ORIGINAL ARTICLE

Risk factors for pneumothorax and pulmonary hemorrhage following computed tomography-guided transthoracic core-needle biopsy of subpleural lung lesions

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Abstract

Background: Identifying the risk factors for complications may alert the physicians and help them adjust their plans before performing computed tomography–guided lung biopsies. Reportedly, a pleura-nodule distance longer than 2.0 cm is a strong predictor for pneumothorax and pulmonary hemorrhage. However, the rate and risk factors of biopsy-associated complications in subpleural lesions have not been assessed. This study aimed to identify the risk factors for pneumothorax and pulmonary hemorrhage in subpleural lesions ≤2.0 cm in depth.

Methods: Altogether, 196 patients (196 subpleural lesions, lesion depth: 0.1–2.0 cm) who underwent computed tomography–guided transthoracic core-needle biopsies between March 2017 and November 2017 were retrospectively analyzed. Univariate analysis of risk factors including patient-related, lesion-related, and procedure-related characteristics was performed for pneumothorax ≥1 cm and pulmonary hemorrhage ≥2 cm after the biopsy. Multivariate logistic regression analysis was performed to identify the independent risk factors.

Results: Pneumothorax ≥1 cm and pulmonary hemorrhage ≥2 cm were identified in 35 (17.9%) and 32 (16.3%) cases, respectively. In the multivariate analysis, a longer needle path (odds ratio [OR], 1.976; 95% confidence interval [CI], 1.113–3.506; p = 0.020) and low attenuation along the biopsy tract (OR, 3.080; 95% CI, 1.038–9.139; p = 0.043) were predictors of pneumothorax ≥ 1 cm. Ground-glass lesions (OR, 2.360; 95% CI, 1.009–5.521; p = 0.048) and smaller needle-pleura angle (OR, 0.325; 95% CI, 0.145–0.728; p = 0.006) were associated with pulmonary hemorrhage ≥2 cm.

Conclusion: For subpleural lesions ≤2.0 cm in depth, a puncture route having a shorter needle path and passing through the lung parenchyma with higher attenuation may reduce the risk of biopsy-associated pneumothorax ≥1 cm. A higher needle-pleura angle may reduce the risk of pulmonary hemorrhage ≥2 cm in the short axis.

Keywords: Computed tomography; Image-guided biopsy; Lung; Pneumothorax; Pulmonary hemorrhage

1. INTRODUCTION

Pneumothorax and pulmonary hemorrhage are the most common complications associated with computed tomography (CT)–guided transthoracic biopsies, with an incidence of 16%–40% and 3%–68%, respectively, according to previous studies.[1–3] Known risk factors for pneumothorax include a smaller lesion size,[4] greater lesion depth,[5] longer needle path,[6,7] smaller needle-pleura angle,[5,8] needle track across the fissure,[8] male sex, older age,[3] and the presence of lung emphysema or chronic obstructive pulmonary disease.[9] CT-guided biopsy of small-sized lesions is more difficult, as it requires a greater number of attempts to adjust the needle. The pleural hole created by a needle via an oblique puncture route is postulated to be larger than that created via a vertical route[8] and larger pleural hole is associated with a higher risk of air leakage and pneumothorax. Older age is reportedly a risk factor, since elderly patients experience difficulties in following the instruction to hold their breath than that experienced by younger patients,[3] potentially increasing the risk of alveolar rupture during needle adjustment. Men are at a higher risk as they exhibit a greater prevalence of smoking than that exhibited by women. Smoking is a well-recognized cause of emphysema, which induces lung inflammation and alveolar destruction,[10] thereby resulting in lower parenchymal attenuation on CT scans.

The known risk factors for pulmonary hemorrhage include a smaller lesion size, greater lesion depth,[4,11] longer needle path,[6] subsolid lesion, and older age.[11] A smaller lesion is considered to require a greater number of attempts to adjust the biopsy

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needle and a longer needle path that traverses a greater number of pulmonary vessels, thereby increasing the risk of pulmonary hemorrhage.

In clinical practice, technical difficulties are commonly encountered during CT-guided transthoracic biopsy of subpleural lesions due to their proximity to the ribs and pleura. While most of the previous studies reported that the risk of pneumothorax increased with an increase in the depth of the lesion (distance from the pleura), two studies pointed out that subpleural lesions 0.1–2.0 cm in depth exhibited the highest risk of developing pneumothorax after a core-needle biopsy.[4,12] Using a longer transpulmonary needle path in a CT-guided biopsy of subpleural lesions is also associated with a higher frequency of chest tube insertions for pneumothorax and a higher rate of bleeding.[13,14] For obtaining tissue from the peripheral lung, radial endobronchial ultrasound-guided transbronchial biopsy is an alternative to CT-guided biopsy. It is associated with fewer occurrences of biopsy-associated pneumothorax compared with those associated with CT-guided transthoracic biopsy.[15] However, for lesions <2 cm in size, the diagnostic yield of radial endobronchial ultrasound-guided transbronchial biopsies is inferior to that of CT-guided transthoracic biopsies[16] due to the difficulty experienced in placing the ultrasound probe at the center of a small lesion.

The present study aimed to identify the risk factors for pneumothorax and pulmonary hemorrhage after CT-guided transthoracic biopsies of subpleural lesions 0.1–2.0 cm in depth.

2. METHODS

2.1. Study population

This retrospective study was approved by the local institutional review board and the requirement for informed consent was waived. Data regarding patients who underwent CT-guided lung biopsy between March 2017 and November 2017 were retrieved from the radiology information system. Mediastinal lesions, lesions directly contacting the pleura, or lesions >2 cm away from the pleura were excluded from the analyses. Lesions that had undergone previous CT-guided biopsy, bronchoscopy-guided, or ultrasound-guided thoracic intervention within 1 month were also excluded.

2.2. Biopsy technique

Informed consent for undergoing CT-guided biopsy was obtained from all patients. All procedures were performed by or under the supervision of one of eight attending radiologists with 6–24 years of experience in image-guided biopsy. A 19-gauge coaxial introducer and a 20-gauge cutting needle system with a cutting throw length of 10 mm or 20 mm were used for all biopsies. The positioning of the patients (prone, supine, oblique, or in a lateral decubitus position) was decided by the supervising radiologist according to the lesion location. The biopsy needle system was inserted under CT guidance. Multiple coaxial biopsies were routinely performed for each target lesion by slightly tilting the needle system in multiple directions, with an average of seven specimens per lesion. There were no on-site cytologists during the biopsy procedure. The specimens were sent for histopathological analyses, imprint cytology, and microbial culture. Imprint cytology specimens were prepared by lightly pressing the tissue on glass slides. The coaxial needle system was withdrawn after adequate specimen retrieval. Whole-lung CT scans with a slice thickness of 5 mm were subsequently obtained to screen for biopsy-associated complications such as pneumothorax, hemothorax, and pulmonary hemorrhage.

2.3. Image analysis

CT images were retrospectively reviewed and various lesion-related or procedure-related factors were determined or measured on the images using electronic calipers in the lung window setting (window level, 650 Hounsfield units [HU]; window width, 1600 HU) of a DICOM viewer software (SmartIris, SYSPOWER, Taipei, Taiwan). The measurement scheme is depicted in Fig. 1. Lesion-related factors included lesion size, morphology, depth (pleura-lesion distance), and location in the upper or lower lobe. Procedure-related factors included lung

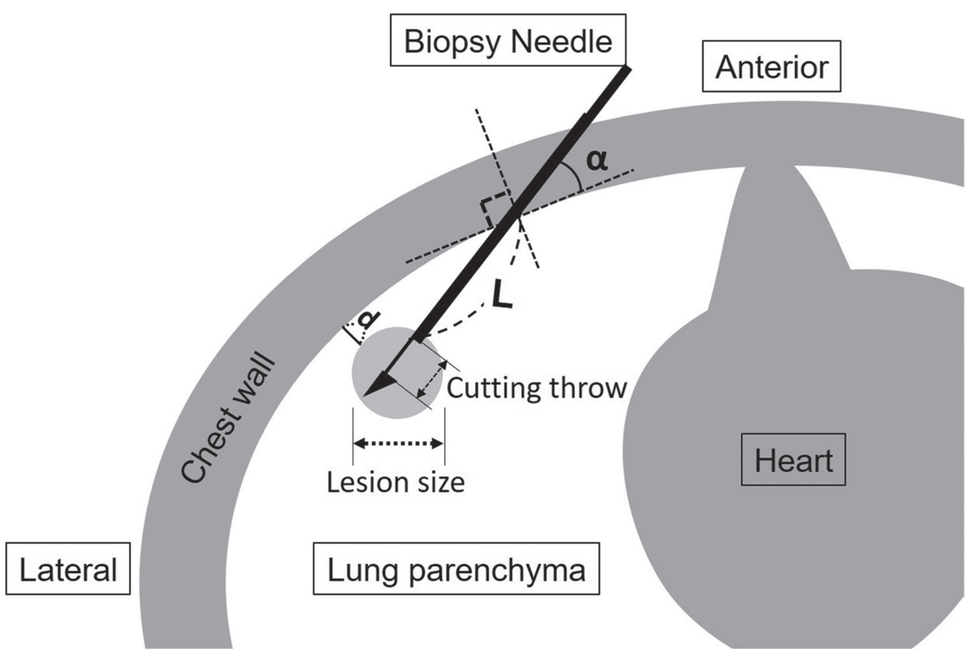

Fig. 1 Illustration of manually measured parameters on an axial computed tomography scan. The needle-pleura angle (α), needle-path length (L), pleura-lesion distance (d), and lesion size are specified in the figure.

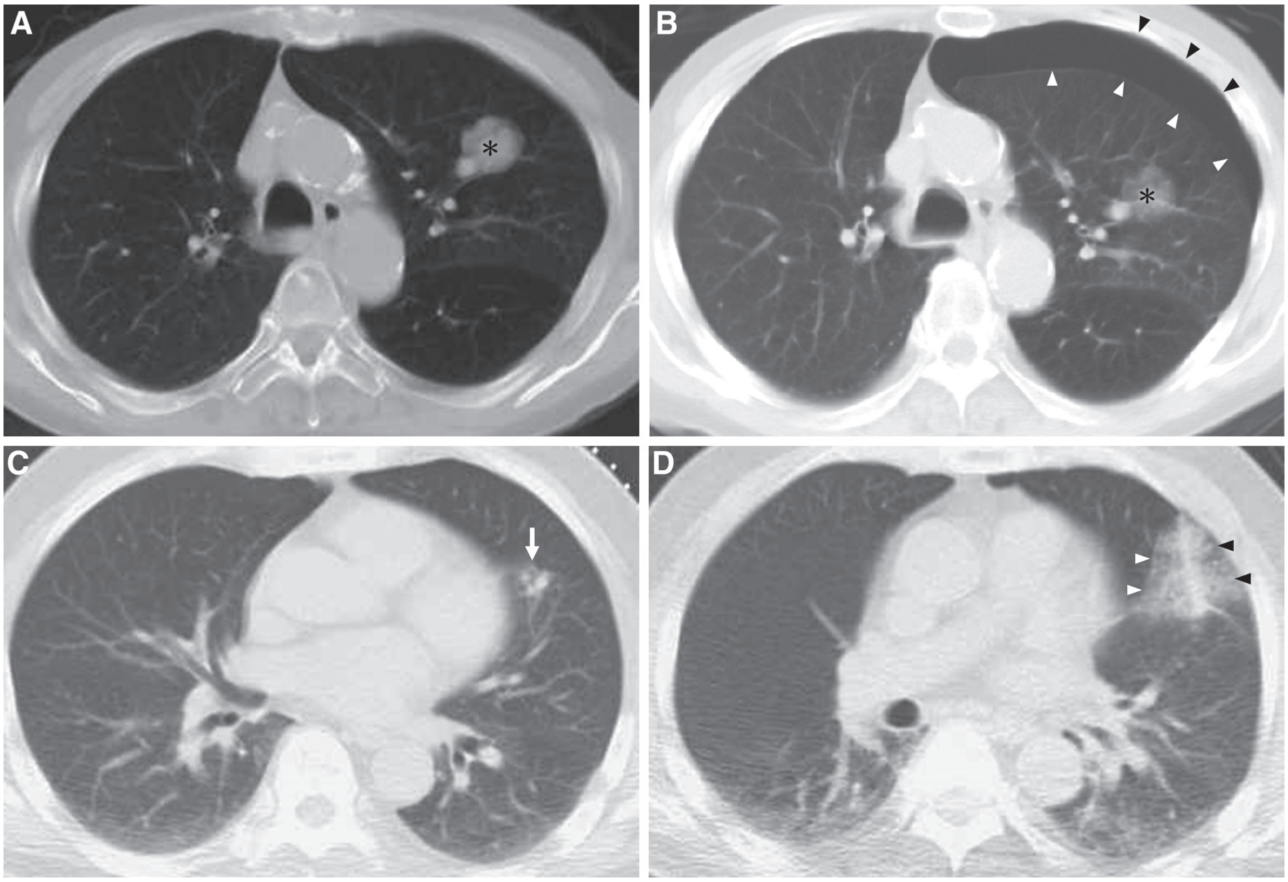

Fig. 2 Noncontrast axial lung computed tomography scan immediately after biopsy in two different patients. A, B, The lesion is in the left upper lung, denoted by an asterisk before (A) and after (B) the biopsy. After the biopsy, the presence of gas between the chest wall (B, black arrowhead) and lung surface (B, white arrowhead) indicates pneumothorax. C, In another patient, the lesion (arrow) is well-defined, without any ground-glass opacities surrounding the lesion before the biopsy. D, After the biopsy, the new ill-defined centrilobular nodules with ground-glass opacities along the needle tract (arrowhead) indicate pulmonary hemorrhage.

attenuation along the needle path (measured in HU), length of the needle path across the aerated parenchyma, needle-pleura angle, patient position, duration of the procedure, and the number of specimens.

Pneumothorax and pulmonary hemorrhage were the primary outcomes and both were evaluated on an axial CT scan immediately after the biopsy (Fig. 2). The size of pneumothorax was defined as the vertical distance between the chest wall or the hemidiaphragm and the lung surface. According to this definition, cases with significant pneumothorax in the lung base (significant vertical distance between the lung surface and the hemidiaphragm) were also considered to avoid classifying them under the category of minimal pneumothorax. This resulted in more accurate classification of the size of the pneumothorax. Pulmonary hemorrhage was defined as newly identified ground-glass opacities, centrilobular nodules, or consolidation around the target lesion or along the needle track after the biopsy. The size of the pulmonary hemorrhage was measured along its short-axis diameter.

As pneumothorax <1 cm rarely requires further management,[17] biopsy-related pneumothorax was classified dichotomously as pneumothorax ≥1 cm and pneumothorax <1 cm. Since previous studies have classified pulmonary hemorrhage >2 cm as high-grade hemorrhage,[11] biopsy-related hemorrhage was classified dichotomously as presence or absence of pulmonary hemorrhage ≥2 cm. The timing of the pulmonary hemorrhage relative to the pneumothorax was also classified into two categories: (1) no pulmonary hemorrhage or hemorrhage presenting after the pneumothorax and (2) presence of pulmonary hemorrhage simultaneously with or before the pneumothorax. The lesion size was classified as ≤3 cm or >3 cm.

2.4. Statistical analysis

All statistical analyses were performed using the R software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria). Comparisons of patient-related, lesion-related, and procedure-related factors were performed between the pneumothorax outcome groups and between the pulmonary hemorrhage outcome groups. Lung attenuation along the needle path was classified as low when the HU value for attenuation along the needle path was in the lowest quintile. In the univariate analysis, an independent *t*-test and chi-squared test were used to compare the continuous and categorical variables, respectively. Variables with a p value <0.10 in the univariate analysis were included in the multivariate analysis for the prediction of biopsy-related pneumothorax ≥1 cm or pulmonary hemorrhage ≥2 cm using binary logistic regression. Statistical significance was set at $p < 0.05$.

3. RESULTS

According to the inclusion criteria, 196 patients with 196 subpleural lesions (depth: 0.1–2.0 cm) who underwent CT-guided core-needle biopsy were included (Fig. 3).

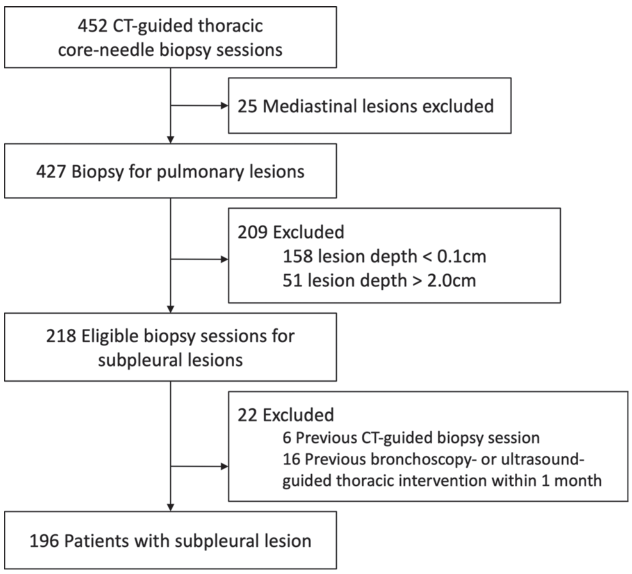

Fig. 3 Flow chart representing the study population. Cumulatively, 196 subpleural lesions in 196 patients were included in the study.

The characteristics of patients, lesions, and biopsy procedures are presented in Table 1. The study population included 56 (28.6%) previous or current smokers. The mean age was 67 years. Men constituted 48% of the study population. The average size of the target lung nodule was 2.52 ± 1.41 cm, with a mean distance of 0.90 ± 0.45 cm from the pleura. The average attenuation along the needle path was −756 ± 107 HU. The lowest quintile of attenuation in the lung parenchyma traversed by the needle path was −838 HU. Attenuation of the lung parenchyma ≤ −838 HU along the needle path was classified as low attenuation according to the defined method.

Pneumothorax occurred in 110 (56.1%) patients and the mean size of the pneumothorax was 0.49 cm. Among these patients, 35 (17.9%) had pneumothorax ≥1 cm. Pulmonary hemorrhage occurred in 144 (73.5%) patients and the mean size of the hemorrhage was 1.04 cm. Among these, 32 (16.3%) had pulmonary hemorrhage ≥2 cm. All cases of pneumothorax and pulmonary hemorrhage were self-limiting. None of the patients required transfusion, drainage catheter insertion, or angiographic or operative procedures. No biopsy-associated hemothorax was observed in our study population. Pathologically, the 196 subpleural lesions included 128 (65.3%) cases of non-small cell carcinomas, 25 (12.8%) of other lung malignancies or metastatic tumors, 30 (15.3%) of inflammation or infection, and 10 (5.1%) of other nonmalignant diagnoses or benign lung parenchyma. Two specimens showing fragments of alveolar parenchyma or fibrous tissue under the microscope were deemed inadequate by the pathologist, although they were retrieved with six and three pieces of gray soft tissue, respectively. One lesion's specimen could not be acquired due to technical failure. The lesion was in the right lower lobe and inaccessible despite a 1-hour trial including different types of breath-holding techniques.

In the univariate analysis (Table 2), the incidence of pneumothorax ≥1 cm was higher among previous or current smokers when compared with nonsmokers (32.1% vs 12.1%, p = 0.001), among lung lesions ≥3 cm when compared with smaller lesions (28.6% vs 13.6%, p = 0.013), among nonground-glass lesions when compared with ground-glass lesions (20.9% vs 7.0%, p = 0.035), among cases with low attenuation of the lung parenchyma along the needle path when compared with cases with high attenuation (35.0% vs 13.5%, p = 0.002), and among cases without pulmonary hemorrhage or hemorrhage after pneumothorax when compared with cases having hemorrhage simultaneously or before pneumothorax (35.0% vs 6.0%, p < 0.001).

Table 1

Characteristics of the 196 procedures

Factors	Value
Patient-related factors	
Age, y	67 ± 12
Gender	
Male	94 (48.0)
Female	102 (52.0)
Smoking status	
Nonsmokers	140 (71.4)
Previous or current smokers	56 (28.6)
Lesion-related factors	
Lesion size, cm	2.52 ± 1.41
Lesion morphology	
Ground-glass[a]	43 (21.9)
Solid[b]	137 (69.9)
Consolidation[c]	16 (8.2)
Pleura-lesion distance, cm	0.90 ± 0.45
Lesion location[d]	
Upper lung	123 (62.8)
Lower lung	73 (37.2)
Procedure-related factors	
Lung attenuation along needle path, HU	−756 ± 107
Needle-path length, cm	1.85 ± 0.96
Needle-pleura angle, °	
<50	52 (26.5)
50–69	59 (30.1)
70–90	85 (43.4)
Patient position	
Supine	81 (41.3)
Prone	89 (45.4)
Oblique or lateral decubitus	26 (13.3)
Procedural duration, min	49 ± 15
Specimen number	7 ± 2

The continuous variables are presented as mean ± standard deviation. Except where indicated otherwise, data represent the number (%) of patients and apply to categorical variables.
[a]Defined as subsolid nodule or opacity including pure ground-glass nodule or opacity, which did not completely obscure the pulmonary vasculature in the background parenchyma.
[b]Lesion with homogeneous attenuation, non-ground-glass opacity, and well-defined margin.
[c]Lesion with heterogeneous attenuation, non-rounded or nodular shape, with or without air-bronchogram, or with appearance resembling lobar pneumonia or organizing pneumonia, and did not fall into the definition of solid lesion and ground-glass lesion.
[d]The location of the lesion was categorized into upper lung and lower lung. The upper lung included lesions in bilateral upper lobes and right middle lobe, and the lower lung included lesions in bilateral lower lobes.
HU = Hounsfield unit

In the univariate analysis (Table 3), the incidence of pulmonary hemorrhage ≥2 cm was higher among ground-glass lesions when compared with nonground-glass lesions (30.2% vs 12.4%, p = 0.005) and among cases with needle-pleura angle <50° when compared with those having higher needle-pleura angles (30.8% vs 11.1%, p = 0.001). The incidence of pulmonary hemorrhage ≥2 cm was higher among lesions <3 cm in size when compared with those ≥3 cm in size, although the difference was not statistically significant (19.3% vs 8.9%, p = 0.076).

Multivariate analysis for the prediction of pneumothorax ≥1 cm after CT-guided biopsy was performed by including the factors with p values <0.10 in the univariate analysis. In the multivariate analysis, previous or current smoking (odds ratio [OR], 4.859; 95% confidence interval [CI], 1.341–17.598; p = 0.016), higher age (per year increase) (OR, 1.061; 95% CI, 1.014–1.110; p = 0.010), low attenuation of the lung parenchyma

Table 2

Characteristics of the 196 procedures, stratified by the presence or absence of pneumothorax ≥1 cm on the computed tomography scan immediately after core-needle biopsy

	Pneumothorax ≥ 1 cm		
	No (n = 161)	**Yes (n = 35)**	***p***
Patient-related factors			
Age, y	66 ± 12	74 ± 11	<0.001
Gender			0.052
Male	72 (76.6)	22 (23.4)	
Female	89 (87.3)	13 (12.7)	
Smoking status			0.001
Nonsmokers	123 (87.9)	17 (12.1)	
Previous or current smokers	38 (67.9)	18 (32.1)	
Lesion-related factors			
Lesion size ≥3 cm			0.013
<3 cm	121 (86.4)	19 (13.6)	
≥3 cm	40 (71.4)	16 (28.6)	
Lesion morphology			0.035
Nonground-glass lesion	121 (79.1)	32 (20.9)	
Ground-glass lesion	40 (93.0)	3 (7.0)	
Pleura-lesion distance, cm	0.88 ± 0.44	1.02 ± 0.46	0.091
Lesion location[a]			0.689
Upper lung	100 (81.3)	23 (18.7)	
Lower lung	61 (83.6)	12 (16.4)	
Procedure-related factors			
Low attenuation lung along needle path[b]			0.002
No	135 (86.5)	21 (13.5)	
Yes	26 (65.0)	14 (35.0)	
Needle-path length, cm	1.77 ± 0.94	2.20 ± 1.00	0.016
Needle-pleura angle			0.165
<50°	46 (88.5)	6 (11.5)	
≥50°	115 (79.9)	29 (20.1)	
Patient position			0.368
Supine	69 (85.2)	12 (14.8)	
Prone	73 (82.0)	16 (18.0)	
Oblique/lateral	19 (73.1)	7 (26.9)	
Procedural duration, min	49 ± 15	49 ± 16	0.975
Specimen number	7 ± 2	7 ± 2	0.520
Presence of pulmonary hemorrhage			0.001
No	35 (67.3)	17 (32.7)	
Yes	126 (87.5)	18 (12.5)	
Timing of pulmonary hemorrhage			<0.001
No or after pneumothorax	52 (65.0)	28 (35.0)	
Simultaneous or before pneumothorax	109 (94.0)	7 (6.0)	

The continuous variables are presented as mean ± standard deviation. Except where indicated otherwise, data represent the number (%) of patients and apply to categorical variables.
[a]The location of the lesion was categorized into upper lung and lower lung. The upper lung included lesions in bilateral upper lobes and right middle lobe, and the lower lung included lesions in bilateral lower lobes.
[b]Lung attenuation along needle path being −838 Hounsfield unit or less.

along the needle path (OR, 3.080; 95% CI, 1.038–9.139; p = 0.043), and greater length of the needle path (OR, 1.976; 95% CI, 1.113–3.506; p = 0.020) were significant predictors of pneumothorax ≥1 cm after a CT-guided core-needle biopsy (Table 4). In the multivariate analysis for the prediction of pulmonary hemorrhage ≥2 cm (Table 5), ground-glass lesions (OR, 2.360; 95% CI, 1.009–5.521; p = 0.048) were significant predictors of pulmonary hemorrhage ≥2 cm after a CT-guided core-needle biopsy. A higher needle-pleura angle was associated with a lower rate of pulmonary hemorrhage ≥2 cm (OR, 0.325; 95% CI, 0.145–0.728; p = 0.006).

Table 3

Characteristics of the 196 procedures, stratified by the presence or absence of pulmonary hemorrhage ≥2 cm in the short axis on the computed tomography scan immediately after core-needle biopsy

	Pulmonary hemorrhage ≥2 cm		
	No (n = 164)	**Yes (n = 32)**	***p***
Patient-related factors			
Smoking status			0.625
Nonsmokers	116 (82.9)	24 (17.1)	
Previous or current smokers	48 (85.7)	8 (14.3)	
Age, y	68 ± 12	65 ± 11	0.281
Gender			0.893
Male	79 (84.0)	15 (16.0)	
Female	85 (83.3)	17 (16.7)	
Lesion-related factors			
Lesion size ≥3 cm			0.076
<3 cm	113 (80.7)	27 (19.3)	
≥3 cm	51 (91.1)	5 (8.9)	
Lesion morphology			0.005
Nonground-glass lesion	134 (87.6)	19 (12.4)	
Ground-glass lesion	30 (69.8)	13 (30.2)	
Pleura-lesion distance, cm	0.92 ± 0.45	0.80 ± 0.42	0.154
Lesion location[a]			0.714
Upper lung	102 (82.9)	21 (17.1)	
Lower lung	62 (84.9)	11 (15.1)	
Procedure-related factors			
Low attenuation lung along needle path[b]			0.799
No	130 (83.3)	26 (16.7)	
Yes	34 (85.0)	6 (15.0)	
Needle-path length, cm	1.81 ± 0.94	2.02 ± 1.06	0.272
Needle-pleura angle			0.001
<50°	36 (69.2)	16 (30.8)	
≥50°	128 (88.9)	16 (11.1)	
Patient position			0.460
Supine	67 (82.7)	14 (17.3)	
Prone	77 (86.5)	12 (13.5)	
Oblique/lateral	20 (76.9)	6 (23.1)	
Procedural duration, min	49 ± 15	47 ± 16	0.393
Specimen number	7 ± 2	7 ± 2	0.299

The continuous variables are presented as mean ± SD. Except where indicated otherwise, data are represented as the number (%) of patients and apply to categorical variables.
[a]The location of the lesion was categorized into upper lung and lower lung. The upper lung included lesions in bilateral upper lobes and right middle lobe, and the lower lung included lesions in bilateral lower lobes.
[b]Lung attenuation along needle path being −838 Hounsfield unit or less.

4. DISCUSSION

To our knowledge, the present study is the first to assess the risk factors for pneumothorax and pulmonary hemorrhage following CT-guided core-needle biopsies of subpleural lesions 0.1–2.0 cm in depth. We observed that previous or current smoking, higher age, low attenuation of the lung parenchyma along the needle path, and greater length of the needle path were significant predictors of biopsy-associated pneumothorax ≥1 cm. Ground-glass lesions predicted pulmonary hemorrhage ≥2 cm and a higher needle-pleura angle was associated with a lower incidence of pulmonary hemorrhage ≥2 cm.

Table 4

Multivariate analysis using a binary logistic regression for the prediction of pneumothorax ≥1 cm on the computed tomography scan immediately after core-needle biopsy

	Pneumothorax ≥1 cm	
	OR (95% CI)	*p*
Smoking status		0.016
Nonsmokers	1 (reference)	
Previous or current smokers	4.859 (1.341–17.598)	
Age, y	1.061 (1.014–1.110)	0.010
Female gender	1.243 (0.337–4.580)	0.744
Lesion size ≥3 cm	0.999 (0.369–2.710)	0.999
Lesion morphology		0.922
Nonground-glass lesion	1 (reference)	
Ground-glass lesion	0.927 (0.201–4.273)	
Pleura-lesion distance, cm	1.321 (0.427–4.085)	0.629
Low attenuation lung along needle path[a]	3.080 (1.038–9.139)	0.043
Needle-path length, cm	1.976 (1.113–3.506)	0.020
Timing of pulmonary hemorrhage		<0.001
No or after pneumothorax	1 (reference)	
Simultaneous or before pneumothorax	0.047 (0.013–0.169)	

CI = confidence interval; OR = odds radio.

[a]Lung attenuation along needle path being −838 Hounsfield unit or less.

A needle-pleura angle >50° was associated with a lower incidence of pulmonary hemorrhage ≥2 cm. We speculated that this was because a larger angle could result in needle direction more parallel to the pulmonary vessel, thereby decreasing the rate of vascular puncture. A previous study showed that the needle-pleura angle was not associated with a higher grade of hemorrhage.[11] However, the classification of the angulation group in the aforementioned study was dichotomous (90° or <90°). We speculate that the use of a dichotomous classification for the prediction of hemorrhage should be based on a value other than 90°. The present study showed that a needle-pleura angle <50° was associated with a greater incidence of pulmonary hemorrhage ≥2 cm. In the present study, a post hoc receiver operating characteristic curve analysis for the needle-pleura angle and pulmonary hemorrhage ≥2 cm yielded a cutoff value of 63.6° for predicting high-grade pulmonary hemorrhage.

We observed that a lower needle-pleura angle exhibited weak to moderate correlation with longer needle path ($r = -0.330$, $p < 0.001$) and the size of pulmonary hemorrhage in the short axis ($r = -0.296$, $p < 0.001$). However, longer needle path was a well-known risk factor for pneumothorax and a statistically significant predictor of pneumothorax ≥1 cm in the present study (OR, 1.976; 95% CI, 1.113–3.506; $p = 0.020$). The negative linear correlation between the needle-pleura angle and the length of the needle path in the present study may be due to the subpleural location of the lesions where a biopsy route with a longer needle path inevitably results in a smaller needle-pleura angle. A smaller needle-pleura angle simultaneously correlated with one risk factor (longer needle path) and one protective factor (pulmonary hemorrhage) for pneumothorax in the present study. This may explain its inability to significantly predict biopsy-associated pneumothorax, as previously reported in the literature.

In 2014, Wang et al[18] reported a higher rate of pneumothorax in patients with emphysema and in active or former smokers. The present study showed that previous or current smokers exhibited a higher incidence of pneumothorax ≥1 cm (32.1% vs 12.1%, $p = 0.001$) when compared with nonsmokers, which is consistent with the results reported by Wang et al. However, previous or current smokers in the present study did not always develop subpleural emphysema (defined as <−960 HU[19]). The proportion of low attenuation of the lung parenchyma along the needle path in the present study was not significantly different between nonsmokers and previous or current smokers (19.3% vs 23.2%, $p = 0.538$). This finding is consistent with the heterogeneous nature and severity of smoking-induced emphysema, a disease entity that remains poorly understood.[20] These characteristics of smoking-induced emphysema may support the finding of the present study that the local factor of low attenuation along the needle path could serve as an independent risk factor for pneumothorax ≥1 cm.

The present study found that older age was a significant predictor of pneumothorax ≥1 cm (annual increase in age: OR, 1.061; 95% CI, 1.014–1.110; $p = 0.010$). Aging is an important cause of emphysema and enlarged alveolar air spaces without alveolar wall destruction were observed in asymptomatic nonsmoking elderly individuals, also known as the senile lung[21,22] and is a risk factor for pneumothorax.

Previous literature has suggested that needle-tract bleeding serves as a protective factor against pneumothorax.[2,23] Although our results were consistent with this finding, our approach explored the relationship between pneumothorax and pulmonary hemorrhage by considering the timing of pulmonary hemorrhage relative to pneumothorax. To our knowledge, this factor has not been discussed in previous literature. The findings related to our approach might support the speculation that the presence of pulmonary hemorrhage concomitant with pneumothorax or before pneumothorax may have a greater effect on sealing the needle tract, thereby leading to a lower amount of air leak and providing a solid support for the proposed preventive effect of pulmonary hemorrhage against the development of pneumothorax.

A high-diagnostic rate was noted in the present study wherein only three out of 196 lesions (1.5%) were associated with inadequate specimens or technical failure. Hiraki et al[24] studied CT fluoroscopy-guided biopsies in 1000 pulmonary lesions and reported that the rate of nondiagnostic results was 0.6% (n = 6). Choi et al[25] studied CT-guided core-needle biopsies in 153 lesions and reported that the rate of nondiagnostic results was 4.5%. Poulou et al[26] studied CT-guided core-needle biopsies in 245 pulmonary lesions and reported that the rate of nondiagnostic results was 6.1%. The rate of nondiagnostic results in the present study was comparable to that in previous research investigating the diagnostic value of CT-guided biopsy for general location of lesions without specific analysis of subpleural locations. Thus, our results suggest that CT-guided biopsy has a good diagnostic value for subpleural lesions.

The present study has several limitations. Selection bias was inevitable due to the retrospective and single-center study design. Pneumothorax was associated with multiple variables, leading to the presence of confounding factors. Nevertheless, a multivariate analysis was performed to minimize the confounding effects. Variations may occur in the manual measurements of

Table 5

Multivariate analysis using a binary logistic regression for the prediction of pulmonary hemorrhage ≥2 cm on the computed tomography scan immediately after core-needle biopsy

	Pulmonary hemorrhage ≥2 cm	
	OR (95% CI)	*p*
Lesion size ≥3 cm	0.535 (0.187–1.530)	0.243
Lesion morphology		0.048
Nonground-glass lesion	1 (reference)	
Ground-glass lesion	2.360 (1.009–5.521)	
Needle-pleura angle >50°	0.325 (0.145–0.728)	0.006

CI = confidence interval; OR = odds radio.

the needle-pleura angle. Most of the literature, including the present study, defines the needle-pleura angle as the angle between the biopsy needle path and a tangential line manually drawn at the puncture point on the pleura.

In conclusion, when planning a CT-guided core-needle biopsy of subpleural lesions ≤2.0 cm in depth, selecting a puncture route with a shorter needle path and a higher needle-pleura angle may reduce the risk of biopsy-associated pneumothorax and pulmonary hemorrhage, respectively. Caution should be exercised when traversing the lung parenchyma with low attenuation to avoid biopsy-associated pneumothorax.

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REFERENCES

1. Lee HY, Lee IJ. Assessment of independent risk factors of developing pneumothorax during percutaneous core needle lung biopsy: focus on lesion depth. *Iran J Radiol* 2016;**13**:e30929.
2. Zhang HF, Liao MY, Zhu DY, Chen J, Wang YF. Lung radiodensity along the needle passage is a quantitative predictor of pneumothorax after CT-guided percutaneous core needle biopsy. *Clin Radiol* 2018;**73**:319.e1–7.
3. Takeshita J, Masago K, Kato R, Hata A, Kaji R, Fujita S, et al. CT-guided fine-needle aspiration and core needle biopsies of pulmonary lesions: a single-center experience with 750 biopsies in Japan. *AJR Am J Roentgenol* 2015;**204**:29–34.
4. Yeow KM, Su IH, Pan KT, Tsay PK, Lui KW, Cheung YC, et al. Risk factors of pneumothorax and bleeding: multivariate analysis of 660 CT-guided coaxial cutting needle lung biopsies. *Chest* 2004;**126**:748–54.
5. Saji H, Nakamura H, Tsuchida T, Tsuboi M, Kawate N, Konaka C, et al. 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* 2002;**121**:1521–6.
6. Huang MD, Weng HH, Hsu SL, Hsu LS, Lin WM, Chen CW, et al. Accuracy and complications of CT-guided pulmonary core biopsy in small nodules: a single-center experience. *Cancer Imaging* 2019;**19**:51.
7. Leger T, Jerjir N, Gregory J, Bennani S, Freche G, Revel MP, et al. Does ipsilateral-dependent positioning during percutaneous lung biopsy decrease the risk of pneumothorax? *AJR Am J Roentgenol* 2019;**212**:461–6.
8. Ko JP, Shepard JO, Drucker EA, Aquino SL, Sharma A, Sabloff B, et al. Factors influencing pneumothorax rate at lung biopsy: are dwell time and angle of pleural puncture contributing factors? *Radiology* 2001;**218**:491–6.
9. Topal U, Ediz B. Transthoracic needle biopsy: factors effecting risk of pneumothorax. *Eur J Radiol* 2003;**48**:263–7.
10. Kheradmand F, You R, Hee Gu B, Corry DB. Cigarette smoke and DNA cleavage promote lung inflammation and emphysema. *Trans Am Clin Climatol Assoc* 2017;**128**:222–33.
11. Tai R, Dunne RM, Trotman-Dickenson B, Jacobson FL, Madan R, Kumamaru KK, et al. Frequency and severity of pulmonary hemorrhage in patients undergoing percutaneous CT-guided transthoracic lung biopsy: single-institution experience of 1175 Cases. *Radiology* 2016;**279**:287–96.
12. Yeow KM, See LC, Lui KW, Lin MC, Tsao TC, Ng KF, et al. Risk factors for pneumothorax and bleeding after CT-guided percutaneous coaxial cutting needle biopsy of lung lesions. *J Vasc Interv Radiol* 2001;**12**:1305–12.
13. Gupta S, Krishnamurthy S, Broemeling LD, Morello FA Jr, Wallace MJ, Ahrar K, et al. Small (</=2-cm) subpleural pulmonary lesions: short- versus long-needle-path CT-guided Biopsy–comparison of diagnostic yields and complications. *Radiology* 2005;**234**:631–7.
14. Yu JH, Li B, Yu XX, Du Y, Yang HF, Xu XX, et al. CT-guided core needle biopsy of small (≤20 mm) subpleural pulmonary lesions: value of the long transpulmonary needle path. *Clin Radiol* 2019;**74**:570.e13–8.
15. Gupta A, Suri JC, Bhattacharya D, Sen MK, Chakrabarti S, Singh A, et al. Comparison of diagnostic yield and safety profile of radial endobronchial ultrasound-guided bronchoscopic lung biopsy with computed tomography-guided percutaneous needle biopsy in evaluation of peripheral pulmonary lesions: A randomized controlled trial. *Lung India* 2018;**35**:9–15.
16. Han Y, Kim HJ, Kong KA, Kim SJ, Lee SH, Ryu YJ, et al. Diagnosis of small pulmonary lesions by transbronchial lung biopsy with radial endobronchial ultrasound and virtual bronchoscopic navigation versus CT-guided transthoracic needle biopsy: a systematic review and meta-analysis. *PLoS One* 2018;**13**:e0191590.
17. Zarogoulidis P, Kioumis I, Pitsiou G, Porpodis K, Lampaki S, Papaiwannou A, et al. Pneumothorax: from definition to diagnosis and treatment. *J Thorac Dis* 2014;**6**(Suppl 4):S372–6.
18. Wang Y, Li W, He X, Li G, Xu L. Computed tomography-guided core needle biopsy of lung lesions: diagnostic yield and correlation between factors and complications. *Oncol Lett* 2014;**7**:288–94.
19. Madani A, Zanen J, de Maertelaer V, Gevenois PA. Pulmonary emphysema: objective quantification at multi-detector row CT–comparison with macroscopic and microscopic morphometry. *Radiology* 2006;**238**:1036–43.
20. Miller M, Cho JY, Pham A, Friedman PJ, Ramsdell J, Broide DH. Persistent airway inflammation and emphysema progression on CT scan in ex-smokers observed for 4 years. *Chest* 2011;**139**:1380–7.
21. Verbeken EK, Cauberghs M, Mertens I, Clement J, Lauweryns JM, Van de Woestijne KP. The senile lung. Comparison with normal and emphysematous lungs. 1. Structural aspects. *Chest* 1992;**101**:793–9.
22. Brandsma CA, de Vries M, Costa R, Woldhuis RR, Königshoff M, Timens W. Lung ageing and COPD: is there a role for ageing in abnormal tissue repair? *Eur Respir Rev* 2017;**26**:170073.
23. Soylu E, Ozturk K, Gokalp G, Topal U. Effect of needle-tract bleeding on pneumothorax and chest tube placement following CT guided core needle lung biopsy. *J Belg Soc Radiol* 2019;**103**:21.
24. Hiraki T, Mimura H, Gobara H, Iguchi T, Fujiwara H, Sakurai J, et al. CT fluoroscopy-guided biopsy of 1,000 pulmonary lesions performed with 20-gauge coaxial cutting needles: diagnostic yield and risk factors for diagnostic failure. *Chest* 2009;**136**:1612–7.
25. Choi SH, Chae EJ, Kim JE, Kim EY, Oh SY, Hwang HJ, et al. Percutaneous CT-guided aspiration and core biopsy of pulmonary nodules smaller than 1 cm: analysis of outcomes of 305 procedures from a tertiary referral center. *AJR Am J Roentgenol* 2013;**201**:964–70.
26. Poulou LS, Tsagouli P, Ziakas PD, Politi D, Trigidou R, Thanos L. Computed tomography-guided needle aspiration and biopsy of pulmonary lesions: a single-center experience in 1000 patients. *Acta Radiol* 2013;**54**:640–5.