# TRANSBRONCHIAL LUNG CRYOBIOPSY FOR DIFFUSE AND LOCALIZED PERIPHERAL PULMONARY LESIONS: A RETROSPECTIVE REVIEW OF OUR EARLY EXPERIENCE

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**ABSTRACT:**
**Background:** Transbronchial lung cryobiopsy (TBLC) is an emerging technique for obtaining lung biopsy. This retrospective study aimed to evaluate the performance and safety of TBLC performed on diffuse peripheral pulmonary lesions (DPPL) and localized peripheral pulmonary lesions (LPPL).
**Methods:** 58 patients underwent TBLC. They were divided into two groups (DPPL and LPPL) based on radiological findings. The patients' demographic data, procedural details, complications, and radiological and pathologic diagnostic results were analyzed.
**Results:** The overall diagnostic yield for TBLC was 72.4%. In the subgroup analysis, the diagnostic yield was 74.3% for DPPL and 69.6% for LPPL. For LPPL, the overall diagnostic yield was 87.5% and 12.5% for lesions with positive and negative bronchus signs, respectively (P = 0.01). In both groups, the success of TBLC was not influenced by the size, number, or location of the biopsy. Thirty-two (82%) patients had mild bleeding, while six (15.4%) had moderate bleeding. Pneumothorax occurred in four (6.9%) patients, with three patients requiring chest tube drainage. The mean duration of hospital stay was longer for patients who either bled or developed pneumothorax compared to those who did not (5.64 days vs. 3.47 days; P = 0.014) and (14.25 days vs. 4.24 days; P = 0.035) respectively.
**Conclusion:** TBLC provided an acceptable diagnostic yield for DPPL and LPPL under fluoroscopy guidance without the use of ancillary devices such as radial endobronchial ultrasound or guide sheath. The safety profile of TBLC corresponded with a low incidence of pneumothorax and manageable bleeding complications with the routine use of an endobronchial balloon.

**Keywords:** Lung Cryobiopsy, Interventional Pulmonology, Peripheral Pulmonary Lesion, Lung Cancer, Interstitial Lung Disease.

## BACKGROUND

The diagnosis of DPPL depends on the patient's clinical history corresponding with consistent radiological findings. However, some cases require tissue sampling for histological confirmation [1]. For DPPL, such as those found in idiopathic interstitial pneumonia (IIP), surgical lung biopsy (SLB) provides a high diagnostic yield compared to conventional transbronchial lung forceps biopsy (TBFB) [2, 3]. However, SLB is associated with a significant mortality rate of 1.7%–21.7% [4]. Although TBFB is considered a safe option, small biopsy specimens (1–2 mm) generally limit its use.

TBLC is an emerging technique for obtaining biopsies with good size and lung architecture preservation from the peripheral lung parenchyma. TBLC has been shown to be capable of improving diagnostic yields compared to TBFB. The retrieval through TBLC of a more significant portion of alveolar tissue with fewer tissue crush artifacts facilitates histopathological interpretation and further immunohistochemistry and oncogenic driver mutation analyses of malignancies [5–7]. TBLC is a less invasive procedure than SLB. However, TBLC comes with a substantial risk of bleeding and pneumothorax, which should be emphasized [7, 9, 10]. To date, TBLC has been widely explored for DPPL and, to a lesser extent, for LPPL [11].

## METHODS

### *Study Design*

This work reports on a retrospective cohort study of all patients who underwent TBLC at Serdang Interventional Pulmonology Center in Malaysia between January 1, 2016, and December 31, 2020. Electronic medical records and a picture archiving and communication system were used to retrieve all information relevant to the study. Demographic data, procedural details, complications, and radiological and pathologic diagnostic results were analyzed and recorded.

### *Pre-procedure Evaluation*

For pre-procedure planning, patients' medical histories and computerized tomography (CT) thorax images were reviewed in a radiological meeting attended by interventional pulmonologists, a pulmonologist managing interstitial lung diseases, and two thoracic radiologists. The patients' blood and coagulation profiles were checked, and antiplatelet and anti-coagulant agents were withheld according to guidelines [12].

### *Radiological Evaluation*

High-resolution CT thorax images of all patients (1-mm-thin sections) were reviewed independently by two thoracic radiologists with three years of experience each prior to them reaching a final consensus. For DPPL, the radiological patterns distinguished were categorized IIP according to published guidelines [13, 14]. Other radiological patterns (e.g., diffuse distributions) were subsequently categorized under non-interstitial idiopathic pneumonias (NIIP) based on glossary terms for thoracic imaging provided by the Fleischner Society [15]. Similarly, LPPL were categorized as either masses or consolidations as defined by the Fleischner Society [15].

### *Application of Anesthesia and Intubation*

Xylocaine 10% was used as a topical anesthetic agent before intubation. All patients were provided with total intravenous anesthesia. Target-controlled infusion of propofol and remifentanil was used for the induction and maintenance of sedation. The patients were ventilated using a rigid bronchoscope (Efer-Dumon, France).

### *Bronchoscopy and Use of a Cryoprobe*

Before TBLC, all patients underwent routine bronchoscopic airway assessments. A rigid tracheoscope with a fiberoptic flexible bronchoscope was used (Olympus BF-1T240, Tokyo, Japan). We used a flexible cryo-recanalization probe 1.9 m in length and 2.4 mm in diameter. The cryoprobe (Erbe Elektromedizin GmbH, Tübingen, Germany) used nitrous oxide to induce a temperature of −89.5°C at its tip. A rigid bronchoscope was positioned in the airway for ventilation and allowed rapid reentry of the flexible cryoprobe and flexible bronchoscope. An endobronchial balloon (Chartis balloon catheter, Pulmonx, United States) was used for bronchial blockage. The procedure was performed by two consultants with a minimum of five years of experience each in interventional pulmonology.

### *Biopsy Procedures and Tissue Sampling*

The bronchoscope was placed at the segment chosen for biopsy. Through the working channel of the flexible bronchoscope, the cryoprobe was advanced and passed into the identified distal airways according to pre-procedure planning. The location of the probe was also confirmed through fluoroscopic guidance. For DPPL, the cryoprobe was withdrawn distally (1–2 cm) from the maximal point of resistance. For LPPL, the TBLC was targeted at the localized lesion after careful evaluation of the multiplanar CT. We employed tracing techniques using the bronchus sign and bronchial branch reading, as described previously [16, 17, 18]. Under fluoroscopy guidance, a 4 s freeze time was applied during the patient's exhalation phase. The cryoprobe and bronchoscope were removed en bloc from the airway, and the bronchoscope was kept rigid. After withdrawal of the cryoprobe and bronchoscope, an endobronchial blocker was prophylactically inflated into the biopsied segment with 3 mL of air. A minimum of two biopsy specimens were obtained from each patient. The frozen specimens were thawed in sterile 0.9% sodium chloride saline before being fixed in formalin.

### *Evaluation and Control of Complications*

After 60 s of endobronchial balloon inflation, the balloon was deflated to observe any ongoing bleeding. The severity of endobronchial bleeding was determined based on the recommendations of the British Thoracic Society [19]. For cases with bleeding, the instillation of cold saline (+4°C), diluted adrenalin (1 mg in 10 mL saline; 1 in 10,000), or argon plasma coagulator was one interventional option used before the balloon was reinflated for another 60 s. A chest radiograph was performed for all patients 2 h post-procedure for the evaluation of pneumothorax.

### *Histological Evaluation*

The specimens were fixed in 10% buffered formalin solution and were carefully evaluated by a pathologist with more than five years of experience. The variables specified by the literature as important for evaluating the performance and safety of TBLC, such as the number of specimens, the corresponding biopsy site, and each specimen's size, were inspected carefully and recorded prior to full evaluation.

The biopsy results were identified as indicating either interstitial lung disease or malignancy based on histological diagnoses: 1 = interstitial lung disease: (a) usual interstitial pneumonia, (b) nonspecific interstitial pneumonia, (c) organizing pneumonia, (d) hypersensitive pneumonitis, (e) granulomatous lung disease, (f) pneumoconiosis, and (g) eosinophilic pneumonia; 2 = malignancy: (a) lung adenocarcinoma, (b) small cell lung carcinoma, (c) carcinoid tumor, (d) lung squamous cell carcinoma, and (e) metastatic disease; and 3 = inconclusive.

### *Diagnostic Yield and Final Multidisciplinary Discussion*

The final diagnoses were established through a final multidisciplinary discussion involving a pulmonologist, rheumatologist, radiologist, and pathologist. The TBLC was considered diagnostic when the biopsy specimens demonstrated consistency in histology patterns and radiological findings.

***Statistical Analysis***

IBM SPSS Statistics for MAC (version 23.0, IBM Corp., Armonk, NY) was used for all statistical analyses. The mean (standard deviation) and median (interquartile range) were used for the results of normally distributed grouped data and non-normally distributed data, respectively. The categorical variables were reported as the frequencies (n) and percentages (%) of the total number of subjects. Baseline data were compared using an independent samples t-test for variables with an assumed normal distribution and the Mann–Whitney U test for non-normally distributed variables. The categorical variables between the two groups were compared using Pearson's chi-square test or Fisher's exact test. The significance level of the analyses was set to 5% ($P < 0.05$).

## RESULTS

Fifty-eight patients were included in this study. The patients were divided into two groups based on their radiological patterns (DPPL or LPPL). Their demographic information and other characteristics are presented in Table 1.

The patients' overall mean age was 54 years (SD, 14 years). In both groups, the patients were predominantly non-smokers and ex-smokers. Only three patients were active smokers: one (2.9%) in the DPPL group and two (8.7%) in the LPPL group. A small fraction of the patients in both groups were on antiplatelet medications, with eight (22.9%) and four (17.4%) patients in the DPPL and LPPL groups, respectively. The patients' blood coagulation profiles and platelet counts were similar. The radiological (CT) findings for the DPPL and LPPL groups are presented in Tables 2 and 3, respectively. The most frequent CT pattern for the DPPL group was a nodular pattern (n = 15, 42.9%). Most of the LPPL were categorized as masses (n = 18, 78.3%), with a mean size of 5.31 cm (SD, 2.4 cm).

The overall mean diameters of the biopsy samples obtained for DPPL and LPPL were 6.74 mm (SD, 2.7) versus 9.65 mm (SD, 6.4), respectively. Most of the biopsies were taken from a single lobe. Of the 62 biopsies taken, 41 (66.1%) and 21 (33.9%) originated from the right and left lungs, respectively. Four patients had biopsy samples taken from two lobes because they bled from the first biopsied lobe. The median number of samples per procedure was three (range, 1–6). The overall diagnostic yield of TBLC was 72.4% (42 of 58 patients), which correlated with the clinical, radiological, and histopathologic findings. In the subgroup analysis, the diagnostic yields were 71.4% (25 of 35 patients) for DPPL and 73.9% (17 of 23 patients) for LPPL. For DPPL, the diagnostic yield of TBLC for IIP cases was 75% (6 out of 8 cases), compared to 70.4% (19 out of 27) for NIIP cases. The histology diagnoses for both groups of patients are presented in Table 4. The histology results based on the radiological patterns of NIIP are shown in Table 5.

Six of the ten patients with granulomatous biopsies were diagnosed with pulmonary sarcoidosis after further testing that excluded an underlying infective cause. In the LPPL group, the overall diagnostic yields were 87.5% and 12.5% for positive and negative bronchus signs, respectively ($P = 0.01$). The diagnostic yields based on tissue size were 71.4% (10 out of 14 [size < 10 mm]) and 75% (3 out of 4 [size 10–20 mm and > 20 mm]). The presence of bronchus signs also demonstrated statistical significance (92.9% vs. 7.1%) in the diagnostic yields for the biopsies of mass lesions ($P = 0.02$) (Table 3 and Figure 1). The outcomes for cases with inconclusive transbronchial lung cryobiopsies are shown in Table 6.

Out of 10 DPPL (one ground-glass and two nodular pattern) cases, three had spontaneous resolutions in subsequent radiological surveillance. Three out of six LPPL cases that were inconclusive on TBLC were found to be malignant using subsequent CT scan-guided biopsies (two cases of lung adenocarcinoma and one case of squamous cell lung carcinoma).

Further analyses of both groups were unsuccessful in demonstrating the influence of the number, size, and location of biopsies on the outcome of the TBLC (Table 7).

Table 1: Characteristics of patients underwent transbronchial lung cryobiopsy (n=58).

| Variable | | DPPL (n = 35) | LPPL (n = 23) | P-value |
|---|---|---|---|---|
| **Sex [n (%)]** | Male | 16 (45.7) | 18 (78.3) | 0.016 |
| | Female | 19 (54.3) | 5 (21.7) | |
| **Age, years [mean (SD)]** | | 53.11 (13.9) | 55.82 (14.5) | 0.96 |
| **Smoking status [n (%)]** | Non-smoker | 30 (85.7) | 11 (47.8) | 0.008 |
| | Ex-smoker | 4 (11.4) | 10 (43.5) | |
| | Current smoker | 1 (2.9) | 2 (8.7) | |
| **Medication [n (%)]** | Aspirin | 6 (17.1) | 3 (13) | 0.881 |
| | Clopidogrel | 2 (5.7) | 1 (4.3) | |
| | None | 27 (77.1% | 19 (82.6) | |
| **Coagulation profile [mean (SD)]** | INR | 1.10 (0.2) | 2.57 (7.4) | 0.68 |
| | Prothrombin time | 13.80 (1.2) | 13.48 (1.01) | 0.55 |
| | Activated partial thromboplastin time | 37.46 (5.7) | 39.01 (4.9) | 0.54 |
| | Platelet count | 292.65 (85.4) | 298.82 (86.1) | 0.99 |
| **Biopsy size (mm) [mean (SD)]** | | 6.74 (2.7) | 9.65 (6.4) | 0.08 |
| **Biopsy size (mm) [n (%)]** | <10 | 27 (77.1) | 15 (65.2) | 0.88 |
| | 20-Oct | 8 (22.9) | 4 (17.4) | |
| | >20 | 0 (0) | 4 (17.4) | |
| **Locations of transbronchial lung cryobiopsies (n=62)** | | | | |
| **Site [n (%)]** | RUL | 9 (23.1) | 6 (26.1) | 0.52 |
| | RML | 1 (2.6) | 3 (13.0) | |
| | LUL | 8 (20.5) | 7 (30.4) | |
| | Lingula | 3 (7.7) | 1 (4.3) | |
| | RLL | 8 (20.5) | 3 (13.1) | 0.25 |
| | LLL | 10 (25.6) | 3 (13.1a) | |

RUL: right upper lobe; RML: Right middle lobe; LUL: Left upper lobe; RLL: Right lower lobe; LLL: Left lower lobe.

***Safety Analysis***

The safety outcome of TBLC for DPPL and LPPL is presented in Table 8. Bleeding complications were observed in 39 cases (67.2%); 32 (82%) patients bled mildly, and six (15.4%) bled moderately. One (2.6%) patient suffered severe bleeding, required a blood transfusion, and had a prolonged stay in the intensive care unit (five days) post-procedure. The mean duration of hospital stay was longer for patients who bled than those who did not (5.64 days vs. 3.47 days; P = 0.014).

Overall, pneumothorax occurred in four (6.9%) patients, with three patients requiring drainage. Patients with pneumothorax had longer hospital stays than other patients (14.25 days vs. 4.24 days, P = 0.035). Two patients also subsequently developed pneumonia and persistent air leaks requiring 17- and 9-day intercostal chest drainage, respectively. No mortality was associated with the

procedure. Overall, there was no association between the number, size, or location of biopsies and the risk of bleeding or pneumothorax (Table 9 and 10).

Table 2: Radiological pattern of DPPL.

| DPPL (n = 35) | | n (%) |
|---|---|---|
| Radiological pattern | **Idiopathic interstitial pneumonias** | |
| | UIP | 2 (5.7) |
| | NSIP | 3 (8.6) |
| | OP | 1 (2.8) |
| | **Non idiopathic interstitial pneumonias** | |
| | HP | 5 (14.3) |
| | Ground-glass opacities | 5 (14.3) |
| | Nodular pattern | 15 (42.9) |
| | Reticular nodular pattern | 4 (11.4) |

UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia; OP: organizing pneumonia; HP: hypersensitivity pneumonitis

Table 3: Radiological pattern of LPPL.

| LPPL (n = 23) | | n (%) | Bronchus sign present | Bronchus sign absent | P-value |
|---|---|---|---|---|---|
| **Radiological pattern** | Mass | 18 (78.3) | | | |
| | Consolidation | 5 (21.7) | | | |
| **Positive diagnostic yield** | Overall | 16 (69.6) | 14 (87.5) | 2 (12.5) | 0.01 |
| | Mass | 14 (77.8) | 13 (92.9) | 1 (7.1) | 0.02 |
| | Consolidation | 2 (40.0) | 1 (50.0) | 1 (50.0) | 1 |

## DISCUSSION

Obtaining good tissue samples for histopathological diagnosis has presented a challenge with many respiratory diseases. The size of a tissue sample is crucial for histopathological interpretation. Thus, interest in exploring a safer biopsy modality that can secure larger biopsy samples without crush artifacts has emerged. Cryobiopsy (CB) is a new lung biopsy method based on the principle of cryotechnology [8]. TBLC provides a larger specimen size, more viable and alveolated tissue, and fewer crush artifacts [6, 7]. Numerous studies have been conducted on the use of CB, especially for interstitial lung disease. However, studies on the use of CB in LPPL remain limited [11, 20]. Conventional techniques, such as transbronchial or CT scan-guided biopsy, remain the standard approach, especially for LPPL.

In the past, the diagnostic yield of TBLC varied among studies because different devices or techniques were used. A recent large, comprehensive meta-analysis of 27 studies comprising 1,443 patients reported an overall diagnostic yield of 72.9% [21]. This meta-analysis was performed on studies involving TBLC in ILD patients. In another recent study, a meta-analysis of nine TBLC studies on LPPL reported a diagnostic yield of 77%, with eight studies conducted using radial endobronchial ultrasound (rEBUS) +/− guided sheath (GS) or fluoroscopy for the localization of lesions [22].

The current study used a 2.4-mm cryoprobe fixed at 4 s of freeze time. The sizes of our biopsies and overall diagnostic yields for both groups (DPPL

Table 4: Histological results of transbronchial lung cryobiopsy for cases of DPPL versus LPPL.

| Overall diagnostic yield | DPPL (n = 35) Frequency (%) 25 (71.4) | | LPPL (n = 23) Frequency (%) 17 (73.9) |
|---|---|---|---|
| Histopathological examination | IIP (n=8) | NIIP (n=27) | |
| UIP | 3 | 0 | 0 |
| NSIP | 2 | 0 | 0 |
| OP | 1 | 0 | 0 |
| HP | 0 | 3 | 0 |
| Pneumoconiosis | 0 | 1 | 0 |
| Eosinophilic pneumonia | 0 | 1 | 0 |
| Granulomatous | 0 | 8 | 2 |
| Adenocarcinoma | 0 | 6 | 9 |
| Squamous cell carcinoma | 0 | 0 | 2 |
| Small cell carcinoma | 0 | 0 | 1 |
| Carcinoid tumor | 0 | 0 | 3 |
| Inconclusive | 2 | 8 | 6 |

Table 5: Histological results base on radiological pattern of NIIP.

| | NIIP (n = 27) | | |
|---|---|---|---|
| | Ground-glass opacities (n = 3) | Nodular pattern (n = 18) | Reticular nodular pattern (n = 6) |
| Adenocarcinoma | 0 | 6 | 0 |
| Granuloma | 2 | 2 | 4 |
| Eosinophilic pneumonia | 0 | 1 | 0 |
| Pneumoconiosis | 0 | 1 | 0 |
| HP | 0 | 2 | 1 |
| Inconclusive | 1 | 6 | 1 |

and LPPL) did not differ much compared to previous studies, which applied a freezing time of 3–5 s. For DPPL, this study demonstrated that the use of TBLC was able to provide reasonable diagnostic yields for IIP and NIIP cases. TBLC is also helpful in obtaining adequate tissue specimens in cases of locally advanced lung malignancy. All six cases diagnosed with lung adenocarcinoma had multiple nodularity patterns (contralateral lobe involvement in four cases and involvement of two lobes on the same side in the remaining two). Three cases in the DPPL cohort (one with ground-glass opacities and two with nodular patterns) that witnessed radiological resolutions on repeated imaging were likely of infective origin. The remaining cases with inconclusive diagnoses from TBLC were either not feasible for CT-guided transthoracic biopsy or the patients opted for surveillance over surgical biopsy. They remained stable on subsequent imaging.

TBLC was preferred over CT-guided transthoracic biopsy (even for LPPL with a mean size of 5.31 cm [SD, 2.4 cm]) after the increased risk of

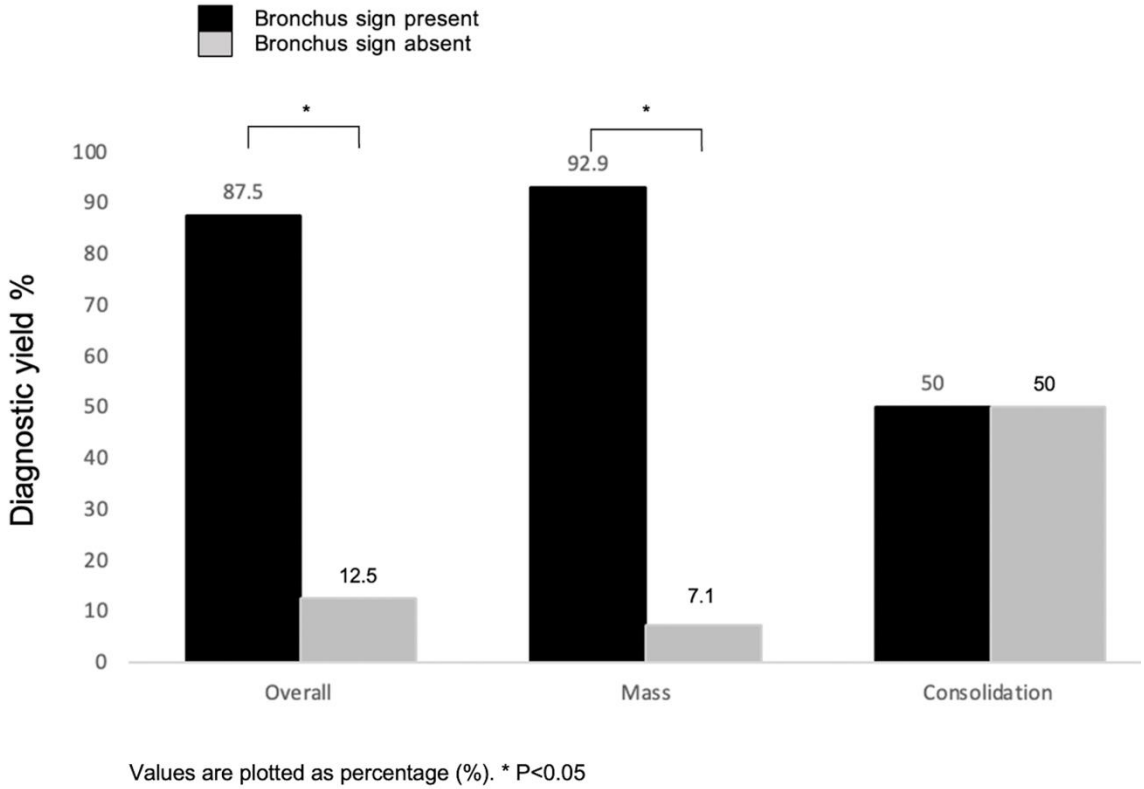


Figure 1: Diagnostic yield of LPPL from TBLC

Table 6: Outcome for inconclusive TBLC.

| | DPPL (n = 10) | LPPL (n = 6) |
|---|---|---|
| Lesion resolved on repeated imaging | 3 | |
| Lesion remained similar on surveillance imaging | 7 | |
| Malignancy | | 3 |
| Infection (Tuberculosis) | | 2 |
| Organizing pneumonia | | 1 |

pneumathorax associated with emphysematous lung changes and the long waiting time for CT-guided transthoracic biopsy were considered. Slightly more than a quarter of LPPL (6 out of 23) had false negative results on TBLC, but the diagnoses were clinched using CT-guided transthoracic biopsy. The factors that could have contributed to a lower diagnostic yield in the LPPL group included the biopsy sites' precision and reduced precision in the placements of the cryoprobe (without rEBUS or GS). A comparison of the groups showed that LPPL lesions were generally more proximal. Thus, the cryoadhesive effects of probes can also be reduced in areas with cartilage and greater collagen content, which may affect biopsy results. A higher diagnostic yield was seen in cases with bronchus signs, consistent with the results published in the past [16, 23, 24]. We found that identifying and navigating the sites of the lesions using an approach combining the bronchial branch reading technique [17, 18] and fluoroscopy were effective in providing reasonable diagnostic yields in the absence of rEBUS, with or without GS. Safety is one of the two most critical concerns when using CB.

Table 7: Univariable logistic regression in predicting the successful diagnosis of DPPL versus LPPL.

| Variable | | DPPL OR (95% CI) | LPPL OR (95% CI) | P-value |
|---|---|---|---|---|
| **Size of biopsies (mm)** | <10 | 1 | 1 | 0.97 |
| | 10–20 | 0.844 (0.219 - 3.255) | INFINITE | |
| | >20 | INFINITE | INFINITE | |
| **Number of biopsies** | ≤ 3 | 1 | 1 | 0.382 |
| | > 3 | 0.597 (0.188–1.898) | 1.674 (0.527–5.319) | |
| **Location** | Lingula | 1 | 1 | 0.882 |
| | LLL | INFINITE | INFINITE | |
| | LUL | INFINITE | INFINITE | |
| | RLL | INFINITE | INFINITE | |
| | RML | INFINITE | INFINITE | |
| | RUL | INFINITE | INFINITE | |

Table 8: Safety outcome of TBLC performed for DPPL versus LPPL.

| Complication | | DPPL (n = 35) | LPPL (n = 23) | P-value |
|---|---|---|---|---|
| **Pneumothorax** | | 1 (2.9%) | 3 (13.0%) | 0.29 |
| **No pneumothorax** | | 34 (97.1%) | 20 (87%) | |
| **Pneumothorax requiring drainage** | | 1 (2.9%) | 2 (8.7%) | |
| **Bleeding** | No | 10 (28.6%) | 9 (39.1%) | 0.361 |
| | Mild | 22 (62.9%) | 10 (43.5%) | |
| | Moderate | 3 (8.6%) | 3 (13.0%) | |
| | Severe | 0 (0%) | 1 (4.3%) | |
| **Other complications** | Prolonged ventilation | 2 (5.7%) | 1 (4.3%) | 1 |
| | No prolonged ventilation | 33 (94.3%) | 22 (95.7%) | |

Bleeding and the occurrence of pneumothorax are the two most important potential complications. A comparative analysis of the complications of TBLC performed for DPPL and PPL is lacking due to the limited number of studies on TBLC performed for LPPL.

For DPPL, the pooled incidence of moderate and severe bleeding reported in a large meta-analysis was 14.2% [21]. A recent prospective single-arm study concluded that TBLC conducted without a bronchial blocker is still a relatively safe procedure for obtaining histology samples for both peripheral and central lung cancer lesions, with only one patient exhibiting severe bleeding [25]. The higher percentage of moderate bleeding observed in our cohort (especially in the LPPL cohort) could be attributed to the lower threshold for the instillation of local adrenaline and cold

Table 9: Univariable logistic regression in predicting bleeding from TBLC.

| Variable | | OR (95% CI) | P-value |
|---|---|---|---|
| **CT interstitial pattern** | | 1 | 0.402 |
| **CT non-interstitial pattern** | | 1.607 (0.528–4.892) | |
| **Size of biopsy (mm)** | <10 | 1 | 0.795 |
| | 10-20 | 1.371 (0.132-14.226) | |
| | >20 | 0.229 (0.019 - 2.708) | |
| **Number of biopsies** | ≤ 3 | 1 | 0.466 |
| | > 3 | 1.568 (0.466–5.273) | |
| **Location** | 0 (all other lobes) | 1 | 0.159 |
| | 1 (upper lobe) | 0.450 (0.147–1.379) | |

Table 10: Univariable logistic regression in predicting pneumothorax from TBLC

**(B) Pneumothorax**

| Variable | | OR (95% CI) | P-value |
|---|---|---|---|
| **CT interstitial pattern** | | 1 | 1 |
| **CT non-interstitial pattern** | | 2.063 (0.201–21.142) | |
| **Size of biopsy (mm)** | <10 | 1 | 0.126 |
| | 10-20 | 2.036 (0.197–21.069) | |
| | >20 | INFINITE | |
| **Number of biopsies** | < 3 | 1 | 0.38 |
| | > 3 | 1.674 (0.527–5.319) | |
| **Location** | 0 (all other lobes) | 1 | 0.785 |
| | 1 (upper lobe) | 0.768 (0.263–2.245) | |

saline and the use of a larger CB probe (2.4 mm). Biopsy of LPPL also potentially increases the risk of bleeding due to its proximity to the pulmonary vasculature. In addition, the estimation of the degree of bleeding can be subjective, or dependent on the operator, as the degree of bleeding varies with various severity scales [12].

Evidence of the bleeding risk associated with biopsy size is not well established due to heterogeneity in the designs of clinical studies. In accordance with previous reports and analyses [26, 27], we observed that the risk of bleeding increased with the size of the biopsy (comparing samples < 10 mm vs. 10–20 mm), but it remained non-statistically significant in univariable logistic regression. Moreover, this study could not establish any relationship between other previously debated potential factors associated with bleeding, such as the number of biopsies and the location of the biopsy (i.e., the lobe in which it

took place). Therefore, the results of this study reinforce the contention that the bleeding risk is similar regardless of the biopsy being performed at different sites or lobes28, at single or different sites of a single lobe or different lobes, or with the prophylactic application of a balloon [29, 30].

In terms of pneumothorax, the overall rate of 6.8% was acceptable (5.1% required chest drainage). For DPPL, an increased risk of pneumothorax was previously reported with the use of a larger CB probe (2.4 mm) or when TBLC was performed in a different segment in the same lobe or different lobes [22, 29, 30]. The lower incidence of pneumothorax seen in our cohort was primarily due to TBLC being performed at a single site and in a single lobe aided by fluoroscopy (except for four cases in which biopsy was performed in different lobes due to bleeding). Given the lack of robust data in the literature on the occurrence of pneumothorax in LPPL patients, drawing any plausible conclusions would be premature. Overall, we were not able to demonstrate any significant differences in procedural complications between the DPLD and LPPL groups.

The current study has several limitations. The sample size was small and came from a single center. We acknowledge that retrospective studies have the potential for selection bias. Furthermore, prior to 2020, a standardized technique for TBLC sampling (number and location of biopsies) was also lacking [12].

## CONCLUSION

TBLC enables optimal lung tissue sampling to facilitate a favorable histological tissue diagnosis for DPPL and LPPL. Similar to DPPL, TBLC provides an acceptable diagnostic yield for LPPL using concomitant fluoroscopy without rEBUS or GS. Pre-procedure planning with ancillary techniques, such as bronchial branch reading, also seems useful. TBLC is associated with a low incidence of pneumothorax, and bleeding complications can be managed with the routine use of an endobronchial balloon. Additional research is needed to provide further insights into patient selection, complication rates associated with different devices and biopsy techniques, and the standardization of the TBLC technique when used for the biopsy of LPPL.

## STATEMENT OF ETHICS

Ethical approval for this retrospective study was granted by the National Medical Research Register of Malaysia (NMRR ID: NMRR-20-3170-57192).

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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## DATA AVAILABILITY STATEMENTS:

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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