 (79.01%)		
Technique Characteristics						
Patient position					1.619	0.445
Supine	104 (30.32%)		13 (3.79%)	91 (26.53%)		
Prone	192 (55.98%)		32 (9.33%)	160 (46.65%)		
Lateral decubitus	47 (13.70%)		5 (1.46%)	42 (12.24%)		
Needle puncture site					1.559	0.816
Anterior	42 (12.24%)		7 (2.04%)	35 (10.20%)		
Anterolateral	54 (15.75%)		6 (1.75%)	48 (14.00%)		
Lateral	37 (10.79%)		5 (1.46%)	32 (9.33%)		
Posterior	165 (48.10%)		27 (7.87%)	138 (40.23%)		
Posterolateral	45 (13.12%)		5 (1.46%)	40 (11.66%)		
Length of intrapulmonary needle tract (mm)	0~70.3 11.6 (0.0~19.9)		11.0 (0.0~21.8)	11.6 (0.0~19.9)	-0.405	0.685
Dwell time (s)	200 (169~283)	70~1200	240 (174~360)	200 (168~271)	-1.992	0.046
Needle-pleural angle (°)	65 (48~80)	0~90	69 (52~85)	63 (48~80)	-1.078	0.281
Needle redirections					1.118	0.290
Yes	31 (9.04%)		7 (2.04%)	24 (7.00%)		
No	312 (90.96%)		43 (12.54%)	269 (78.42%)		
No. of pleural punctures	1 (1~1)	1~2	1 (1~1)	1 (1~1)	-0.492	0.622
No. of cores	2 (1~2)	1~6	2 (2~3)	2 (1~2)	-1.014	0.311
Diagnostic Characteristics					1.476	0.671
Malignant	248 (72.30%)		40 (11.66%)	208 (60.64%)		

Benign	80 (23.32%)	9 (2.62%)	71 (20.70%)
Borderline	2 (0.58%)	0	2 (0.58%)
Non-Diagnostic/Inadequate	13 (3.79%)	1 (0.30%)	12 (3.50%)

* Data are shown as number *N* (%) for categorical variables or median (lower quartile to upper quartile) for quantitative variables with non-normal distribution.

‡ Range only for quantitative variables.

† Chi-square test for categorical variables. Mann-Whitney U test for quantitative variables. All quantitative data showed non-normal distribution by Shapiro-Wilk test.

Table 2 Pathological types after CT guided lung puncture (343 cases)

Diagnostic characteristics	N (%)
Malignant	248 (72.30%)
Adenocarcinoma	191 (55.69%)
Squamous cell carcinoma	34 (9.91%)
Small cell carcinoma	6 (1.75%)
Metastasis from other tumor sites	6 (1.75%)
Neuroendocrine tumor	4 (1.17%)
Malignant pleural mesothelioma	3 (0.87%)
Undifferentiated carcinoma	2 (0.58%)
Adenosquamous carcinoma	1 (0.29%)
Lymphoepithelioid carcinoma	1 (0.29%)
Benign	80 (23.32%)
Chronic pneumonia	71 (20.70%)
Alveolitis	2 (0.58%)
Pulmonary hamartoma	2 (0.58%)
Tuberculosis	2 (0.58%)
Sclerosing pneumocytoma	2 (0.58%)
Neurilemmoma	1 (0.29%)
Borderline	2 (0.58%)
Solitary fibrous tumor	1 (0.29%)
Inflammatory myofibroblastic tumor	1 (0.29%)
Non-Diagnostic / Inadequate	13 (3.79%)

Table 3 Differences in pulmonary function between groups with and without pneumothorax evaluated by univariate analysis*

Clinical Characteristics	All Patients Studied		Pneumothorax		Z	P Value [†]
	Median	Lower quartile -Upper quartile	Yes*	No*		
No. of Cases Analyzed	343		50 (14.58%)	293 (85.42%)		
Pulmonary Function Characteristics						
VC (L)	3.32	2.83~3.94	3.42(2.78~3.98)	3.29(2.83~3.94)	-0.616	0.538
VC (% pred)	104.04	91.39~114.33	105.90(93.44~114.55)	103.80(91.19~114.32)	-0.179	0.858
FVC (L)	3.20	2.71~3.84	3.38(2.72~3.89)	3.19(2.71~3.83)	-0.733	0.464
FVC (% pred)	103.32	91.97~115.53	105.01(93.28~114.76)	103.01(91.59~115.70)	-0.363	0.716
FEV ₁ (L)	2.44	1.95~2.93	2.41(1.91~2.72)	2.44(1.96~2.95)	-0.700	0.484
FEV ₁ (% pred)	98.02	81.73~109.90	94.83(79.38~106.81)	98.39(81.98~110.13)	-1.101	0.271
FEV ₁ /FVC ratio (%)	75.95	69.13~81.21	72.54(67.14~78.44)	76.61(69.80~81.51)	-2.897	0.004
FEV ₁ /FVC ratio (% pred)	96.95	89.35~103.23	94.43(86.64~98.86)	97.45(90.73~103.54)	-2.825	0.005
FEF _{25%} (% pred)	88.36	63.99~106.12	73.51(56.45~102.49)	89.47(66.59~106.46)	-1.950	0.051
FEF _{50%} (% pred)	72.77	48.85~94.61	58.45(39.83~84.48)	77.45(51.67~95.88)	-2.458	0.014
FEF _{75%} (% pred)	66.40	44.66~89.90	55.74(42.07~79.40)	70.48(45.36~91.14)	-2.085	0.037
FEF _{25-75%} (% pred)	58.02	37.44~78.57	44.34(29.98~66.30)	59.61(39.40~79.84)	-2.134	0.033
PEF (% pred)	104.35	84.40~119.59	101.45(83.24~114.74)	104.54(84.97~121.03)	-1.253	0.210

* Data are shown as median (lower quartile to upper quartile).

[†] Mann-Whitney U test. All the quantitative data showed non-normal distribution by Shapiro-Wilk test.

Table 4 Relationship between incidence of pneumothorax and different types and severity of pulmonary function abnormalities

	Pneumothorax		χ^2	PValue [†]
	Yes*	No*		
Normal Ventilation Function	18	150		
Small Airway Dysfunctions[‡]	10	59	0.670	0.413
Types of Function Abnormalities[‡]				
Obstructive function abnormalities	18	55	7.786	0.005
Restrictive function abnormalities	1	10	0	1.000
Mixed function abnormalities	3	19	0.002	0.961
Severity of All Function Abnormalities[‡]			4.612	0.312
Mild spirometric abnormality ($70 \leq FEV_1\%$ pred)	14	40		
Moderate spirometric abnormality ($60 \leq FEV_1\%$ pred < 70)	2	21		
Moderately severe spirometric abnormality ($50 \leq FEV_1\%$ pred < 60)	3	9		
Severe spirometric abnormality ($35 \leq FEV_1\%$ pred < 50)	1	10		
Very severe spirometric abnormality ($FEV_1\%$ pred < 35)	2	4		
Severity of Obstructive Function Abnormalities[‡]			2.167	0.604
Mild spirometric abnormality ($70 \leq FEV_1\%$ pred)	14	35		
Moderate spirometric abnormality ($60 \leq FEV_1\%$ pred < 70)	2	14		
Moderately severe spirometric abnormality ($50 \leq FEV_1\%$ pred < 60)	2	5		
Severe spirometric abnormality ($35 \leq FEV_1\%$ pred < 50)	0	1		
Very severe spirometric abnormality ($FEV_1\%$ pred < 35)	0	0		

* Data are presented as number.

[‡] Each group compared with normal ventilation function group.

[‡] Overall comparison among different severity levels in obstructive, restrictive and mixed function abnormalities.

[‡] Overall comparison among different severity levels in obstructive function abnormalities.

[†] Chi-square test.

% pred, percent predicted.

Table 5 Logistic regression model estimates roles of pulmonary function parameters on pneumothorax

		Odds Ratio	95% CI	<i>P</i> value [†]
FEV ₁ /FVC ratio (%)	< 70 vs. ≥ 70	2.182	1.173~4.060	0.014
FEF _{50%} (% pred)	< 65 vs. ≥ 65	2.366	1.286~4.352	0.006
FEF _{75%} (% pred)	< 65 vs. ≥ 65	2.303	1.228~4.319	0.009
FEF _{25-75%} (% pred)	< 65 vs. ≥ 65	1.974	1.007~3.871	0.048

Table 6 Multivariable logistic regression model for predictors of pneumothorax (PTX) in all patients studied

Multivariable Predictors*	All patients (PTX = 50, without PTX = 293)		
	Odds Ratio	95% CI	<i>P</i> value
Location of lesion	2.128	1.117~4.051	0.022
Presence of emphysema	4.937	2.193~11.115	1.150×10⁻⁴
Dwell time (s)	1.001	0.999~1.003	0.206
FEV ₁ /FVC ratio (%)	0.988	0.961~1.016	0.407

* Logistic regression model only included significant covariates from univariate analysis. Since FEF_{50%}, FEF_{75%} and FEF_{25-75%} are related to FEV₁/FVC, only FEV₁/FVC ratio (%) is retained.

Figures

Figure 1

(a) CT-guided core needle biopsy of a solitary suspected lesion in the right lower lobe, in a 56-year-old male patient with 6 pack-years smoking. (b) Showed the biopsy needle (arrow) inserted within the lesion, which was later pathologically confirmed to be pulmonary adenocarcinoma. The patient was in lateral position on the CT table. The needle-pleural angle (curved white arrow), that is the minimum angle formed by a line tangent to the pleura at the puncture point and a line drawn along the needle, was 63° . The length of the needle track from the pleura to the lesion was 14.4 mm. The dwell time was 660 s. (c) CT image after the removal of the biopsy needle showed pneumothorax (arrowhead), which continued to increase until the chest drainage catheter was inserted.

Supplementary Files

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