Supplementary Material

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Supplementary Appendix 1- Full search terms used in the literature search of each database.

1. PubMed

| Search ID | Search Terms                                                                 |
|-----------|-----------------------------------------------------------------------------|
| #1        | ("Cryobiopsy" OR "Cryoprobe biopsy" OR "Forceps biopsy" OR "pleural cryobiopsy") |
| #2        | (" Pleura*" OR " Pleural effusion " OR " pleural biopsy " OR "pleuroscopy" OR “thoracoscopy”) |
| #3        | #1 AND #2 (Results retrieved n= 68)                                         |

2. Embase

| Search History | Searches                                                                 |
|----------------|---------------------------------------------------------------------------|
| 1              | (‘cryobiopsy’/exp OR cryobiopsy OR ‘cryoprobe’/exp OR cryoprobe) AND (‘biopsy’/exp OR biopsy) OR ‘forceps’/exp OR ‘forceps’) AND (‘biopsy’/exp OR biopsy) OR ‘pleural’ AND (‘cryobiopsy’/exp OR cryobiopsy) |
| 2              | (‘pleura*’ OR ‘pleural’) AND (‘effusion’/exp OR effusion) OR ‘pleural’) AND (‘biopsy’/exp OR biopsy) OR ‘pleuroscopy’/exp OR ‘pleuroscopy’ OR ‘thoracoscopy’/exp OR thoracoscopy |
| 3              | #1 AND #2 (Results retrieved n= 93)                                       |

3. Scopus

TITLE-ABS-KEY ( ("Cryobiopsy" OR "Cryoprobe biopsy" OR "Forceps biopsy" OR "pleural cryobiopsy") AND (" Pleura*" OR " Pleural effusion" OR " pleural biopsy" OR "pleuroscopy" OR "thoracoscopy") ) (Results retrieved n= 106)

4. Web of Science

| Search History | Searches                                                                 |
|----------------|---------------------------------------------------------------------------|
| #1 | TS=("Cryobiopsy" OR "Cryoprobe biopsy" OR “Forceps biopsy” OR “pleural cryobiopsy") |
|---|---|
| #2 | TS=("Pleura*" OR "Pleural effusion" OR "pleural biopsy" OR "pleuroscopy" OR “thoracoscopy”) |
| #3 | #1 AND #2 (Results retrieved n=94) |
Supplementary Figure 1. Quality assessments of included studies using the QUADAS-2 tool. A) Risk of bias graph: Review authors’ judgments about each risk of bias item presented as percentages across all included randomized controlled studies. B) Risk of bias summary: Review authors’ judgments for each risk of bias item for the included studies.
Supplementary Figure 2. Funnel plot to detect publication bias for studies comparing specimen size.
Supplementary Figure 3. Leave-one-out sensitivity analysis of specimen size between cryobiopsy and forceps biopsy

| Study                        | Std. Mean Difference IV, Random, 95% CI | Std. Mean Difference IV, Random, 95% CI |
|------------------------------|----------------------------------------|----------------------------------------|
| Omitting Baess et al         | 1.22 [0.50; 1.94]                      |                                        |
| Omitting Chen et al          | 1.16 [0.43; 1.88]                      |                                        |
| Omitting Dhooria et al       | 1.14 [0.42; 1.86]                      |                                        |
| Omitting El Sayad et al      | 0.98 [0.38; 1.58]                      |                                        |
| Omitting Lee et al           | 1.22 [0.50; 1.94]                      |                                        |
| Omitting Matura et al        | 1.06 [0.42; 1.71]                      |                                        |
| Omitting Muhhamad et al      | 1.32 [0.90; 1.73]                      |                                        |
| Omitting Nakai et al         | 1.06 [0.42; 1.71]                      |                                        |
| Omitting Pathak et al        | 1.18 [0.47; 1.90]                      |                                        |
| Omitting Thomas et al        | 1.19 [0.47; 1.91]                      |                                        |
| Omitting Tousheed et al      | 1.18 [0.46; 1.91]                      |                                        |
| Omitting Wurps et al         | 1.23 [0.51; 1.95]                      |                                        |

Total (95% CI) 1.16 [0.51; 1.82]
Supplementary Figure 4. Funnel plot to detect publication bias for studies comparing diagnostic yield between cryobiopsy and forceps biopsy
Supplementary Figure 5. Forest plot of leave-one-out meta-analysis of the diagnostic yield

| Study                    | Odds Ratio   | Odds Ratio   |
|--------------------------|--------------|--------------|
| Omitting Ahmed et al     | 1.41 [0.80; 2.49] |               |
| Omitting Baess et al     | 1.32 [0.79; 2.21] |               |
| Omitting Chen et al      | 1.17 [0.69; 1.99] |               |
| Omitting Dhooria et al   | 1.42 [0.77; 2.63] |               |
| Omitting El Sayad et al  | 1.32 [0.79; 2.21] |               |
| Omitting Ismail et al    | 1.32 [0.79; 2.21] |               |
| Omitting Lee et al       | 1.34 [0.79; 2.29] |               |
| Omitting Matura et al    | 1.28 [0.76; 2.15] |               |
| Omitting Muhhamad et al  | 1.32 [0.79; 2.21] |               |
| Omitting Nakai et al     | 1.23 [0.73; 2.07] |               |
| Omitting Pathak et al    | 1.32 [0.79; 2.21] |               |
| Omitting Rozman et al    | 1.37 [0.82; 2.31] |               |
| Omitting Thomas et al    | 1.35 [0.79; 2.29] |               |
| Omitting Touheed et al   | 1.26 [0.75; 2.14] |               |
| Omitting Wurps et al     | 1.48 [0.83; 2.64] |               |

**Total (95% CI)**: 1.32 [0.79; 2.21]
Supplementary Figure 6. Forest plot of the leave-one-out meta-analysis of crush artifacts

| Study                  | Odds Ratio          | Odds Ratio          |
|------------------------|---------------------|---------------------|
| Omitting Baess et al   | 0.04 [0.01; 0.28]   |                     |
| Omitting Dhooria et al | 0.04 [0.01; 0.20]   |                     |
| Omitting Matura et al  | 0.06 [0.01; 0.36]   |                     |
| Omitting Muhhamad et al| 0.06 [0.01; 0.38]   |                     |
| Omitting Thomas et al  | 0.12 [0.05; 0.34]   |                     |
| Total (95% CI)         | 0.06 [0.01; 0.26]   |                     |
Supplementary Figure 7. Funnel plot to detect publication bias for studies comparing crush artifacts between cryobiopsy and forceps biopsy.
Supplementary Figure 8. Forest plot of specimen depth of pleural cryobiopsy versus forceps biopsy

| Study          | Cryobiopsy | Forceps | Odds Ratio |
|----------------|------------|---------|------------|
|                | Events     | Total   |            |
| Baess et al    | 8          | 24      | 1.00 [0.30; 3.32] |
| Dhooria et al  | 30         | 46      | 2.72 [1.18; 6.25] |
| Matura et al   | 4          | 6       | 16.20 [0.59; 441.68] |
| Muhhamad et al | 21         | 30      | 3.50 [1.20; 10.20] |
| Nakai et al    | 2          | 5       | 2.67 [0.16; 45.14] |
| Thomas et al   | 14         | 22      | 17.50 [3.22; 95.16] |
| Wurps et al    | 49         | 99      | 1.51 [0.86; 2.63] |

Total (95% CI): 232 Cryobiopsy, 238 Forceps, 2.68 [1.39; 5.16]

Heterogeneity: Tau² = 0.3407; Chi² = 11.58, df = 6 (P = 0.07); I² = 48%
Test for overall effect: Z = 2.94 (P < 0.01)
Supplementary Figure 9. Funnel plot to detect publication bias for studies comparing specimen depth between cryobiopsy and forceps biopsy
Supplementary Figure 10. Forest plot of the leave-one-out meta-analysis of specimen depth

| Study               | Odds Ratio MH, Random, 95% CI | Odds Ratio MH, Random, 95% CI |
|---------------------|-------------------------------|-------------------------------|
| Omitting Baess et al| 3.26 [1.56; 6.80]              |                               |
| Omitting Dhooria et al| 2.91 [1.18; 7.19]            |                               |
| Omitting Matura et al| 2.48 [1.30; 4.74]            |                               |
| Omitting Muhhamad et al| 2.70 [1.16; 6.26]          |                               |
| Omitting Nakai et al | 2.74 [1.34; 5.60]            |                               |
| Omitting Thomas et al| 1.99 [1.27; 3.11]            |                               |
| Omitting Wurps et al | 3.36 [1.49; 7.58]            |                               |
| Total (95% CI)      | 2.68 [1.39; 5.16]             |                               |
Supplementary Figure 11. Forest plot of mild to moderate bleeding events occurred during pleural cryobiopsy versus forceps biopsy

| Study            | Cryobiopsy Events | Forceps Events | Odds Ratio MH, Random, 95% CI |
|------------------|-------------------|----------------|-----------------------------|
| Ahmed et al      | 0                 | 1              | 0.32 [0.01; 8.24]            |
| Chen et al       | 8                 | 92             | 1.37 [0.45; 4.10]            |
| Dhooria et al    | 0                 | 46             | 0.94 [0.30; 2.69]            |
| El Sayad et al   | 10                | 26             | 0.92 [0.10; 20.10]           |
| Lee et al        | 3                 | 28             | 3.67 [0.12; 113.73]          |
| Nakai et al      | 1                 | 5              | 1.32 [0.30; 5.77]            |
| Thomas et al     | 5                 | 22             |                             |
| Wurps et al      | 0                 | 6              |                             |

Total (95% CI) 255 246 100.0% 1.21 [0.64; 2.29]

Heterogeneity: Tau² = 0; Chi² = 1.45, df = 5 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)
Supplementary Figure 12. Funnel plot of studies comparing cryobiopsy versus forceps biopsy for mild to moderate bleeding events
Supplementary Figure 13. Forest plot of the leave-one-out meta-analysis of mild to moderate bleeding events

| Study                  | Odds Ratio MH, Random, 95% CI | Odds Ratio MH, Random, 95% CI |
|------------------------|-------------------------------|-------------------------------|
| Omitting Ahmed et al   | 1.27 [0.66; 2.44]             |                               |
| Omitting Chen et al    | 1.13 [0.51; 2.49]             |                               |
| Omitting Dhooria et al | 1.21 [0.64; 2.29]             |                               |
| Omitting El Sayad et al| 1.36 [0.62; 2.96]             |                               |
| Omitting Lee et al     | 1.16 [0.60; 2.26]             |                               |
| Omitting Nakai et al   | 1.16 [0.60; 2.22]             |                               |
| Omitting Thomas et al  | 1.18 [0.58; 2.40]             |                               |
| Omitting Wurps et al   | 1.21 [0.64; 2.29]             |                               |
| Total (95% CI)         | 1.21 [0.64; 2.29]             |                               |
### Supplementary Table 1. Average specimen size obtained by pleural cryobiopsy and forceps biopsy

| Study (year) | Average biopsy size cryobiopsy | Average biopsy size forceps biopsy |
|--------------|---------------------------------|-----------------------------------|
| Ahmed et al  | NR                              | NR                                |
| Baess et al  | 4.1 ± 2.4 cm² (Surface area ± SD)| 2.7 ± 1 cm² (Surface area ± SD)   |
| Chen et al²   | 9.4mm ± 4.9 mm (mean size ± SD) | 4.2mm ± 2.3 mm (mean size ± SD)   |
| Dhoooria et al³ | 7 mm (6–10) (median size, range) | 4 (3–5) (median size, range)        |
| El Sayad et al| 14.07 ± 4.29 (mean size ± SD)   | 5.04 ± 0.53 (mean size ± SD)     |
| Ismail et al | NR                              | NR                                |
| Lee et al¹³   | 9.1 ± 5.7 mm (mean size ± SD)   | 5.3 ± 3.8 (mean size ± SD)        |
|               | 56.0 ± 61.3 mm² (mean area ± SD)| 10.2 ± 14.3 mm² (mean area ± SD) |
|               | 232.1 ± 411.4 mm³ (volume ± SD) | 13.4 ± 22.6 mm³ (volume ± SD)     |
| Matura et al¹⁴| 9.17 ± 1.84 mm (mean size ± SD) | 3.75 ± 0.96 mm (mean size ± SD)   |
| Muhhamad et al¹⁵| 0.338±0.247 cm² (Surface area ± SD) | 0.819±0.404 cm² (Surface area ± SD) |
| Nakai et al¹⁶ | 18.9 (15.2–19.8) mm² (cross-sectional area ; median, range) | 6.7 (5.9–6.8) mm² (cross-sectional area ; median, range) |
| Pathak et al¹⁷| 320 mm³ mean tissue volume      | 80 mm³ mean tissue volume         |
| Rozman et al²¹ | NR                              | NR                                |
| Thomas et al¹⁸| 10 (7-15.8) mm (median size, range) | 4 (3-8) mm (median size, range) |
| Tousheed et al¹⁹| 13.2± 6.7 mm (mean size ± SD)   | 6.8± 3.3 mm (mean size ± SD)      |
| Wurps et al²⁰ | 14.4 ± 12.8 mm² (mean area ± SD) | 7.1 ± 9.3 mm² (mean area ± SD)    |

NR = Not reported
Supplementary Table 2. Artefacts reported in included studies comparing pleural cryobiopsy versus forceps biopsy

| Author          | Occurrence of artefacts     | Number of patients in CB, n (%) | Number of patients in FB, n (%) |
|-----------------|----------------------------|---------------------------------|---------------------------------|
| Baess et al     | Crushed cells negative     | 17/24 (70.8)                    | 6/24 (25)                       |
|                 | Crushed cells <5%          | 6/24 (25)                       | 14/24 (58.3)                    |
|                 | Crushed cells 5-10%        | 1/24 (4.2)                      | 0/24 (0)                        |
|                 | Crushed cells 10-25%       | 0/24 (0)                        | 4/24 (16.7)                     |
| Dooria et al    | None                       | 45/46 (97.8)                    | 46/49 (93.9)                    |
|                 | Crush                       | 1/46 (2.2)                      | 3/49 (6.1)                      |
|                 | Freeze                      | 0/46 (0)                        | 0/49 (0)                        |
| Matura et al    | Crush artefacts            | 0/6 (0)                         | 3/4 (75)                        |
| Muhhamad et al  | Crushed cells              | 0/30 (0)                        | 9/30 (30)                       |
|                 | No crushed cells           | 30/30 (100)                     | 21/30 (70)                      |
| Thomas et al    | Crush artefacts nil        | 20/22 (91)                      | 1/22 (4.5)                      |
|                 | Crush artefacts mild       | 1/22 (4.5)                      | 19/22 (86.4)                    |
|                 | Crush artefacts moderate   | 1/22 (4.5)                      | 2/22 (9.1)                      |
|                 | Crush artefacts severe     | 0/22 (0)                        | 0/22 (0)                        |
Supplementary Table 3. Qualitative analysis of depth of biopsy between pleural cryobiopsy and forceps biopsy

| Author          | Depth of tissue                                      | Number of patients in CB, n (%) | Number of patients in FB, n (%) |
|-----------------|-----------------------------------------------------|---------------------------------|---------------------------------|
| Baess et al     | Fat cells negative                                  | 12/24 (50)                      | 8/24 (33.3)                     |
|                 | Fat cells ≤5%                                       | 4/24 (16.7)                     | 8/24 (33.3)                     |
|                 | Fat cells (5-10%)                                   | 5/24 (20.8)                     | 2/24 (8.3)                      |
|                 | Fat cells (10-25%)                                  | 3/24 (12.5)                     | 6/24 (25)                       |
| Dooria et al    | Up to mesothelial connective tissue                 | 16/46 (34.8)                    | 29/49 (59.2)                    |
|                 | Up to extrapleural fat or deeper                    | 30/46 (65.2)                    | 20/49 (40.8)                    |
| Matura et al    | Subpleural adipose tissue                           | 4/6 (66.7)                      | 0/4 (0)                         |
| Muhhamad et al  | Biopsies containing fatty tissue                    | 21/30 (70)                      | 12/30 (40)                      |
|                 | Biopsies containing no fat tissue                   | 9/30 (30)                       | 18/30 (60)                      |
| Nakia et al     | Pleural surface                                     | 1/5 (20)                        | 4/5 (80)                        |
|                 | Adipose tissue                                      | 2/5 (40)                        | 1/5 (20)                        |
|                 | Skeletal muscle                                     | 2/5 (40)                        | 0/5 (0)                         |
| Thomas et al    | Fibrotic pleura                                     | 22/22 (100)                     | 21/22 (95.5)                    |
|                 | Adipose tissue                                      | 14/22 (63.6)                    | 5/22 (22.7)                     |
|                 | Skeletal muscle                                     | 10/22 (45.5)                    | 2/22 (9.1)                      |
|                 | Lung                                                | 1/22 (4.5)                      | 1/22 (4.5)                      |
|                 | Fragments                                           | 0/22 (0)                        | 1/22 (4.5)                      |
| Wurps et al     | Biopsies including fatty tissue                     | 49/99 (49.5)                    | 41/104 (39.4)                   |
|                 | Biopsies Negative for fatty tissue                  | 50/99 (50.5)                    | 63/104 (60.6)                   |

CB, cryobiopsy; FB, Forceps biopsy