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SYSTEMATIC REVIEW

Pneumothorax rates in CT-Guided lung biopsies: a comprehensive systematic review and meta-analysis of risk factors

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Objective: This systematic review and meta-analysis investigated risk factors for pneumothorax following CT-guided percutaneous transthoracic lung biopsy.
Methods: A systematic search of nine literature databases between inception to September 2019 for eligible studies was performed.
Results: 36 articles were included with 23,104 patients. The overall pooled incidence for pneumothorax was 25.9% and chest drain insertion was 6.9%. Pneumothorax risk was significantly reduced in the lateral decubitus position where the biopsied lung was dependent compared to a prone or supine position [odds ratio (OR):3.15]. In contrast, pneumothorax rates were significantly increased in the lateral decubitus position where the biopsied lung was non-dependent compared to supine (OR:2.28) or prone position (OR:3.20). Other risk factors for pneumothorax included puncture site up compared to down through a purpose-built biopsy window in the CT table (OR:4.79), larger calibre guide/needles (≤18G vs >18G: OR 1.55), fissure crossed (OR:3.75), bulla crossed (OR:6.13), multiple pleural punctures (>1 vs 1: OR:2.43), multiple non-coaxial tissue sample (>1 vs 1: OR 1.99), emphysematous lungs (OR:3.33), smaller lesions (<4 cm *vs* 4 cm: OR:2.09), lesions without pleural contact (OR:1.73) and deeper lesions (≥3 cm vs <3cm: OR:2.38).
Conclusion: This meta-analysis quantifies factors that alter pneumothorax rates, particularly with patient positioning, when planning and performing a CT-guided lung biopsy to reduce pneumothorax rates.
Advances in knowledge: Positioning patients in lateral decubitus with the biopsied lung dependent, puncture site down with a biopsy window in the CT table, using smaller calibre needles and using coaxial technique if multiple samples are needed are associated with a reduced incidence of pneumothorax.

INTRODUCTION

CT-guided percutaneous transthoracic lung biopsy (CT-PTLB) is a well-established procedure to obtain tissue from pulmonary lesions.[1,2] Previous studies identify that pneumothorax is the most frequent complication.[3] This can lead to complications associated with chest tube insertion and increased length of hospitalization.[3] Several societies have published guidelines which include the risks of CT-PTLB as outlined in Table 1.

As per British Thoracic Society Society guidelines, operators performing radiologically guided lung biopsy should strive to achieve the lowest possible complication rate to minimize morbidity and mortality.[1] Multiple studies have concluded that pneumothorax is dependent on factors that can and cannot be modified by the clinician.[3–6] Modifiable factors include patient position, needle biopsy type and technique factors. Non-modifiable factors include patient age and presence of emphysema. The impact of these factors on pneumothorax rates varies in reported literature.[1,7,8] Post-biopsy manoeuvres such as tract sealants and patient positioning also impact complication rates. These have been recently reviewed.[9]

This systematic review and meta-analysis aims to collate the best available evidence into single effect estimates that can be utilized by clinicians. These, in turn, can be used to inform consent, optimize patient selection, technique, inform guidelines and direct future research

METHODS

Search strategy

The search strategy was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis checklist and recommendations made by the Cochrane Collaboration.[10,11] The study was registered with PROSPERO (ID: CRD42018084414) We performed an

Table 1. Selected reference guidelines for pneumothorax rates and pneumothorax rates requiring chest drains for CT-PTLB

Society/Guideline	Pneumothorax rate	Pneumothorax rate requiring drain/intervention
SIR with the ACR	45%	20%
BTS	20.5%	3.1%
Cardiovascular and interventional CIRSE	18.8–25.3%	4.3–5.1%

ACR, American College of Radiology; BTS, British Thoracic Society; PTLB, percutaneous transthoracic lung biopsy; SIR, Society of Interventional Radiology.

electronic search of nine literature databases including Medline, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, ACP Journal Club, Database of Abstracts of Reviews and Effectiveness, Google Scholar and NHS Economic Evaluation Database for articles published between inception to September 2019. Search terms included the terms *pneumothorax, biopsy, lung, computed tomography, complications, risks* and *injuries* inclusive of relevant truncations, MeSH terms and keywords. Results were limited to studies of the English Language and humans. Duplicates were removed. Reference lists of included studies were screened to identify additional potentially relevant studies.

Study selection

The literature search and abstracts were reviewed for eligibility independently by two investigators (ARH and IL) and disagreements or omissions were resolved by senior investigators (MVC and YRH). Articles were eligible for full-text review if the (1) lung biopsies were performed using CT-guidance, (2) reported pneumothorax and/or chest drain insertion rates with and without at least one risk factor, (3) had ethics approval, and (4) have a study sample >200 patients. Abstracts, editorials, case reports, case series, systematic reviews, meta-analyses and unpublished articles were excluded. Studies that examined post-biopsy manoeuvres such as tract sealants and rollover were excluded.

Data extraction

The data were extracted independently by two investigators (ARH and IL). Any discrepancies were resolved by consensus amongst all authors. Data extraction focused on the rate of pneumothorax and chest drain insertion following lung biopsy and associated risk factors. Pneumothorax detection protocols via plain film and/or CT were noted. Non-modifiable patient and lesion factors identified and included age, gender, smoking history, emphysema presence, lesion size, depth and lobe location. Modifiable factors were stratified into four categories: operator factors, biopsy needle factors, biopsy technique and patient position during biopsy. Operator factors included experience (attending *vs* resident) and whether sample adequacy was reviewed by cytologist immediately. Biopsy needle factors included fine needle aspiration (FNA) *vs* core biopsy, non-coaxial *vs* coaxial and largest guide/biopsy needle gauge (guide if coaxial technique used or biopsy needle if non-coaxial needle used) (≤18G *vs* >18G). Biopsy technique factors included needle entry location on chest wall (anterior, lateral, posterior), needle angle, whether a bulla or fissure was crossed, number of pleural punctures and number of tissues samples. Patient factors included position during biopsy, puncture site location, breath-hold, and sedation method.

Data analysis

The random effects model was used to pool the odds ratios for each risk factor. Heterogeneity was tested using the I^2 statistic. Statistical analysis was performed using Review Manager (v. 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Bias was assessed using the Newcastle-Ottawa Scale for non-randomized studies.[12]

RESULTS

Included studies

4011 unique articles were identified through 9 electronic databases searches, of which 72 met the criteria for full-text review as potentially relevant studies (Figure 1). 36 studies met the inclusion criteria.[4,13–47] There were 31 retrospective cohort studies, 3 prospective cohort studies and 2 randomized controlled trials (Table 2). These studies enrolled a total of 23,104 participants. Table 2 provides information of the study characteristics

Figure 1. Flowchart describing selection of studies included in systematic review and meta-analysis of modifiable factors associated with pneumothorax and pneumothorax requiring chest tube following CT-PTLB. PTLB,percutaneous transthoracic lung biopsy.

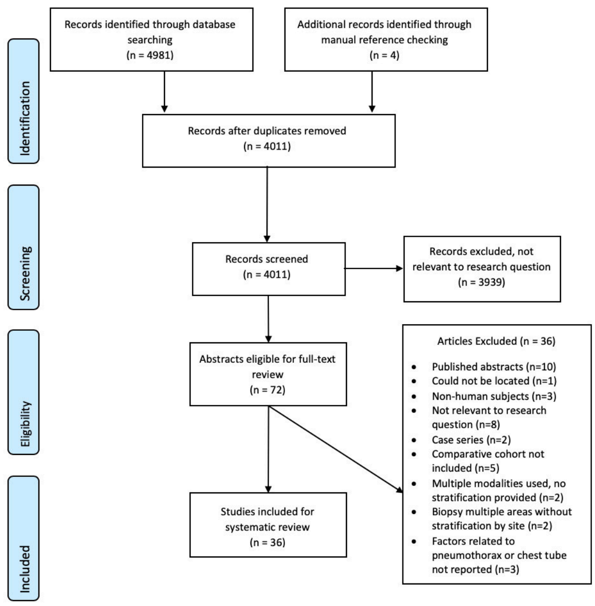

Table 2. Study characteristics, pneumothorax rates and chest tube insertion rates of included studies

Study	Study design	Study Country	Biopsy #	PTX %	PTX + CD %	Follow-up protocol	Technique	Needle Gauge	Criteria for Chest Drain insertion	NOS Score
2019 Drumm	R	Ireland	373	18.7%	4.8%	CT immediately +CXR 3 h post-biopsy	Coaxial NR	19G guide 20G biopsy needle	Symptomatic OR Hypoxia	8
2019 Taslakian	R	USA	338	34%	8.9%	CT immediately +CXR 1–2 h post-biopsy	Coaxial Automated / FNA (some)	19G guide, 20G biopsy needle 21G FNA needle	Lung surface retraction >2 cm, expanding OR symptomatic	7
2019 Yan	R	China	1452	22.5%	4.3%	CT immediately	Non-axial (before 06/2017) Coaxial (after 06/2017)	18G biopsy needle	Symptomatic OR ratio of lung compression >50%	7
2018 Ozturk	R	Turkey	822	15.4%	3.5%	CT immediately +CXR 2 h post-biopsy	Non-coaxial Semi-automated	18G biopsy needle	Symptomatic OR Expanding	8
2018 Zhang	R	China	677	40.2%	2.8%	CT immediately +CXR 4 h post-biopsy	Coaxial Automated	17G guide, 18G biopsy needle	NR	7
2018 Kuriyama	R	Japan	325	49.2%	NR	CT immediately	Coaxial Automated	19G guide, 22G or 20G biopsy needle	NR	7
2017 Uzun	R	Turkey	442	19.0%	2.9%	CT immediately +CXR 6 h & 24 h post-biopsy	Non-coaxial FNA	20G or 22G aspiration needle	Symptomatic OR ≥30% hemithorax	8
2017 Ashraf	RCT	Denmark/Norway	301	40%	10%	CT immediately +CXR 1–2 h post-biopsy	Coaxial Automated	16G guide, 18G biopsy needle	NR	-
2016 Vagn-Hansen	R	Denmark	520	30%	15%	CXR 2 h post-biopsy	Non-coaxial	18G biopsy needle	NR	6
2016 Sangha	R	Canada	254	52.4%	2.8%	CT immediately +CXR post-biopsy	Non-Coaxial FNA	22G aspiration needle	Symptomatic OR ≥25% hemithorax	8
							Coaxial Automated	19G guide, 20G biopsy needle		
2016 Ocak	R	Belgium	204	24.5%	10.3%	CT immediately +CXR 2 h & 24 h post-biopsy	Non-Coaxial FNA	22G aspiration needle	Symptomatic, Hypoxia, Tension OR pleura completely separated from base to apex and >2 cm between lung to chest wall at hilum level	8
							Coaxial Manual	13G guide, 14G biopsy needle		
2016 Nour-Eldin	R	Germany	650	25.1%	4.3%	CT immediately +CXR 4–6 h	Coaxial Automated	17G guide 18G biopsy needle	≥4 cm retraction OR 2–4 cm retraction and progressive after immediate manual evacuation of air	8
							Non-Coaxial Automated	18G biopsy needle		
2016 Lee	R	South Korea	591	16.9%	4.1%	CXR 2hrs + 12hrs post-biopsy	Non-coaxial Automated	18G biopsy needle	Symptomatic OR "Large" pneumothorax	7
2015 Anzidel	R	Italy	342	45.3%	11.4%	CT immediately +CXR 4 h	Non-coaxial FNA	14–21G aspiration needle	86.7% of PTX with >4 cm retraction	8
2015 Wei	R	China	1106	18.7%	0.3%	CT immediately +CXR 4 h post-biopsy	Non-coaxial automated	23G biopsy needle	≥4 cm retraction	8
2015 Schulze	R	Germany	664	21.7%	6%	CT immediately +CXR 3–4 h & 24 h post-biopsy	Coaxial Semi-automatic	17G guide, 18G biopsy needle	NR	6
2015 Kuban	R	USA	4262	30.2%	15%	CT immediately,+CXR 3 h post-biopsy	Coaxial Automatic	18G/19G guide 20/22G biopsy needle	Symptomatic, expanding, OR ≥30% hemithorax	6

(Continued)

Table 2. (Continued)

Study	Study design	Study Country	Biopsy #	PTX %	PTX + CD %	Follow-up protocol	Technique	Needle Gauge	Criteria for Chest Drain insertion	NOS Score
2015 Kim	R	South Korea	1227	21.4%	2.9%	CT immediately & CXR 3 h post-biopsy	Coaxial	17G guide, 18G biopsy needle	Symptomatic, Hypoxia OR ≥35% hemithorax	6
2014 De Filippo	R	Italy	538	28.6%	0%	CT immediately	Non-coaxial	22G cutting	NR	6
2014 Wang	R	China	343	17.5%	1.5%	CT immediately +CXR 12 h post-biopsy	Non-coaxial Automated	18G biopsy needle	NR	6
2014 Lim	R	Taiwan	381	29.9%	1.8%	CT immediately +CXR 4 h post-biopsy	Coaxial	19G guide, 20G biopsy needle	Symptomatic AND >2 cm retraction	7
2014 Lee	R	South Korea	1153	17%	6.9%	CT immediately	Coaxial Semi-automated	17G guide, 18G biopsy needle	NR	6
2013 Yazar	R	Iran	316	9.2%	1.6%	CT immediately +CXR 2–4 h post-biopsy	Non-coaxial	22G biopsy needle	NR	6
2013 Malone	R	USA	242	30.6%	13.2%	CT immediately +CXR 1 h & 3 h post-biopsy	Coaxial Automated	17G/19G guide, 18G/20G biopsy needle	NR	8
2013 Lim	R	South Korea	430	19.8%	NR	CT immediately	Coaxial Semi-automated	18G guide, 20G biopsy needle	NR	8
2010 Priola	P	Italy	321	26.8%	4.0%	CT immediately +CXR 3 h post-biopsy	FNA	21G or 20G aspiration needle	Symptomatic OR "Large" PTX	7
							Coaxial Automated	17G guide 18G biopsy needle		
2010 Hiraki	R	Japan	1098	42.4%	11.9%	CT immediately +CXR 3 h post-biopsy	Coaxial	19G guide, 20G biopsy needle	Symptomatic OR ≥30% hemithorax	8
2010 Fassina	P	Italy	305	4.3%	0%	CT immediately	Non-coaxial FNA	20–22G aspiration needle	NR	8
2006 Kinoshita	R	Japan	236	23.7%	8.4%	CT immediately +CXR 2 h & 12 h post-biopsy	Non-coaxial Automated	20G biopsy needle	"Severe" Symptoms	7
2006 Karam	R	Iran	505	6.7%	0%	CT immediately	Non-coaxial	20G biopsy needle	NR	6
2005 Topal	R	Turkey	284	35%	5.6%	CT immediately +CXR 2 h post-biopsy	Non-coaxial Semi-automated	18G, 20G, 22G biopsy needle	Symptomatic OR expanding on CXR 4 h post-biopsy	6
2004 Covey	P	USA	453	23.3%	6.3%	CT immediately +CXR 2 h post-biopsy	Non-coaxial	22G, 20G biopsy needle	Symptomatic, circumferential OR expanding between CXR	7
2004 Yeow	R	Taiwan	660	23%	1%	CT immediately +4 h post-CXR	Coaxial	Guide + 1G larger than 16–20G biopsy needle	≥30% hemithorax	7
2003 Geraghty	R	USA	846	26.7%	8.7%	CT immediately + CXR 2 h post-biopsy	Coaxial automated	18G, 19G guide, 20/21G biopsy needle	Expanding PTX	6
2000 Laurent	R	France	223	17.9%	2.2%	CT immediately +CXR4-6 h post-biopsy	Coaxial FNA	19G or 18G guide, 22G or 20G biopsy needle	Symptomatic	8
							Coaxial Automated	18.5G guide, 19.5G biopsy needle		

(Continued)

Table 2. (Continued)

Study	Study design	Study Country	Biopsy #	PTX %	PTX + CD %	Follow-up protocol	Technique	Needle Gauge	Criteria for Chest Drain insertion	NOS Score
1997 Santambrogio	RCT	Italy	220	23.6%	5.5%	CT immediately	Non-coaxial FNA	21G or 23G aspiration needle	NR	-
TOTAL			23,104							
MEAN				**25.9%**	**6.9%**					

-, not reported; %, incidence; #, number; CD, Chest drain; FNA, fine needle aspiration; NOS, Newcastle Ottawa Scale; NOS, Newcastle-Ottawa Scale;NR, Not reported; P, Prospective Study; PTX, Pneumothorax; R, Retrospective study; RCT, Randomized Controlled Trial; UK, UnitedKingdom; USA, United States of America.

including study design, total biopsies, pneumothorax incidence, and follow-up protocol to diagnose a pneumothorax. No studies distinguished how the individual patient's pneumothorax were diagnosed. There were 6, 13, and 17 studies from the North America, Asia, and Europe/Middle East region respectively. The criteria for chest drain insertion was described in 22 studies but not described in 14 studies. The most common criteria used by the studies included patient being symptomatic (17 studies), an expanding pneumothorax (6 studies), and ≥30% hemithorax (4 studies) (Table 2). The median Newcastle-Ottawa risk of bias score was 7 out of 9 (range: 6–8). Significant and non-significant risk factors for pneumothorax and chest drain insertion are summarized in Table 3.

Overall pneumothorax and chest drain incidence

The pooled overall pneumothorax incidence was 25.9% (range: 4.3–52.4%) (Table 2). The highest pneumothorax rates were in patients where a bulla was crossed (59.2%), fissure was crossed (52.8%) and patients positioned in lateral decubitus during biopsy (43%) (Table 4).

The pooled incidence of pneumothorax requiring chest tube was 6.9% (Range: 0–15%) (Table 2). The highest chest drain insertion rates were in patients where a fissure was crossed (27.9%), had emphysema (27.2%), and the anterior biopsy approach (20.4%) (Table 5).

The pneumothorax rates were 30.4%, 25.4%, and 22.4% in the North America, Asia and Europe/Middle East regions respectively. The chest drain insertion rates were 12.7, 4.4 and 4.9% in the North America, Asia, Europe/Middle East regions respectively.

Significant risk factors for pneumothorax and/or chest drain insertion

Lateral decubitus position with biopsied lung non-dependent (vs supine and prone)

Lateral patient position with the biopsied lung non-dependent significantly increased the risk of a pneumothorax compared to supine position (43% *vs* 20.4%, OR 2.28, 95% CI 1.21–4.32) and prone position (43% *vs* 17.4%, OR 3.20, 95% CI 2.48–5.79) (Table 4). No studies assessed the association with chest drain insertion rates.

PRONE OR SUPINE (*VS* LATERAL DECUBITUS POSITION WITH BIOPSIED LUNG-DEPENDENT)

The study by Drumm and colleagues[16] compared patients who were biopsied in prone or supine *vs* those who placed in lateral decubitus position with the biopsied lung down (dependent) and the biopsy needle entered either via the anterior or posterior chest wall.[16] They demonstrated a significant decrease in pneumothorax rates in patients placed in the lateral decubitus position with the biopsied lung=dependent (12.9% *vs* 41.6%, OR 3.20 95% CI 2.54–4.05). However, there was no significant difference in chest drain insertion rates (4.2% *vs* 5.4%).

Table 3. Significant and non-significant risk factors for pneumothorax and chest drain insertion

	Pneumothorax	Pneumothorax requiring chest drain insertion
Significant risk factors	Larger guide/Needle gauges (≤18G) Bullae crossed Fissure crossed Emphysema No pleural contact Puncture site up (*vs* site down with aperture in CT Gantry table) Prone or supine (*vs* lateral decubitus position with biopsied lung-dependent) Lateral decubitus position with biopsied lung non-dependent (*vs* prone or supine) Multiple non-coaxial tissue Samples Smaller lesions Deeper lesions >1 Pleural puncture Interactive breath-hold	Larger guide/Needle gauges (≤18G) Bullae crossed Fissure crossed Emphysema No pleural contact Puncture site up (*vs* site down with aperture in CT Gantry table)
Non-significant risk factors	Training level Immediate evaluation by cytologist FNA *vs* core Non-coaxial *vs* coaxial Number of samples from coaxial Biopsy approach Needle entry angle Sedation Age Sex Smoking status Lobe	Training Level Immediate evaluation by cytologist FNA *vs* core Non-coaxial *vs* coaxial Needle entry angle Number of pleural punctures Number of samples from coaxial Patient position Puncture site location Interactive breath-hold Sedation Sex Lobe

FNA, fine needle aspiration.

PUNCTURE SITE UP (*VS* SITE DOWN BIOPSY VIA APERTURE IN CT GANTRY TABLE)

Kinoshita and colleagues[22] had an aperture in the CT gantry table and biopsied lung lesions from below the patient.[22] They demonstrated patients who were placed with puncture site down during biopsy significantly reduced pneumothorax rates (12.9% *vs* 41.6%, OR 4.79 95% CI 2.53–9.09). Chest drain insertion rates also significantly reduced in those with the puncture site down (2.7% *vs* 18.0%, OR 7.84, 95% CI 2.53–24.29).

LARGER GUIDE/NEEDLE GAUGES ≤18G

A total of four studies compared pneumothorax rates based on gauge size, however three studies used coaxial technique so the gauges refers to the coaxial guide gauge,[18,23,30] whilst one study used non-coaxial technique so the gauge refers to the biopsy needle gauge.[39] Pooled outcomes demonstrated larger gauges (≤18G) had significantly higher pneumothorax rates compared to smaller gauges (>18G) (35.3% *vs* 25.1%, OR 1.55, 95% CI 1.19–2.01) (Table 4). Similarly, chest drain insertion rates were also significantly higher in larger gauges (≤18G) (16.1% *vs* 11.7%, OR 1.39, 95%CI1.18–1.62) (Table 5).

BULLAE CROSSED

Only one study compared pneumothorax and chest drain insertion rates if a bulla was crossed.[21] If a bulla was crossed, it resulted in the highest pneumothorax rates (59.2% *vs* 19.1%, OR 6.13 95% CI 3.73–10.06) and chest drain insertions (18.3% *vs* 1.9%, OR 11.04 95% CI 5.32–22.90) (Tables 4 and 5).

FISSURE CROSSED

Biopsies where the needle crossed a fissure had a significant increase in the risk of pneumothorax (52.8% *vs* 24.6%, OR 3.75 95% CI 2.57–5.46) (Table 4). Moreover, the highest pooled chest drain insertion rate was found when a fissure was crossed (27.9%). The risk of chest drain insertion increased more than threefold (OR 3.54, 95% CI 2.32–5.40) (Table 5).

Needle entry through the anterior chest wall (compared to posterior or lateral entry)

Two studies have compared pneumothorax rates based on location of needle entry on the chest wall.[4,23] One study stated they placed all their patients in a supine position following biopsy regardless of needle entry,[23] whilst the other study did not comment on post-biopsy management of patients.[4]

Pooled outcomes demonstrated needle entry through the anterior chest wall significantly increased the risk of a pneumothorax compared to the needle access through the posterior chest wall (39.4% *vs* 26.8%, OR 1.83, 95% CI 1.51–2.21) (Table 4). There were no significant differences in pneumothorax rates between the anterior *vs* lateral needle entry, and the posterior *vs* lateral needle entry.

Similarly, needle entry through the anterior chest wall significantly increased the risk of a chest drain compared to entry via the posterior chest wall (20.4% *vs* 11.6%, OR: 1.94, 95% CI 1.62–2.32) and lateral approach (20.4% *vs* 13.6%, OR: 1.64, 95% CI

Table 4. Pooled pneumothorax incidence and odds ratio based on risk factors

	Study #	Pneumothorax rate		Pooled odds ratio (95% CI)	I^2
		Group A	Group B		
OPERATOR FACTORS					
Attending (A) *vs* Resident (B)	2	23.6%	16.4%	1.07 (0.75–1.55)	0%
Immediate evaluation by cytologist: Yes (A) *vs* No (B)	1	26.4%	20.9%	1.35 (0.72–2.53)	-
BIOPSY NEEDLE TYPE					
FNA (A) *vs* Automated core (B)	5	33.2%	30.0%	1.20 (1.04–1.39)a	0%
FNA (A) *vs* Manual core (B)	1	18.6%	30.4%	0.52 (0.27–1.01)	-
Non-coaxial (A) *vs* Coaxial (B)	1	23.2%	27.0%	0.81 (0.57–1.16)	-
Larger guide/Needle gauge:≤18G (A) *vs* >18G (B)	4	35.3%	25.1%	1.55 (1.19–2.01)**	61%
BIOPSY TECHNIQUE					
Chest wall needle entry location:					
Anterior (A) *vs* Posterior (B)	2	39.4%	26.8%	1.83 (1.51–2.21) ***	14%
Anterior (A) *vs* Lateral (B)	2	39.3%	27.7%	1.10 (0.33–3.65)	90%a
Posterior (A) *vs* Lateral (B)	2	26.8%	27.7%	0.53 (0.12–2.34)	94%a
Needle angle:					
≤30 (A) *vs* >30(B) degrees	4	26.4%	21.7%	1.03 (0.70–1.52)	23%
≤45 (A) *vs* >45(B) degrees	2	27.9%	39.0%	0.79 (0.21–2.88)	86%a
Perpendicular (A) *vs* Oblique (B)	1	10.3%	4.7%	2.34 (0.69–7.99)	-
Bulla crossed: Yes (A) *vs* No (B)	1	59.2%	19.1%	6.13 (3.73–10.06)***	-
Fissure crossed: Yes (A) *vs* No (B)	5	52.8%	24.6%	3.75 (2.57–5.46) ***	46%
Pleural punctures: >1 (A) *vs* 1 (B)	6	30.1%	19.0%	2.43 (1.39–4.25)**	78%a
Coaxial tissue Ssmples: ≤2 (A) *vs* >2 (B)	3	21.2%	19.9%	1.09 (0.76–1.56)	60%
Coaxial tissue samples: >1 (A) *vs* 1 (B)	1	27.8%	26.6%	1.06 (0.64–1.76)	-
Non-coaxial tissue samples: >1 (A) *vs* 1 (B)	1	29.7%	17.5%	1.99 (1.18–3.34)**	-
PATIENT FACTORS					
Patient position during biopsy:					
Supine (A) *vs* Prone (B)	10	24.5%	21.6%	1.22 (0.45–1.76)	89%a
Lateral (A) *vs* Supine (B)	7	43.0%	20.4%	2.28 (1.21–4.32)a	85%a

(Continued)

Table 4. (Continued)

	Study #	Pneumothorax rate		Pooled odds ratio (95% CI)	I^2
		Group A	Group B		
Lateral (A) *vs* Prone (B)	7	43.0%	17.4%	3.20 (2.54–4.05) ***	20%
Puncture site up (A) *vs* Site down +with aperture in CT Gantry table (B)	1	41.6%	12.9%	4.79 (2.53–9.09) ***	-
Prone or supine (A) *vs* Lateral decubitus position with biopsied lung down (B)	1	27.2%	10.6%	3.15 (1.79–5.55) ***	-
Interactive breath-hold: Yes (A) *vs* No (B)	1	46.9%	33.9%	1.72 (1.08–2.75)a	-
Conscious sedation (A) *vs* Local anesthesia (B)	1	19.1%	24.9%	0.72 (0.42–1.21)	-
NON-MODIFIABLE FACTORS					
>50 years (A) *vs* ≤50 years (B)	6	26.7%	10.4%	1.3 (0.91–1.86)	59%a
Male (A) *vs* Female (B)	14	28.3%	25.7%	1.17 (0.98–1.41)	77%a
Ex/current smoker (A) *vs* Non-smoker (B)	4	25.4%	28.5%	0.89 (0.66–1.20)	43%
Emphysema (A) *vs* No emphysema (B)	11	41.1%	24.3%	3.33 (2.15–5.16)***	93%a
Lesion size					
≤1 cm (A) *vs* >1 cm (B)	4	32.7%	23.9%	1.57 (0.75–3.28)	76%a
≤2 cm (A) *vs* >2 cm (B)	4	39.9%	24.1%	1.98 (1.55–2.51)***	61%
≤3 cm (A) *vs* >3 cm (B)	4	32.7%	19.1%	1.72 (1.49–1.99)***	0%
≤4 cm (A) *vs* >4 cm (B)	4	28.8%	16.2%	2.09 (1.33–3.31)**	79%a
≤5 cm (A) *vs* >5 cm (B)	2	24.5%	7.4%	2.94 (1.54–5.62)**	48%
Lesion depth					
>1 cm (A) *vs* ≤1 cm (B)	2	23.0%	11.8%	2.36 (0.70–7.95)	96%a
>2 cm (A) *vs* ≤2 cm (B)	6	36.1%	18.0%	2.16 (1.31–3.57)**	94%a
>3 cm (A) *vs* ≤3 cm (B)	1	34.9%	12.2%	2.38 (1.60–3.53)***	-
>5 cm (A) *vs* ≤5 cm (B)	1	14.7%	2.0%	8.47 (3.44–20.9)***	-
Upper/Middle lobe (A) *vs* Lower lobe (B)	15	26.7%	25.6%	0.95 (0.75–1.20)	87%a
No pleural contact (A) *vs* Pleural contact (B)	3	40.0%	28.8%	1.73 (1.17–2.55)**	79%a

CI, confidence interval.
[a]*p*-value < 0.05; ***p*-value < 0.01, ****p*-value < 0.001, 95% CI - 95% CI.

Table 5. Pooled chest drain insertion incidence and odds ratios based on risk factors

	Study #	Pneumothorax requiring chest drain		Odds ratio (95% CI)	I^2
		Group A	Group B		
OPERATOR FACTORS					
Training level: Attending (A) *vs* Resident (B)	2	7.6%	4.5%	0.74 (0.30–1.87)	35%
Immediate evaluation by cytologist: Yes (A) *vs* No (B)	1	6.4%	4.5%	1.43 (0.44–4.64)	-
BIOSPY NEEDLE FACTORS					
FNA (A) *vs* Automated core (B)	3	12.5%	13.3%	0.99 (0.77–1.27)	0%
FNA (A) *vs* Manual core (B)	1	10.8%	9.8%	1.11 (0.45–2.75)	-
Non-coaxial (A) *vs* Coaxial (B)	1	3.6%	5.0%	0.71 (0.33–1.52)	-
Larger guide/Needle gauge: £18G (A) *vs* > 18G (B)	3	16.1%	11.7%	1.39 (1.18–1.62)***	0%
BIOPSY TECHNIQUE					
Chest wall needle entry location:					
Anterior (A) *vs* Posterior (B)	1	20.4%	11.6%	1.94 (1.62–2.32)***	-
Anterior (A) *vs* Lateral (B)	1	20.4%	13.6%	1.64 (1.24–2.15)***	-
Posterior (A) *vs* Lateral (B)	1	11.6%	13.6%	0.84 (0.64–1.11)	-
Needle angle:					
£30 (A) *vs* > 30(B) degrees	1	4.8%	7.8%	0.59 (0.17–1.98)	-
£45 (A) *vs* > 45(B) degrees	1	5.2%	4.4%	1.18 (0.58–2.38)	-
Bulla crossed: Yes (A) *vs* No (B)	1	18.3%	1.9%	11.04 (5.32–22.90)***	-
Fissure crossed: Yes (A) *vs* No (B)	5	27.9%	10.7%	3.54 (2.32–5.40)***	39%
Pleural punctures:>1 (A) *vs* 1 (B)	2	7.8%	4.5%	1.25 (0.07–21.80)	89%*
Coaxial tissue samples: £2 (A) *vs* > 2 (B)	1	2.0%	3.3%	0.61 (0.27–1.41)	-
PATIENT FACTORS					
Supine (A) *vs* Prone (B)	4	5.4%	3.3%	1.54 (0.75–3.16)	74%*
Puncture site up (A) *vs* Site down + with aperture in CT Gantry table (B)	1	18.0%	2.7%	7.84 (2.53–24.29)***	-
Prone or supine (A) *vs* Lateral decubitus position with biopsied lung down (B)	1	5.4%	4.2%	1.30 (0.50–3.37)	-
Interactive breath-hold: Yes (A) *vs* No (B)	1	10%	9.4%	1.08 (0.50–2.33)	-
Conscious sedation (A) *vs* Local anesthesia (B)	1	7.8%	6.8%	1.16 (0.52–2.59)	-
NON-MODIFIABLE FACTORS					
Male (A) *vs* Female (B)	5	11.0%	9.5%	1.11 (0.48–2.55)	88%*

(Continued)

Table 5. (Continued)

Emphysema (A) *vs* No emphysema (B)	4	27.2%	8.8%	6.44 (4.27–9.72)***	58%
Upper/Middle lobe (A) *vs* Lower lobe (B)	5	11%	7.0%	1.37 (0.90–2.10)	70%*
No pleural contact (A) *vs* Pleural contact (B)	2	4.7%	2.4%	1.97 (1.21–3.21)**	0%

CI, confidence interval.
[a]*p*-value < 0.05; ***p*-value < 0.01, ****p*-value < 0.001, 95% CI - 95% CI.

1.24–2.15) (Table 5). There was no significant difference in chest drain insertion rates between the posterior *vs* lateral needle access.

MULTIPLE PLEURAL PUNCTURES

Multiple pleural punctures (>1) more than tripled the risk of a pneumothorax rate compared to one pleural puncture (30.1% *vs* 19.0%, OR:2.43, 95% CI1.39–4.25). However, chest drain insertion rates did not significantly increase (7.8% *vs* 4.5%, OR 1.25, 95% CI 0.07–21.80) with more than one pleural puncture.

MULTIPLE NON-COAXIAL TISSUE SAMPLES

Multiple non-coaxial tissue samples (>1) significantly increased the risk of pneumothorax compared to one tissue sample (29.7% *vs* 17.5%, OR 1.99, 95% CI 1.18–3.34). No studies investigated rates of chest drain insertion.

EMPHYSEMA

Emphysema was significantly associated with an increased pneumothorax incidence (41.1% *vs* 24.3%, pooled from 11 studies OR: 3.33, 95% CI 2.15–5.16). The risk of chest drain insertion was even greater in patients with emphysema compared to those without emphysema (27.2% *vs* 8.8%, pooled from four studies OR: 6.44, 95% CI 4.27–9.72).

The most common definition of emphysema was radiologic findings along the needle path and categorized as "present" or "absent".[19,21,23,27] Some studies only stated the presence of emphysema and did not specify the location,[37,47] whilst others defined emphysema was present if it was in the same lobe of the biopsy.[26] De-Filippo and colleagues only considered patients with severe emphysema (>50%) positive for emphysema and graded patients with mild (<25%) and moderate (25–50%) emphysema into no emphysema.[15] One study defined emphysema as ≤900 Hounsfield unit along needle path and stratified emphysema into: not present, surrounding the lesion but distant from the needle tract, and along the needle tract.[43]

SMALLER LESIONS

Pneumothorax incidence was significantly higher in tumors ≤ 2 cm (39.9%) compared to >2 cm (24.1%) (pooled OR: 1.98, 95% CI 1.55–2.51) in four studies that examined this.[23,38,43,47] Similarly, this correlation remained present with the 3 cm threshold (32.7% *vs* 19.1%; OR 1.72, 95% CI 1.49–1.99), 4 cm threshold (28.8% *vs* 16.2%; OR 2.09, 95% CI 1.33–3.31) and 5 cm threshold (24.5% *vs* 7.4%; OR 2.94, 95% CI 1.52–5.62) (Table 4). No studies assessed association between lesion size and chest drain insertion rate.

DEEPER LESIONS

Pneumothorax incidence was significantly higher in tumors > 2 cm deep (36.1%) compared to more superficial tumors (18.0%) (pooled OR: 2.16, 95% CI 1.31–3.57) in six studies that examined this.[23,27,39,43,46,47] Similarly, this correlation remained present with the 3 cm threshold (34.9% *vs* 12.2%; OR 2.38, 95% CI 1.60–3.53) and 5 cm threshold (14.7% *vs* 2.0%; OR 8.47, 95% CI 3.44–20.9) (Table 5). No studies assessed the association between lesion depth and chest drain insertion rate.

NO PLEURAL CONTACT

Tumors without pleural contact had a significantly higher risk of pneumothorax compared to tumors with pleural contact (40% *vs* 28.8%, OR 1.73, 95% CI 1.17–2.55); pooled from three studies.[19,21,46] Similarly, chest tube insertion rates were significantly higher in tumors without pleural contact (4.7% *vs* 2.4%, OR 1.97, 95% CI 1.21–3.21; pooled from two studies.[19,21]

FINE NEEDLE BIOPSIES

Fine needle biopsies had an increased pneumothorax rate compared to automated core biopsies (33.2% *vs* 30.0%, OR 1.20 95% CI 1.04–1.39) (Table 4). A significant difference was not demonstrated for drain insertion rates (12.5% *vs* 13.3%, OR 0.99 95% CI 0.77–1.27) (Table 5). No significant difference was demonstrated between FNA and semi-automated core pneumothorax or drain insertion rates.

INTERACTIVE BREATH-HOLD

Interactive breath-hold significantly increased pneumothorax rate compared to no interactive breath-hold (46.9% *vs* 33.9%, OR 1.72 95% CI 1.08–2.75) (Table 4). There was no effect on drain insertion rates (10% *vs* 9.4%, OR 1.08 95% CI 0.50–2.33) (Table 5).

Heterogeneity analysis

The risk factors that were significantly associated with pneumothorax which had significant heterogeneity included pleural punctures (I^2:78%), lateral patient position compared to supine patient position (I^2:85%), emphysema (I^2:93%), lesion size 4 cm threshold (I^2:79%), lesion depth 2 cm threshold (I^2:94%), and pleural contact (I^2:79%) (Table 4). There was no significant heterogeneity between the remaining risk factors significantly associated with pneumothorax or those associated with chest drain insertion (Table 5).

DISCUSSION

Pneumothorax is the most common complication that occurs during or immediately after a percutaneous CT-guided lung biopsy. This meta-analysis included 23,104 cases with an incidence of 25.9% and chest drain insertion rate of 6.9%. This present meta-analysis demonstrates substantially higher pneumothorax rates when larger guide/needle gauges are used (≤18G), a bulla is crossed, a fissure is crossed, puncture site up (*vs* site down with biopsy via an aperture in CT Gantry table), emphysematous lungs, lesions with no pleural contact, a lateral decubitus position (with the biopsied lung ante-dependent) compared to supine and prone position, prone or supine position (*vs* lateral decubitus position with biopsied lung down), multiple pleural punctures, multiple tissue samples from non-coaxial technique, FNA biopsies compared to automated core, breath-hold during biopsy, smaller lesions and deeper lesions. The higher pneumothorax rates from FNA sampling may be due to sampling technique contributing to more pleural agitation and/or injury to normal lung.

The risk of a chest drain insertion was significantly associated when larger guide/needle gauges are used (≤18G), a bulla is crossed, a fissure is crossed, puncture site up, emphysematous lungs, lesions with no pleural contact.

Whilst many of these factors have long been factored into proceduralists' consideration for performing CT-PTLB, this meta-analysis highlights interesting techniques that may have not been considered such as modifying the CT table with a biopsy window to enable the operator to perform the procedure with the patient positioned biopsy side-down as demonstrated by Kinoshita and colleagues.[22]

A logistically simpler technique described by Drumm and colleagues[16] where patients were placed in a lateral decubitus position with the target lesion in the dependent lung is promising.[16] This position significantly reduced pneumothorax rates, increased technical success rate and reduced haemoptysis incidence. It is hypothesized that the reduction in pneumothorax rates with the biopsy-side-down/lateral decubitus dependent lung position is due to the weight of the lung that compresses the alveoli and increases pleural apposition, which helps to seal the biopsy tract.[16,48] However, both these techniques were only examined in one study, and additional studies are warranted to confirm these findings.

The importance of having the biopsied lung-dependent is further supported by the finding in this meta-analysis that patients in the lateral decubitus position where the biopsied lung was ante-dependent had significantly higher pneumothorax rates than the supine and prone position. The study by Wang and colleagues found significantly higher pneumothorax rates in the lateral decubitus position (44%) compared to supine (15.2%) and prone (12.8%) position ($p > 0.05$). They hypothesized that the lateral decubitus position with the biopsied lung up (ante-dependent) separates the parietal and visceral pleura more than the supine and prone positions, and therefore air is more likely to enter the pleural cavity as the needle is taken out.

Therefore, in terms of descending order of preferred patient position based on pneumothorax risk: lateral decubitus position with biopsy the dependent lung, prone position, supine position, and finally lateral decubitus position with biopsy of the ante-dependent lung. However, it is important to also consider how patient position influences other complications, particularly an air embolism which is a rare but very serious complication. Fortunately, the lateral decubitus position has the lowest published rates of air embolism, followed by supine position and the highest rates are seen in the prone position.[49] We hypothesize this may be due to increased partial pressure of dependent lung, reducing the potential difference between the needle tip and outside air.

Although this meta-analysis demonstrated a significantly higher pneumothorax rates when the biopsy needle entered the anterior chest wall compared to the posterior chest wall, we believe this finding to be confounded by patient position post-biopsy. Two studies examined this issue: one of which clearly stated that all patients were placed in a supine position following biopsy regardless of needle entry,[23] whilst the other did not comment and thus we presumable also placed patients in the supine position post-biopsy.[4] A recent meta-analysis has demonstrated the "roll-over" of patient post-biopsy to the needle entry location side-down significantly reduced pneumothorax rates.[9] Hence, the patients where the biopsy needle entered via the posterior wall essentially had the "roll-over" manoeuvre post-biopsy as patients were all placed in the supine position. We hypothesize the "roll-over" effect accounts for the lower rates of pneumothorax in the posterior approach. Therefore, we suggest placing patient in a prone position following an anterior needle entry to reduce the risk of a pneumothorax.

Smaller lesions were also associated with higher pneumothorax rates and in principle, biopsy of normal lung would increase the risk of complication without any diagnostic benefit. At our institution (Concord Repatriation General Hospital, NSW, Australia) for small lesions the tip of the coaxial needle would be close to the lesion and the throw of the needle should terminate just beyond the lesion. To achieve this, the biopsy throw would commence within the coaxial needle. Confirmatory evidence for this approach is unlikely to be achievable by trials.

It is also important to highlight factors that are commonly assumed to be correlated with pneumothoraxes did not reach a statistically significant association such as needle angle at skin penetration, training level (attending *vs* resident), conscious sedation *vs* local anaesthesia and upper/middle lobe *vs* lower lobe. It is possible that these factors do not affect pneumothorax rates, however only a small number of published studies assessing these are available in the literature. This highlights the need for larger, more comprehensive studies to assess these factors to confirm which factors influence pneumothorax rates.

These findings must be considered in the context of their limitations. Firstly, a majority were retrospective studies. Retrospective studies have an increased risk of bias as many of the modifiable factors assessed such as needle size, number of pleural punctures and positioning were not randomized. Secondly, many risk factors were only compared in one study, such as non-coaxial *vs* coaxial biopsies, multiple *vs* one tissue sample from non-coaxial technique. Future studies are warranted to validate these risk factors for pneumothorax and drain placement. Third, another contributing factor between the large variability of pneumothorax rates may be associated by different post-biopsy techniques utilized by studies such as some studies rolling their patients over to puncture site down, whilst others do not. However, a recent meta-analysis demonstrated rapid rollover to puncture site down compared to no rollover did not significantly reduce pneumothorax rates but reduced chest drain insertion rates.[9] Another potential confounder is the methodology of diagnosing pneumothorax with CT being more sensitive. Finally, there was a large variation in incidence of chest drains between studies (lowest 0.3%[43] *vs* highest 15%).[23,41]This indicates variability amongst institutional protocols as to when a chest drain is required for a pneumothorax. These differences contribute to the heterogeneity between studies. As such, a random effects model was used to pool studies in order to minimize the influence of individual differences in response to an effect.

CONCLUSION

This meta-analysis quantifies risks associated with CT-PTLB pneumothorax and drain insertion rates, particularly with inherent patient risk factors, positioning and equipment type. The pooled overall pneumothorax incidence was 25.9% and chest tube insertion rate was 6.9%. Positioning patients in lateral decubitus with the biopsied lung-dependent, puncture site down with a biopsy window in the CT table, using smaller calibre guide/biopsy needles and using coaxial technique if multiple samples are needed are associated with a reduced incidence of pneumothorax.

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