Diagnostic yield and postoperative mortality associated with surgical lung biopsy for evaluation of interstitial lung diseases: A systematic review and meta-analysis

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Objectives: Surgical lung biopsy plays an important role in providing pathologic results, thus complementing the diagnostic rationale for suspected interstitial lung diseases. We performed a systematic review and meta-analysis regarding the diagnostic yield and postoperative mortality rate of surgical lung biopsy in patients with suspected interstitial lung diseases because of the wide variation in previously reported effectiveness and safety concerns.

Methods: We systematically searched for published studies between 2000 and 2014 evaluating surgical lung biopsy in the diagnosis of interstitial lung diseases. Subgroup analysis was performed to identify the possible source of study heterogeneity.

Results: Twenty-three studies contributed 2148 patients for the analysis. The median diagnostic yield was 95% (range, 42%-100%), with idiopathic pulmonary fibrosis as the most frequent diagnosis (618, 33.5%). Surgical lung biopsy was mainly guided by high-resolution computed tomography manifestations. Biopsy site, biopsy number, and the surgical lung biopsy method may not be associated with the diagnostic accuracy. The pooled postoperative mortality rate for included studies was 3.6% (95% confidence interval, 2.1-5.5), with significant heterogeneity observed. Subgroup analysis revealed that exclusion criteria based on immunocompromised status, mechanical ventilation, and severe respiratory dysfunction (diffusing capacity of lung for carbon monoxide <35% or forced vital capacity <55% predicted), but not surgical lung biopsy technique or underlying interstitial lung disease subtype, may be possible sources of heterogeneity.

Conclusions: We demonstrated a satisfactory diagnostic performance with a favorable safety profile of surgical lung biopsy in the diagnosis of suspected interstitial lung diseases. Surgical lung biopsy is especially recommended in patients with clinical information indicative but atypical of idiopathic pulmonary fibrosis, whereas the benefit of surgical lung biopsy should be carefully balanced against the risk for patients with immunocompromised status, mechanical ventilation dependence, or severe respiratory dysfunction. (J Thorac Cardiovasc Surg 2015;149:1394-401)

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Interstitial lung diseases (ILDs) comprise a group of lung diseases with a great diversity regarding the cause, pathologic change, treatment, and prognosis. Therefore, the establishment of an accurate diagnosis is essential to determine the therapeutic intervention and prognosis for a given patient. Histologic results may be required to establish a specific diagnosis or complement diagnostic rationale in cases that remain undefined after thorough clinical information combined with thoracic imaging. Bronchoalveolar lavage or transbronchial lung biopsy via bronchoscopy may be useful in selected subtypes, such as sarcoidosis, hypersensitivity pneumonitis (HP), and eosinophilic pneumonia. However, transbronchoscopic sampling may not be representative and indicative because of the amount and size of biopsies.

The current guidelines emphasize the significant role of surgical lung biopsy (SLB) for the definite diagnosis of ILDs,^{1,2} whereas it may be associated with a relatively higher morbidity and mortality rate. Therefore, the final decision regarding whether or not to perform a SLB must

Abbreviations and Acronyms

CI	= confidence interval
DLCO	= diffusing lung capacity for carbon monoxide
FVC	= forced vital capacity
HP	= hypersensitivity pneumonitis
HRCT	= high-resolution computed tomography
ILD	= interstitial lung disease
IPF	= idiopathic pulmonary fibrosis
MV	= mechanical ventilation
NSIP	= nonspecific interstitial pneumonia
OLB	= open lung biopsy
SLB	= surgical lung biopsy
VATS	= video-assisted thoracoscopic surgery

be based on the balance between benefits to establish a secure diagnosis and the potential risks. Numerous groups have published their experience with SLB in the diagnosis of ILDs. We conducted a systematic review to evaluate the effectiveness and safety of SLB in the diagnosis of ILDs, and meta-analysis were performed where applicable.

MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement, and the study protocol was approved by the Ethics Committee of Guangzhou Medical University.

Literature Search

A systematic search of 2 databases (PubMed and Embase) for relevant citations (from January 1, 2000 to June 30, 2014) was performed in May 2014, with the following search terms used: “surgical lung biopsy” or “open lung biopsy” or “video-assisted thoracoscopic surgery” or “video-assisted thoracoscopy surgery” in combination with “interstitial lung disease” or “interstitial lung diseases” or “diffuse parenchymal lung disease.” The search was restricted to human subjects. Bibliographies from selected articles and major reviews were screened for additional relevant publications that were not identified by the database search.

Outcome Definitions

Two outcomes for this systematic review were diagnostic yield and postoperative mortality. Diagnostic yield indicated the specific diagnosis obtained with SLB samples thus affecting overall patient management. Postoperative mortality was defined as the number of patients who died within 90 days after surgery.

Selection of Studies

Two authors (HQ and LQ) independently reviewed all articles identified by the search strategy for inclusion in this review, sequentially evaluating the title, abstract, and full publication. Discordance was resolved by consensus. Inclusion criteria were as follows: (1) SLB, including both video-assisted thoracoscopic surgery (VATS) and open lung biopsy (OLB) for the diagnosis of suspected ILDs; (2) reported at least 1 of primary outcomes; (3) enrolled at least 30 patients; and (4) published in English. We excluded abstracts, editorials, reviews, and case reports. Studies describing the diagnostic yield of SLB in a specific subset of patients were also excluded. In the event of multiple

publications with overlapping study periods, we included only 1 study with the largest number to prevent double counting of the patient cohorts. Authors of studies not reporting sufficient data were contacted to request additional information.

Data Extraction and Quality Assessment

Data were recorded on a standard data extraction form that included the following items: description of study population (number, age, geographic location, and surgery methods); study design (prospective or retrospective); patient enrollment (key inclusion and exclusion criteria); biopsy site; and number. The quality and validity of each article were assessed using the QualSyst tool for quantitative studies.³ This tool was based on the study design, method of population sampling, strategies of data collection and analysis, and how the conclusions were ascertained. It consists of 14 questions with scores from 0 to 2, with the maximum total score being 28.

Data Synthesis and Statistical Analysis

We conducted a meta-analysis for mortality rate using the variance-stabilization double arc-sine transformation method,⁴ because the inverse variance weight in meta-analyses is suboptimum when dealing with binary data with low mortality rates. We applied DerSimonian-Laird weights for the random effects model where heterogeneity between studies was found. The pooled rate can be calculated as the back-transform of the weighted mean of the transformed rates. The impact of statistical heterogeneity on the pooled estimates of individual outcomes was assessed using the I^2 test, which measures the extent of inconsistency among the results of the studies. An I^2 value greater than 50% indicates significant heterogeneity. Subgroup analysis was performed if heterogeneity was demonstrated, according to common methodological/clinical features of the studies. Statsdirect and STATA 12.0 (StatsDirect Ltd, Altrincham, UK) were used to perform all the tests.

RESULTS**Literature Search and Study Selection**

The selection of included studies is summarized in [Figure 1](#). Screening of titles and abstracts identified 30 articles for full text review. Of these, 7 articles were excluded: Four articles focused on a special subset of patients, such as those with idiopathic pulmonary fibrosis (IPF) or idiopathic interstitial pneumonia, and those dependent on mechanical ventilation (MV); 2 articles evaluated a certain aspect of SLB in the diagnosis of ILDs; and 1 article recruited only 20 patients. Finally, 23 articles met the eligibility criteria of our systematic review.

Study Description and Quality Assessment

Study characteristics are recorded in [Table 1](#). A total of 2148 patients with suspected ILDs undergoing SLB were included (range, 30-311 patients per study). There were 5 prospective studies and 18 retrospective studies. Three studies were multicenter studies, including 1 retrospective study and 2 prospective studies; others were studies from a single institution.

The quality of studies was generally acceptable, with a median (interquartile) QualSyst score of 21 (range, 17-24) ([Table 2](#)). None of the studies were designed as a “double-blind” procedure and could be assessable in “blinding of investigators/subjects” domains. Moreover,

FIGURE 1. Selection of included studies from systematic review. *ILD*, Interstitial lung disease; *SLB*, surgical lung biopsy.

only 2 prospective randomized, controlled studies were assessable in “random allocation” domain.^{5,6}

Subject Characteristics

The mean age of patients ranged from 36.1 to 62.0 years, and 1124 (52.3%) were male. All patients had suspected

ILDs yet remained undefined or unclassified with thorough clinical and radiologic information. There were 1632 patients undergoing VATS (76.0%) and 268 patients undergoing OLB (12.5%) in 21 studies reporting SLB techniques.

Diagnostic Yield

The diagnostic yield for each included study is summarized in Table 2. A formal meta-analysis was not performed because of the heterogeneity of included studies. The median diagnostic yield was 95% (range, 42%-100%), with only 1 study achieving less than 70%,⁷ 8 studies achieving 70% to 90%,⁸⁻¹⁵ 8 studies achieving 90% to 100%,^{5,16-20} and 6 studies achieving 100%.^{6,21-25} Moreover, 8 studies evaluated the frequency in which the biopsy changed the treatment algorithm, ranging from 42% to 90%.^{7,8,10,15,18,20,22,24} The change was driven by specific diagnosis in 6 studies^{8,15,18,20,22,24} and was not necessarily related to specific diagnosis in 2 studies.^{7,10}

A total of 17 studies reported biopsy sites; 11 studies were guided by computed tomography without special

TABLE 1. Main characteristics of selected studies

First author	Year	Country	Patients n (male/female)	Mean age, y	Study design	Patient enrollment	Exclusion criteria
Ayed ⁵	2000	Kuwait	61 (36/25)	39.8	RCT	NA	MV dependence
Miller ⁶	2000	US	42 (23/19)	52.4	RCT (4 centers)	Consecutive (ambulatory)	NA
Blewett ²¹	2001	Canada	32 (ND)	58	Retrospective	Consecutive (ambulatory)	Oxygen dependence, acute illness
Qureshi ⁷	2002	UK	100 (59/41)	51.5	Retrospective	NA	MV dependence
Ayed ²⁶	2003	Kuwait	79 (50/29)	38.9	Prospective	NA	MV dependence
Yamaguchi ²⁴	2004	Japan	30 (18/12)	56.7	Retrospective	Consecutive	Immunocompromised or MV dependence
Lettieri ²²	2005	US	83 (48/35)	57.3	Retrospective	NA	Age <18 y
Ooi ¹⁴	2005	UK	70 (57/13)	56	Retrospective	Consecutive	Histologic diagnoses not ILD
Kreider ¹³	2007	US	68 (30/38)	58	Retrospective	Consecutive (ambulatory)	NA
Bando ¹⁶	2008	Japan	94 (43/51)	59	Retrospective	NA	AE before surgery
Ishie ²⁷	2008	Brazil	48 (23/25)	58.8	Retrospective	NA	MV and oxygen dependence
Coutinho ²⁵	2008	Portugal	120 (60/60)	55.8	Retrospective	Consecutive	NA
Sigurdsson ¹⁵	2009	Iceland	73 (42/31)	57.3	Retrospective (nationwide)	Consecutive	NA
Guerra ¹⁷	2009	Portugal	53 (31/22)	47.2	Retrospective	NA	NA
Fibla ¹⁰	2012	US	311 (164/147)	60.9	Retrospective	Consecutive	NA
Fibla ¹¹	2012	Spain	224 (106/118)	57.1	Prospective (13 centers)	Consecutive (some ambulatory)	MV dependence or Pao ₂ <60 mm Hg
Blackhall ⁸	2012	UK	103 (51/52)	58	Retrospective	Consecutive	NA
Blanco ⁹	2012	Spain	156 (82/89)	57.3	Retrospective	NA	NA
Luo ²³	2013	China	32 (20/12)	52.2	Retrospective	NA	MV dependence or DLCO <50%
Pompeo ¹⁹	2013	Italy	30 (15/15)	62	Prospective	NA	Age >75 y, MV dependence, DLCO <30%, AE in past 6 mo, Pao ₂ <50 mm Hg
Kayatta ¹²	2013	US	194 (100/94)	58	Retrospective	Consecutive	NA
Morris ¹⁸	2014	UK	66 (31/35)	58.9	Retrospective	Consecutive	NA
Sonobe ²⁰	2014	Japan	64 (35/29)	57	Prospective	NA	Age >70 y, FVC <60%, DLCO <40%

RCT, Randomized controlled trial; *NA*, not available; *ND*, not determined; *MV*, mechanical ventilation; *ILD*, interstitial lung disease; *AE*, acute exacerbation; *PaO₂*, arterial oxygen tension; *DLCO*, diffusing lung capacity for carbon monoxide; *FVC*, forced vital capacity.

TABLE 2. Outcomes and quality of included studies

First author	Year	Patient no.	Diagnostic yield (%)	Treatment change (%)	Biopsy location	Biopsy no. (n)	Surgery method (n)	30-d mortality (%)	90-d mortality (%)	Postoperative mortality (%)	Total score
Ayed ⁵	2000	61	95.1	NA	CT	2	VATS (61) OLB (29)	1.6	3.3	3.3	24
Miller ⁶	2000	42	100.0	NA	NA	1.6 (mean)	VATS (42) OLB (22)	0.0	2.4	2.4	23
Blewett ²¹	2001	32	100.0	NA	Lingula	2	OLB	NA	NA	NA	20
Qureshi ⁷	2002	100	42.0	59.5	CT	1 (69)/≥2 (31)	VATS (70) OLB (30)	NA	NA	NA	21
Ayed ²⁶	2003	79	96.2	NA	34 (middle), 45 (other)	1 (34)/2 (45)	VATS	NA	NA	NA	21
Yamaguchi ²⁴	2004	30	100.0	57.0	CT	1 (17)/2 (11)/3 (2)	VATS	0.0	0.0	0.0	20
Lettieri ²²	2005	83	100.0	84.0	NA	NA	VATS (60) OLB (23)	4.8	6.0	6.0	22
Ooi ¹⁴	2005	70	81.4	NA	NA	NA	VATS (55) OLB (15)	NA	NA	NA	17
Kreider ¹³	2007	68	76.5	NA	NA	NA	VATS	2.9	4.4	4.4	22
Bando ¹⁶	2008	94	96.8	NA	Upper and lower lobes	≥2	VATS	0.0	2.1	2.1	22
Ishie ²⁷	2008	48	95.8	NA	NA	1 (42)/2 (6)	VATS	NA	NA	NA	20
Coutinho ²⁵	2008	120	100.0	NA	CT	2	NA	NA	NA	NA	19
Sigurdsson ¹⁵	2009	73	83.6	53.0	CT	1 (51)/2 (17)	VATS (28) OLB (45)	2.7	4.1	4.1	21
Guerra ¹⁷	2009	53	94.3	NA	CT	2-3	VATS (37) OLB (16)	1.9	NA	1.9	18
Fibla ¹⁰	2012	224	87.1	NA	CT	1 (45)/2 (179)	VATS (279) OLB (32)	NA	NA	NA	20
Fibla ¹¹	2012	311	80.7	90.0	NA	1 (50)/2 (198)/3 (59)/4 (4)	VATS	9.0	10.6	10.6	22
Blackhall ⁸	2012	103	69.9	45.6	Right is preferred	2 is preferred	NA	4.9	NA	4.9	20
Blanco ⁹	2012	171	78.4	NA	NA	2-3	VATS (141) OLB (15)	NA	5.8	5.8	18
Luo ²³	2013	32	100.0	NA	CT	1.3 (mean)	VATS	0.0	3.1	3.1	21
Pompeo ¹⁹	2013	30	96.7	NA	CT	NA	VATS	0.0	0.0	0.0	22
Kayatta ¹²	2013	194	88.7	NA	NA	2-3	VATS	NA	6.7	6.7	20
Morris ¹⁸	2014	66	90.9	47.2	CT	1 (38)/≥2 (28)	VATS	1.5	4.5	4.5	19
Sonobe ²⁰	2014	64	96.9	51.6	CT	1 (8)/2 (53)/3 (3)	VATS (55) OLB (9)	0.0	0.0	0.0	21

Biopsy No. is expressed as biopsy number (patient number) where applicable. NA, Not available; CT, computed tomography; VATS, video-assisted thoroscopic surgery; OLB, open lung biopsy.

preference. There were 2 studies predisposed to right lobes,^{8,15} with a diagnostic yield of 84% and 94%, respectively. One study avoided the lingual or middle lobe,¹⁶ and 1 study focused on the lingular lobe,²¹ reporting a diagnostic yield of 97% and 100%, respectively. Two studies demonstrated that biopsy samples from the lingual or middle lobe have the same diagnostic yield as those from others.^{26,27}

A total of 19 studies reported diagnostic performance based on biopsy number. A total of 12 studies obtained 1 to 3 samples, among which 8 studies suggested that 1 sample containing both lesion and normal tissue was sufficient to represent pathologic changes.^{7,11,12,15,23,24,26,27}

Only 1 study stated that multiple biopsies may increase the diagnostic yield.⁸

A total of 21 studies specified SLB methods performed; 10 studies used both VATS and OLB,^{5-7,9,10,14,15,17,20,22} 10 studies used VATS,^{11-13,16,18,19,23,24,26,27} and 2 studies used OLB.²¹ Significant heterogeneity was still observed in subgroup analysis based on different surgical methods (data not shown). Sixteen studies evaluated the diagnostic yield of VATS in 1129 patients, varying from 44% to 100%, and 7 studies evaluated the diagnostic yield of OLB in 167 patients, varying from 37% to 100%. Six studies using both VATS and OLB compared the diagnostic yield of these 2 techniques, and no difference was noted.

FIGURE 2. Forest plots of mortality rate. Squares represent point estimates of mortality rate from each study reporting results eligible for analysis. Solid lines represent 95% CI. Inconsistency (I^2), 65.4%; chi-square, 43.35; $P < .0001$. CI, Confidence interval.

The distribution of 1847 specific diagnoses made by SLB is summarized in Figure E1. IPF accounted for most cases (618, 33.5%), followed by nonspecific interstitial pneumonia (NSIP) (219, 11.9%), HP (178, 9.6%), cryptogenic organizing pneumonia (139, 7.5%), sarcoidosis (126, 6.8%), and connective tissue disease-related ILD (73, 4.0%).

Mortality Rates

Only 16 studies presented sufficient data to allow inclusion in meta-analysis.^{5,6,8-10,12,13,15-20,22-24} The pooled 30- and 90-day mortality rates were 2.2% (95% confidence interval [CI], 1.0-4.0) and 3.4% (95% CI, 1.8-5.5), respectively (Table 2). The composite postoperative mortality was 3.6% (95% CI, 2.1-5.5) (Figure 2). Significant heterogeneity was observed among individual studies (I^2 , 65.4%; chi-square, 43.35; $P < .0001$);

therefore, subgroup analyses were applied to explore the possible source of heterogeneity.

Studies were evaluated on the basis of variable exclusion criteria, including age, immunocompromised status, MV dependence, and spirometry data (Table 3). Significant heterogeneity was witnessed between studies with patients aged more than 70 years and between studies excluding patients aged more than 70 years (data not shown). Subgroup analysis on 9 studies according to the immunocompromised status demonstrated no heterogeneity among studies excluding immunocompromised patients (mortality rate, 0.6%; 95% CI, 0.01-2.3; I^2 , 0%; chi-square, 0.09; $P = .993$). Significant heterogeneity was noted among studies including immunocompromised patients (mortality rate, 6.1%; 95% CI, 3.1-10.1; I^2 , 58.6%; chi-square, 9.66; $P = .047$).

Subgroup analysis strongly suggested that the exclusion of MV dependence is a source of heterogeneity in mortality of SLB among studies. Pooled statistics demonstrated an increased mortality rate for studies including MV-dependent patients (7.8%; 95% CI, 5.3-10.7) compared with those excluding MV-dependent patients (2.4%; 95% CI, 1.5-4.2) ($P < .001$). Subgroup analysis was performed on 11 studies including MV-independent patients, and the heterogeneity was found to be further decreased among studies excluding patients with diffusing lung capacity for carbon monoxide (DLCO) less than 35% or forced vital capacity (FVC) less than 55% predicted (I^2 , 0%; chi-square, 1.35; $P = .85$) but not among those including this subset of patients. Moreover, the pooled statistics demonstrated a mortality rate of 1.0% (95% CI, 0.1-2.7) and 3.7% (95% CI, 1.7-6.3) for 2 subgroups, respectively. This difference was significant ($P = .026$).

Subgroup analysis based on the surgery methods revealed that the heterogeneity was decreased in studies performing VATS (mortality rate, 2.9%; 95% CI, 1.7-4.5; I^2 , 47.7%; chi-square, 28.7; $P = .018$), whereas significant heterogeneity was noted among studies using OLB (mortality rate,

TABLE 3. Results of subgroup analysis stratified by different exclusion criteria

	Study n	Patient no.	Mortality % (95% CI)	I^2 %	Chi-square test
Exclusion of immunocompromised patients					
Yes	4 ^{6,20,23,24}	168	0.6 (0.01-2.3)	0	0.09 ($P = .993$)
No	5 ^{10,13,18,19,22}	558	6.1 (3.1-10.1)	58.6	9.66 ($P = .047$)
Exclusion of MV dependence					
Yes	11 ^{5,8,9,13,16,17,19,20,23,24}	706	2.4 (1.5-4.2)	40.9	16.93 ($P = .076$)
No	4 ^{10,12,15,22}	661	7.8 (5.3-10.7)	35.8	4.67 ($P = .198$)
Exclusion of patients with severe respiratory dysfunction*,†					
Yes	5 ^{5,16,17,19,23}	216	1.0 (0.1-2.7)	0	1.35 ($P = .853$)
No	6 ^{8,9,13,16,20,24}	490	3.7 (1.7-6.3)	42.8	8.75 ($P = .12$)
SLB method					
VATS	16 ^{5-7,9,10,12,14,16-20,23,24,26}	1295	2.9 (1.7-4.5)	47.7	28.7 ($P = .018$)
OLB	8 ^{5-7,9,10,14,17,20}	170	8.0 (1.6-18.5)	77.7	31.4 ($P < .0001$)

CI, Confidence interval; MV, mechanical ventilation; SLB, surgical lung biopsy; VATS, video-assisted thoracoscopic surgery; OLB, open lung biopsy. *The population restricted to MV-independent patients. †Severe respiratory dysfunction defined as DLCO <35% or FVC <55%.

8.0%; 95% CI, 1.6-18.5; I^2 , 77.7%; chi-square, 31.4; $P < .0001$). The surgery method also may contribute to heterogeneity, although the evidence supporting this contention is less clear.

Only 3 studies evaluated the mortality rate on the basis of underlying ILD subtypes. Bando and colleagues¹⁶ and Kreider and colleagues¹³ found all deaths were observed in IPF cases. However, Lettieri and colleagues²² demonstrated that the mortality rate was not related to the underlying ILD, although more deaths were observed in those with IPF compared with those without IPF.

DISCUSSION

Narrative reviews on SLB in the diagnosis of suspected ILDs have been published^{28,29}; however, rigorous systematic evaluation was seldom performed because of the great variability of inclusion criteria, surgery expertise, and methodological quality of different studies. The results, based on our systematic review and meta-analysis, demonstrated a satisfactory diagnostic performance with the favorable safety profile of SLB for evaluation of suspected ILDs. The postoperative mortality may be related to MV dependence, severe respiratory dysfunction, and immunocompromised status, but not surgical method and underlying ILD subtype.

The diagnostic yield of SLB ranges from 42% to 100%, with only 1 study achieving less than 70%, in which the diagnoses were merely established on pathologic results.⁷ This result may indicate the importance and necessity of multidisciplinary consultation, including pulmonary physicians and radiologists with histopathologic conclusions. However, although change in therapy is usually based on specific diagnosis,³⁰ the treatment algorithm was still altered in 55.2% of patients without specific diagnoses, comparable to 59.5% in patients with specific diagnoses.⁷ Fibla and colleagues¹⁰ also reported that 90% of treatment was changed with 81% of specific diagnoses achieved. These results suggested that an alteration in treatment may not be directed by a definitive histologic diagnosis and that nonspecific histologic results also could be useful in clinical practice.

Several studies have assessed factors that may influence the diagnostic effectiveness of SLB. Although the issue of appropriate biopsy site has entertained substantial controversy on whether or not to avoid the lingula or middle lobe,^{5,16,21} most studies suggested the guidance of high-resolution computed tomography (HRCT) may be highly effective to identify active disease and appropriate biopsy location. In regard to the number of biopsies, multiple studies supported that only 1 biopsy may be representative as long as it contains both abnormal- and normal-appearing areas, because biopsies from less-involved areas of the lung may present an active and diagnosable process rather than end-stage nonspecific fibrosis.^{7,11,12,15,23,24,26,27} However,

it should be noted that the evaluation of effective biopsy samples in future studies would be more accurate and meaningful if the biopsy number is combined with the sample size.

Significant heterogeneity was still noted in the subgroup analysis of diagnostic performance based on different surgical methods (ie, VATS and OLB). These results also supported previous observations that the yield of SLB may not be influenced by SLB techniques.⁵⁻⁸ The decision on which technique to use is usually driven by procedure familiarity of surgeons and patient conditions, such as the presence of extensive pleural adhesion and a noncompliant lung.

The most frequent diagnoses by SLB in a patient cohort with suspected ILD was IPF, with most patients being screened by HRCT examinations. In 2 studies comparing the diagnostic yield between HRCT and SLB, IPF was finally diagnosed by SLB in 75% to 91% of suspected cases, whereas 19.2% to 73.9% of IPF cases were not initially suspected by HRCT.^{14,15} These findings suggested that HRCT, although highly specific, is less sensitive in the diagnosis of IPF, therefore necessitating the utility of SLB in the diagnosis of these HRCT-omitted cases. In addition, there were 2 studies reporting NSIP^{17,23} and 2 studies reporting HP^{18,20} as the most common diagnoses. Further research is required to validate whether the diagnostic distinct is derived from the epidemiologic difference or interobserver disagreement among pathologists.

The safety issue is another important consideration when referring patients to SLB. Meta-analysis of 16 studies demonstrated a point postoperative mortality rate of 3.6% (95% CI, 2.1-5.5) with significant heterogeneity noted (I^2 , 65.4%; chi-square, 43.35; $P < .0001$). Subgroup analysis suggested that the exclusion criteria based on MV dependence was a possible source of heterogeneity. The mortality rate was found to be significantly decreased in studies excluding mechanically ventilated patients. Two studies identified ventilator dependence as an independent risk factor for SLB mortality.^{12,22} However, the apparent increased mortality rate in mechanically ventilated patients was more likely to be related to the critical illness rather than the SLB procedure, because the comparison between survivors and nonsurvivors did not show a significant difference regarding the incidence of OLB complications.³¹ Therefore, it is overcautious and inappropriate to indiscreetly refuse SLB in this patient subset given that SLB may greatly benefit patients by validating diagnoses and directing therapeutic modifications.

In studies with MV-independent patients, the pooled mortality rate for studies excluding patients with DLCO less than 35% or FVC less than 55% was significantly reduced compared with those including this subset of patients, indicating that severe respiratory dysfunction,

either compromise of gas exchange or ventilatory restriction, may be associated with a high risk for SLB. Moreover, the pooled mortality rate for studies excluding immunocompromised patients was significantly reduced compared with those lacking this exclusion criterion, suggesting that the immunocompromised status of patients may be another risk factor for postoperative mortality. Nevertheless, it is important to keep certain caveats in mind, because subgroups stratified by exclusion criteria did not actually divide study subjects into those with potential risk factors (eg, immunocompromised status, MV dependence, or severe respiratory dysfunction) and those without. Although subgroups with special exclusion criteria were free of high-risk patients, the subgroup lacking exclusion criteria would still contain many low-risk patients, and this may explain the relatively great heterogeneity within these groups. However, given the limited data at present, the subgroup analyses according to having or lacking these potential risk factors could not be performed, and further studies are required to validate the impact of these features on the mortality rate in SLB.

Subgroup analysis based on the surgery approach revealed that the surgery method also may contribute to heterogeneity, yet significant heterogeneity was still noted in studies performing OLB. Only 2 studies demonstrated a higher mortality rate in patients undergoing OLB compared with VATS.^{9,10} However, the retrospective nature of these studies may exaggerate the difference because the impact of specific surgeons' practices is often ignored. Two randomized studies have shown the opposite results with comparable morbidity and mortality rates between OLB and VATS procedures.^{5,6}

The relationship between the mortality rate and the underlying ILD subtype was controversial, especially in studies that specifically analyzed the mortality rate in patients with IPF: Tiitto and colleagues³² reported a comparable 30-day mortality rate in patients with IPF undergoing SLB with other subtypes, whereas a considerably higher mortality was observed in patients with a usual interstitial pneumonia pattern histologically or in computed tomography scans in 2 studies, and preoperative low DLCO % and FVC% were predictive parameters of postoperative death.^{33,34} These results suggested that a high mortality rate in patients with IPF may be accounted for by more severe respiratory dysfunction in this subset of patients. Prospective studies including patients with different ILD patterns (eg, usual interstitial pneumonia vs NSIP) with comparable respiratory function are required to determine the relative predict importance of ILD pattern in the postoperative mortality of SLB.

Study Limitations

Despite rigorous application of the QualSyst tool for included studies, most studies showed heterogeneity in

the assessment of diagnostic yield. One possible reason was that the sensitivity of SLB partially depended on surgeon experience, which may be variable among different studies. In addition, some factors affecting the performance of SLB were not reported in the majority of studies. These include the size of biopsies and radiologic features. Finally, few included studies attempted to analyze potential risk factors of mortality using a rigorous multivariate regression method, perhaps because of the limited study population size with few fatalities. Despite these limitations, our analysis may set a foundation for future studies in this field and raise potential aspects for further investigation.

CONCLUSIONS

Our study demonstrated that the diagnostic performance of SLB for the investigation of suspected ILDs was good with a favorable safety profile. Postoperative mortality may be related to MV dependence, severe respiratory dysfunction, and immunocompromised status of patients. Multicenter prospective studies are warranted to evaluate the generalizability of results to more clearly defined patient populations, thereby allowing improved understanding of the influence on the diagnostic effectiveness and potential risks of SLB.

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FIGURE E1. Distribution of specific diagnoses after SLB in included studies. The left y-axis represents the total number of cases, and right y-axis represents the proportion of each diagnosis. *AIP*, Acute interstitial pneumonia; *COP*, cryptogenic organizing pneumonia; *CTD-ILD*, connective tissue disease-related interstitial lung disease; *DIP*, desquamative interstitial pneumonitis; *HP*, hypersensitivity pneumonitis; *IIP*, idiopathic interstitial pneumonia; *IPF*, idiopathic pulmonary fibrosis; *LCH*, Langerhans cell histiocytosis; *NSIP*, nonspecific interstitial pneumonia; *RB-ILD*, respiratory bronchiolitis associated interstitial lung disease; *TB*, tuberculosis.