

# Safety and Diagnostic Yield of Transbronchial Lung Cryobiopsy in Diffuse Parenchymal Lung Diseases: A Comparative Study versus Video-Assisted Thoracoscopic Lung Biopsy and a Systematic Review of the Literature

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## Key Words

Interstitial lung disease · Cryobiopsy · Video-assisted thoracoscopic surgery

## Abstract

**Background:** A diagnosis of interstitial lung diseases (ILDs) may include surgical lung biopsy (SLB), which is associated with significant morbidity and mortality and also appreciable costs. Transbronchial lung cryobiopsy (TBLC) is adopting an important role. **Objectives:** The aim of this study was to compare the diagnostic yield (DY) and safety of TBLC and SLB in a large cohort of patients and to perform a systematic review of the literature as well as a meta-analysis. **Methods:** We performed a retrospective analysis of 447 cases with ILD undergoing TBLC and/or SLB and a systematic review of the

literature (MEDLINE and Embase for all original articles on the DY and safety of TBLC in ILDs up to July 2015). **Results:** A total of 150 patients underwent SLB and 297 underwent TBLC. The median time of hospitalization was 6.1 days (SLB) and 2.6 days (TBLC;  $p < 0.0001$ ). Mortality due to adverse events was observed for 2.7% (SLB) and 0.3% (TBLC) of the patients. Pneumothorax was the most common complication after TBLC (20.2%). No severe bleeding was observed. TBLC was diagnostic for 246 patients (82.8%), SLB for 148 patients (98.7%,  $p = 0.013$ ). A meta-analysis of 15 investigations including 781 patients revealed an overall DY of 0.81 (0.75–0.87); the overall pooled probability of developing a pneumothorax, as retrieved from 15 studies including 994 patients, was 0.06 (95% CI 0.02–0.11). **Conclusion:** Cryobiopsy is safe and has lower complication and mortality rates compared to SLB. TBLC might, therefore, be considered the

first diagnostic approach for obtaining tissue in ILDs, reserving the surgical approach for cases in which TBLC is not diagnostic.

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## Introduction

According to current scientific thinking and international guidelines, surgical lung biopsy (SLB) is indicated in diffuse parenchymal lung diseases (DPLDs) when a noninvasive diagnosis cannot confidently be made, with the procedure of choice in today's surgical setting being video-assisted thoracoscopic surgery (VATS) [1, 2]. However, SLB is associated with significant morbidity and mortality as well as appreciable costs [3–6], and many subjects are excluded because of increased risks of perioperative morbidity and mortality (by a combination of advanced age, comorbidity, severe respiratory failure, and pulmonary hypertension). Furthermore, some subjects do not give their consent to a surgical intervention. Cryobiopsy has demonstrated a superior diagnostic yield (DY) in comparison to conventional forceps biopsy [7–10], but only few studies have compared its complications and DY with those of SLB.

Our aim was to retrospectively assess and compare the DY and safety of transbronchial lung cryobiopsy (TBLC) and SLB in a large cohort of patients from clinical practice. Moreover, we performed a systematic review of the literature and a meta-analysis of the data from all the available studies in order to provide an overall estimate of the DY and safety of this procedure.

## Materials and Methods

In this retrospective analysis of a prospective clinical protocol, we analyzed all the patients with interstitial lung disease (ILD) undergoing TBLC from March 2011 through March 2015 and/or SLB from January 2003 through March 2015 because a diagnosis could not be achieved noninvasively according to current international consensus criteria [11, 12]. The study was conducted at the Pulmonology Unit of G.B. Morgagni – L. Pierantoni Hospital in Forlì (Italy) and submitted to the Ethics Committee of IRST IRCCS Area Vasta Romagna. Subjects were identified by a retrospective chart review.

At the time of the procedure, we collected data regarding age, gender, past medical history, medications, smoking history, environmental exposure history, physical examination findings, laboratory results, and pulmonary function. High-resolution computed tomography (HRCT) images performed within 1 month prior to the procedure were reviewed by an expert radiologist (S.P.). One- or 1.5-mm collimation sections were obtained at 10-mm

intervals, or volumetrically on multidetector CT scanners with 0.6- or 1-mm collimation and 1-mm reconstruction; all images were reviewed at window settings optimized for lung parenchyma (width: 1,500–1,600 HU; level: 2,500–2,600 HU). All patients included in this study had an HRCT pattern of ILD defined as 'possible usual interstitial pneumonia' (UIP) or 'inconsistent with UIP', according to current guidelines [12], and also inconsistent with sarcoidosis, Langerhans cell histiocytosis, or other patterns of cystic or nodular diseases.

Cryobiopsy was performed as previously described [10]: patients were deeply sedated with intravenous propofol and remifentanyl and intubated with a rigid tracheoscope; oxygen was administered continuously, and spontaneous breathing was maintained during the procedure. A flexible cryoprobe measuring 90 cm in length and 2.4 mm in diameter was used (ERBE, Germany), and the biopsies were obtained under fluoroscopic guidance using the flexible bronchoscope, which was inserted through the rigid tube into the selected bronchus; once brought into position, the probe was cooled for approximately 5 s, after which it was retracted, with the frozen lung tissue being attached to the probe's tip. A distance <10 mm from the thoracic wall, or from what was considered to be the pleura due to the resistance found by the pulmonologist, was considered optimal. A Fogarty balloon was prophylactically placed in the lobar bronchus near the biopsy segment and routinely inflated after sampling to minimize the consequence of hemorrhage. A bronchoalveolar lavage (BAL) was performed in all patients during the same bronchoscopy as the transbronchial cryobiopsies. BAL was performed with sequential infusions of six 25-ml aliquots of 0.9% saline solution; the first 2 aliquots were used for microbiological investigations, and the fluid retrieved from the successive aliquots was pooled and divided for different analyses (cell count and cytological and cytofluorimetric analysis). BAL had also been performed in all patients of the VATS group. VATS was carried out under general anesthesia, utilizing double-lumen endobronchial intubation and single-lung ventilation. The standard 3-port VATS technique was used. The choice of the site and side of biopsy was guided by CT imaging. A single 32-Fr chest drain was inserted into one of the anterior port sites, with the other two port sites being closed with sutures.

Hematoxylin-eosin-stained slides from biopsies were sent to three pathologists (A.D. and V.P. from our hospital and A.C. from a different hospital). Before the multidisciplinary meeting, the three pathologists examined the pathologic specimens independently and then discussed the cases and reached a final, common pathology interpretation of each case.

At least one fragment of alveolated lung parenchyma was required to classify the biopsy as adequate. The samples were classified as providing a diagnostic pattern or not ('nondiagnostic pattern'). The pathologic diagnosis of UIP was made according to current guideline criteria [12].

All cases that exhibited pathologic findings suggestive of, or definitive for, an alternative diagnosis were considered non-UIP and classified according to the characteristic pathologic features, i.e. nonspecific interstitial pneumonia, desquamative interstitial pneumonia or respiratory bronchiolitis-ILD, organizing pneumonia, diffuse alveolar damage, hypersensitivity pneumonitis, sarcoidosis and other granulomatosis, other, or nondiagnostic. All cases (100%) were subsequently discussed in the multidisciplinary meeting.

Adverse events included pneumothorax, severe bleeding, persistent fever, prolonged air leak, acute exacerbation, transient re-

**Table 1.** Patient characteristics

	SLB (VATS) group (n = 150)	TBLC group (n = 297)	p value
Patients	150	297	
Age, years	59 (15–74)	60 (21–78)	0.278
Gender			
Male	85 (56.7)	172 (57.9)	0.801
Female	65 (43.3)	125 (42.1)	
Smoking			
Current smoker	21 (14.0)	40 (13.5)	
Former smoker	63 (42.0)	124 (41.8)	
Nonsmoker	65 (43.3)	133 (44.8)	0.968
FVC, % predicted	80.0 (20.0–136.0)	86.0 (37.0–137.0)	0.072
FEV <sub>1</sub> , % predicted	83.0 (33.0–133.0)	88.0 (36.0–144.0)	0.034
DLCO, % predicted	57.0 (19.0–122.0)	58.8 (14.0–121.0)	0.078
Tiffeneau index	86 (62.0–105.0)	86 (60.0–124.0)	0.85
Histological pattern			
DIP/RB-ILD	11 (7.3)	12 (4.0)	
UIP	74 (49.3)	92 (31.0)	
NSIP	23 (15.3)	25 (8.4)	
DAD	1 (0.7)	4 (1.3)	
OP	8 (5.3)	31 (10.4)	
HP	7 (4.7)	24 (8.1)	
SAR	8 (5.3)	22 (7.4)	
Other (neoplasms, eosinophilic pneumonia, follicular bronchiolitis, alveolar proteinosis, vasculitis, AFOP, DIPNECH, or PLCH)	16 (10.7)	36 (12.1)	
Nondiagnostic pattern	2 (1.3)	51 (17.2)	0.013

Values are expressed as n (%) or medians (ranges). Italics denote significance. DIP = Desquamative interstitial pneumonia; RB-ILD = respiratory bronchiolitis-ILD; NSIP = nonspecific interstitial pneumonia; DAD = diffuse alveolar damage; OP = organizing pneumonia; HP = hypersensitivity pneumonitis; SAR = sarcoidosis and other granulomatosis; AFOP = acute fibrinous and organizing pneumonia; DIPNECH = diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; PLCH = pulmonary Langerhans cell histiocytosis.

spiratory failure, pneumonia/empyema, and other events. Severe bleeding (grade 3) was defined as ‘causing hemodynamic or respiratory instability, requiring tamponade or other surgical interventions, transfusions, or admission to the intensive care unit’; we did not include mild-to-moderate bleeding of grade 0 (no bleeding), grade 1 (bleeding requiring suction to clear but no other endoscopic procedures), or grade 2 (bleeding requiring endoscopic procedures such as bronchial occlusion-collapse and/or instillation of ice-cold saline) [13]. A prolonged air leak was defined as an air leak lasting  $\geq 5$  days after the procedure [14, 15].

The systematic review of the literature was performed according to the guidelines developed by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group [16]. We searched MEDLINE and Embase for all original articles on the DY and safety of transbronchial cryobiopsy for the diagnosis of DPLDs published up to July 2015, using a combination of free text and MeSH/EMTREE terms related to DPLDs and cryobiopsy technique. The electronic search was supplemented with gray literature and by hand-searching the bibliographies of relevant articles. The following criteria were established for inclusion: (1) studies reporting

data on the DY and safety of transbronchial cryobiopsy for the diagnosis of DPLDs (i.e. suspected ILDs or pulmonary infiltrates) and (2) studies reporting data on the safety of transbronchial cryobiopsy in routine surveillance after lung transplantation or for research purposes. Exclusion criteria were: (1) studies reporting data on the DY and safety of transbronchial cryobiopsy for the diagnosis of peripheral lung lesions; (2) studies reporting data on the DY and safety of transbronchial cryobiopsy for the diagnosis of central lung lesions, and (3) studies reporting data on the DY of transbronchial cryobiopsy in routine surveillance after lung transplantation. Two independent authors (M.B. and C.R.) reviewed all titles/abstracts and retrieved detailed full texts of potentially relevant articles. Disagreements were resolved by discussion. When multiple reports were available on the same cohort of patients, we included the most recent or informative one. The two reviewers independently retrieved information on the country, study design, number of subjects, study population, main outcomes, procedural aspects, number and size of samples, prevalence of (or high probability of/high confidence about) the UIP pattern at histology, DY, and safety. The measure of interest for the DY and safety analyses

**Table 2.** Safety profile results for SLB (VATS) and TBLC

	SLB (VATS) (n = 150)	TBLC (n = 297)	p value
Days of hospitalization	6.1 (3–48)	2.6 (0–17)	<0.0001
Adverse events			
Severe bleeding	0 (0.0)	0 (0.0)	
Persistent fever	7 (4.7)	0 (0.0)	
Prolonged air leak	5 (3.3)	1 (0.3)	
Acute exacerbation	5 (3.3)	1 (0.3)	
Pneumonia/empyema	3 (2.0)	0 (0.0)	
Transient respiratory failure	0 (0.0)	2 (0.7)	
Miscellanea	0 (0.0)	2 (0.7)	
Pneumothorax (in total)	NA (NA)	60 (20.20)	
Pneumothorax with drainage	NA (NA)	46 (15.50)	
Days of drainage	3.75 (2–40)	4.65 (2–15)	0.138
Patients with 0 adverse events	131 (87.3)	220 (74.1)	
Patients with 1 adverse event	16 (10.7)	75 (25.3)	
Patients with 2 adverse events	3 (2.0)	1 (0.3)	
Patients with 3 adverse events	0 (0.0)	1 (0.3)	
Time to 1st adverse event after biopsy, days	27.5±73.9	0.6±2.0	<0.0001
Mortality due to adverse event	4/150 (2.7)	1/297 (0.3)	0.045
	4/20 (20.0)	1/66 (1.5)	0.01
Survival			
Alive	88 (58.7)	272 (91.6)	
Dead	43 (28.7)	13 (4.4)	
Transplantation	4 (2.7)	1 (0.3)	

Values are expressed as n (%), mean (range), or mean ± SD. Italics denote significance. NA = Not applicable.

was the proportion of events. In order to obtain pooled estimates, we performed meta-analyses of proportions using the Freeman-Tukey double arcsine transformation method [17] and generated the corresponding forest plots. Heterogeneity between studies was assessed using the  $\chi^2$  test [18], defining a significant heterogeneity as a p value <0.10, while inconsistency was quantified using the  $I^2$  statistic.

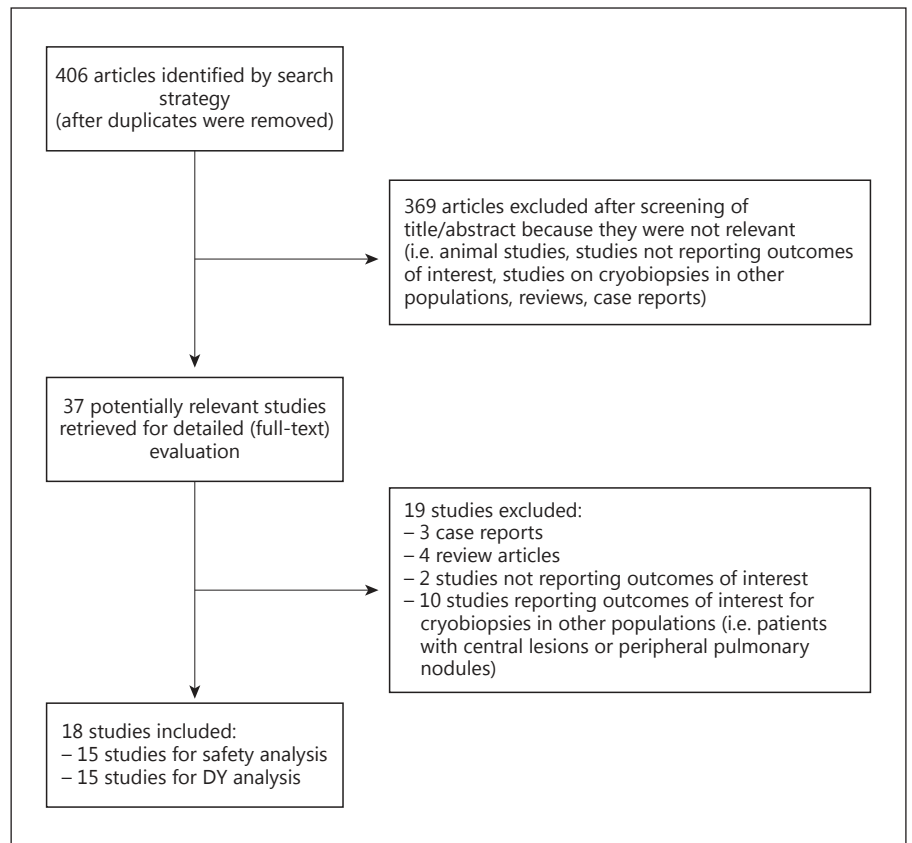
## Results

We collected data on 150 cases in the VATS group and 297 cases in the TBLC group; 14 patients with cryobiopsy subsequently also underwent an SLB due to nondiagnostic samples, and 1 patient subsequently had a cryobiopsy repeated for the same reason. The baseline characteristics of each group were similar (table 1). In the SLB group, the pathologists identified histopathologic criteria sufficient to define a characteristic pattern in 148 patients (98.7%); in the TBLC group, a characteristic pattern was obtained in 246 cases (82.8%;  $p = 0.013$ ).

Safety outcomes are summarized in table 2. The median time of hospitalization was 6.1 days after SLB and 2.6

days after TBLC ( $p < 0.0001$ ); 16 patients were discharged home on the day of the procedure. The time to the first adverse event after biopsy was 27.5 days for VATS versus 0.6 days for cryobiopsy.

Mortality due to adverse events after SLB was observed in 4 patients (2.7% of the total), and 20% of the adverse events (4/20) were fatal; death occurred within 60 days and was caused by acute exacerbation of idiopathic pulmonary fibrosis (IPF) in all cases. Prolonged air leaks were treated with a prolonged chest tube drainage in 3/5 patients; the remaining 2 patients were treated with a blood patch, and in 1 case also with surgical revision. In the TBLC group, only 1 patient died after 7 days (0.3% of the total) with acute exacerbation of IPF (coexistence of diffuse alveolar damage and a UIP pattern at autopsy) following massive pneumothorax (treated with drainage and high-flow oxygen) and a prolonged air leak. Pneumothorax was the most common complication after cryobiopsy, occurring in 60 patients (20.2%), 46 cases (15.5% of the total) requiring drainage. No patients needed an intervention to control bleeding, and there were no cases with persistent fever or pneumonia/empyema. Other complications were: tran-



**Fig. 1.** Flowchart of study selection.

sient respiratory failure (2 patients; 0.7%) and neurologic manifestations (seizures in 2 patients; 0.7%). In the VATS group, lung function was more compromised in patients who developed subsequent complications (FVC  $70.2 \pm 22.0$  vs.  $82.0 \pm 21.2\%$ ;  $p = 0.029$ ), while in the cryobiopsy group, lung function was found not to be related to the occurrence of these complications. As all patients had undergone BAL with the same procedure and aliquots, it was not possible to find any statistically significant correlation between BAL and side effects in either group.

#### *Review of the Literature*

After removing duplicates between MEDLINE and Embase, the systematic review identified 406 references (fig. 1). The initial screening, based on titles/abstracts, led to the exclusion of 369 papers because they were not relevant (i.e. case reports, review articles); the remaining 37 articles were retrieved for detailed full-text evaluation. Eighteen original studies were included in the present review, and their main characteristics are presented in table 3 [7–9, 19–32]: 15 studies reported data on both DY and safety, 2 on safety only, and 1 on DY only.

The summary estimate of DY was provided overall, according to the criteria used for defining diagnostic samples (i.e. either the identification of a specified histological pattern or the final multidisciplinary diagnosis) (fig. 2), and according to selected procedural aspects. The overall DY, derived from 15 investigations including 781 patients, was 0.81 (0.75–0.87), and a significant heterogeneity between studies was detected ( $I^2$  77.76%;  $p < 0.001$ ). As 2 studies [21, 32] provided two different DYs according to the two different diagnostic definitions, we decided to include both values separately in the pooled estimate. However, the sensitivity analysis including only the DY derived from the final histological pattern did not change the overall result (data not shown). The pooled estimates by diagnostic definitions were 0.81 (95% CI 0.66–0.92;  $I^2$  87.41%;  $p < 0.001$ ) from studies considering multidisciplinary discussion as the final diagnosis (7 studies including 300 patients), 0.80 (95% CI 0.72–0.87;  $I^2$  68.10%;  $p < 0.001$ ) from studies referring to the detection of specific histological patterns (8 studies including 564 patients), and 0.90 (95% CI 0.76–0.99;  $I^2$  95.40%;  $p < 0.001$ ) from the 2 studies that did not specify their diagnostic criteria

**Table 3.** Main characteristics of the original studies included in the systematic review

Study	Country	Study design	Population	n	Outcomes	Procedural aspects	Samples, n/average	Mean area, mm <sup>2</sup> /diameter, mm	UIP pattern, n (%)
Hagmeyer [19], 2015	Germany	RCS	Suspected ILD	32	DY, safety	RB, deep sedation with jet ventilation	2/4	NA	3 (9.4)
Kropski [20], 2013	USA	RCS	Suspected ILD/ asymptomatic family members at risk	37	DY, safety	ET, conscious sedation	2	64.2/8.7/-	7 (28)
Pajares [21], 2014	Spain	RCT	Suspected ILD	39	DY, safety	Deep sedation, occlusion balloon	≥3/3.7±0.9	14.7±11/4.1±1.5	7 (17.8)
Griff [22], 2011	Germany	PCS	Suspected ILD/ infiltrations	15	Safety	Conscious sedation	1	17.1±10.7	NA
Griff [23], 2014	Germany	RCS	Suspected ILD	52	DY, safety	Conscious sedation	2	-/6.9±4.4	13 (25)
Pajares [9], 2010	Spain	PCS	Suspected ILD	10	DY, safety	FB, sedation	2	9.5/3.1	0
Hernández-González [24], 2015	Spain	RCS	Suspected ILD	33	DY, safety	Conscious sedation, Fogarty balloon	≥3/2.7	4/-/-	6 (18.2)
Babiak [7], 2009	Germany	RCS	Suspected ILD	41	DY, safety	ET, deep sedation	-/2	15.11	15 (36.6)
O'Donovan [25], 2014	Ireland	PCS	Suspected ILD	14	DY, safety	NA	1-4/2.4	6.8	NA
Azcuna [26], 2014	Spain	CS	Suspected ILD	54	DY, safety	ET, deep sedation, occlusion balloon	3-6	NA	19 (31.1)
Gershman [27], 2015	Israel	RCS	Suspected ILD/ immunocompromised patients with infiltrates/ lung transplanted	300	Safety	Conscious sedation	2-4	NA	NA
Martín [28], 2014	Spain	RCS	Suspected ILD	36	DY, safety	ET	-/2.7±0.8	NA	9 (25)
Yarmus [8], 2013	USA	PCS	Lung transplanted	17	Safety	RB, deep sedation with jet ventilation	5	NA	NA
Ravaglia [this study]	Italy	PCS	Suspected ILD	297	DY, safety	RB, deep sedation	1-8/-	44.4/NA	92 (31)
Pourabdollah [29], 2014	Iran	PCS	Suspected ILD	41	DY	NA	1	22/NA	0
Oezkan [30], 2015	Germany	RCS	Suspected ILD	17	DY, safety	RB	NA	NA	NA
Fruchter [32], 2014	Israel	RCS	Suspected ILD	75	DY, safety	Conscious sedation	2-4/3	9/NA	7 (9.3)
Fruchter [31], 2013	Israel	RCS	Immunocompromised patients with infiltrates	15	DY, safety	Conscious sedation	NA/2	9/NA	-

RCS = Randomized controlled study; RCT = randomized controlled trial; PCS = prospective case study; CS = controlled study; RB = rigid bronchoscopy; ET = endotracheal tube; FB = flexible bronchoscopy; NA = not available.

(fig. 2). The pooled DYs by procedural aspects, in terms of type of sedation and airway control, were 0.81 (95% CI 0.76–0.86) from studies with patients undergoing the procedure intubated under deep sedation (11 studies including 625 patients) and 0.83 (95% CI 0.64–0.97) from studies with patients not intubated under conscious sedation (3 studies including 142 patients) (fig. 3).

With reference to complications, data were retrieved from 15 studies including 994 patients. Overall, 100 pneumothoraces (10%), 4 transient respiratory failures (0.4%), 2 episodes of convulsions (0.2%), 1 death (0.1%), 1 acute exacerbation (0.1%), and 1 prolonged air leak (0.1%) were reported. Out of the 100 pneumothoraces, 70 required chest tube drainage. The overall pooled probability of developing a pneumothorax was 0.06 (95% CI 0.02–0.11), while the probability of developing a pneumothorax requiring chest tube drainage was 0.03 (95% CI 0.01–0.08)

(fig. 4). The pooled proportions of pneumothorax according to procedural aspects, in terms of type of sedation and airway control, were 0.07 (95% CI 0.02–0.14) from studies with patients undergoing the procedure intubated under deep sedation (11 studies including 613 patients) and 0.01 (95% CI 0.00–0.06) from studies with patients not intubated under conscious sedation (3 studies including 367 patients) (fig. 5).

No episodes of severe bleeding (as defined above) were reported. The overall pooled probability of developing a moderate bleeding, as derived from 12 studies including 383 patients, was 0.12 (95% CI 0.02–0.25) (fig. 6). We did not include our cohort study in the analysis, as the routine preventive use of a Fogarty balloon was considered a major procedural difference. No severe episodes (as defined above) were reported.

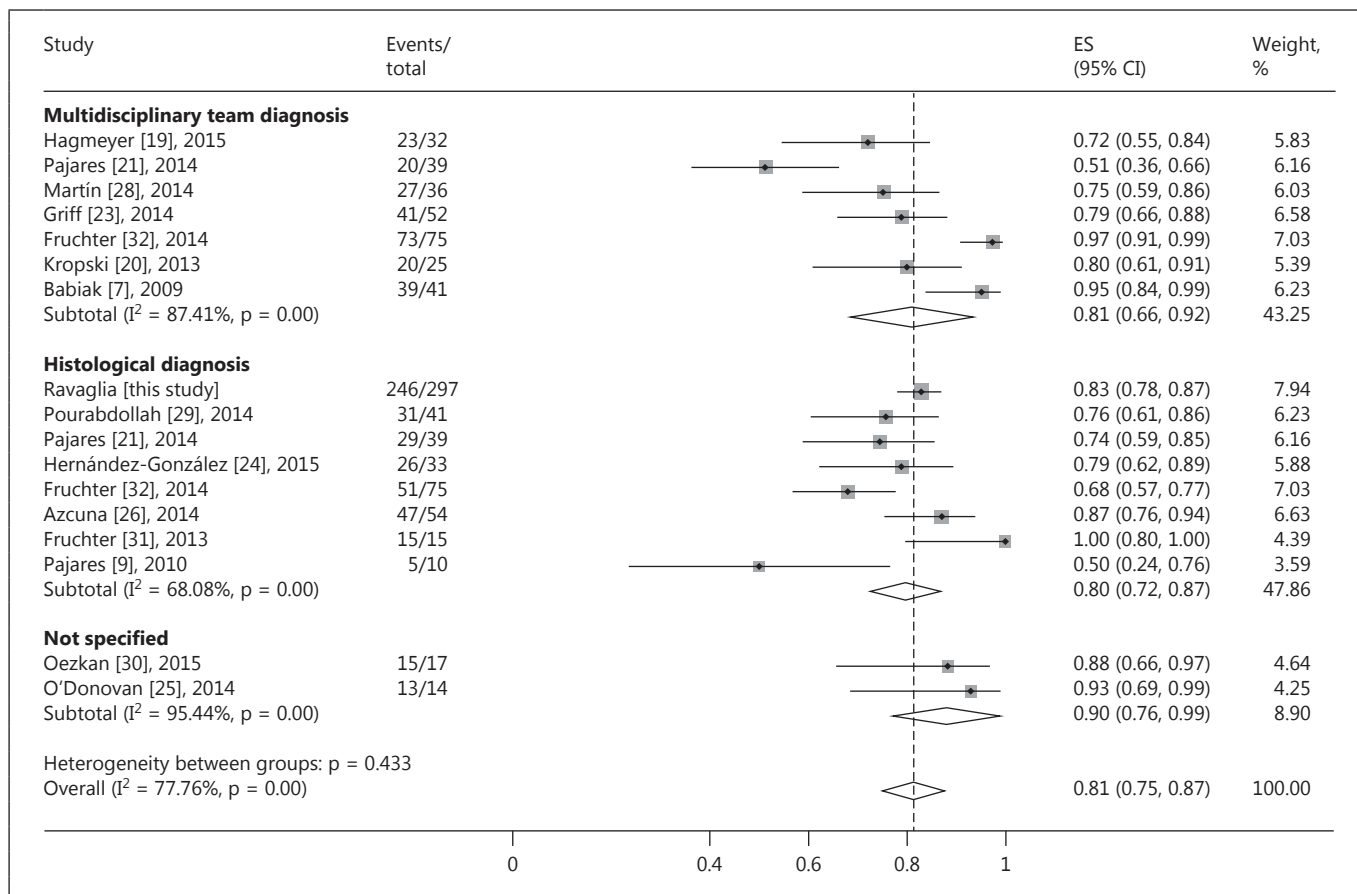


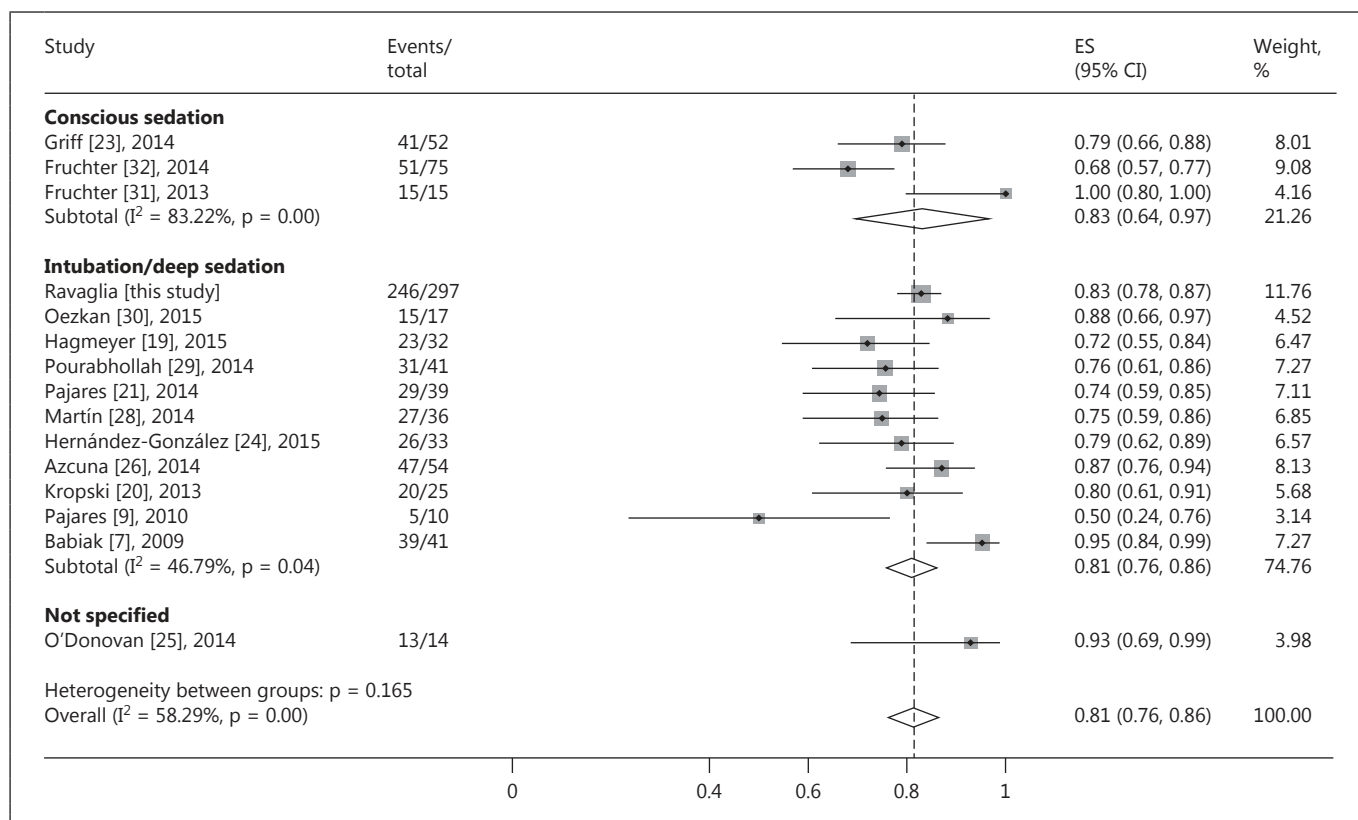
Fig. 2. DY overall and according to diagnostic criteria. ES = Effect size.

## Discussion

Diagnosis of DPLDs is a dynamic multidisciplinary process, requiring close communication between clinicians, radiologists, and pathologists [33, 34]. SLB is recommended in a large patient subgroup for diagnostic confirmation, in particular in the diagnosis of IPF, in the absence of a UIP pattern on HRCT [2]. However, the procedure requires endotracheal intubation, general anesthesia, chest tube placement, and, typically, hospitalization for several days. Mortality can be observed in 2–6% at 90 days [3–6], and there is some risk of persistent pain at 12 months [35, 36], prolonged air leak, and/or bronchopleural fistula (3–12%) requiring prolonged hospitalization and/or reoperation [5, 37]. Moreover, patients who are ultimately diagnosed with IPF subsequently can experience worse postprocedural outcomes than those with other ILDs [4–6, 38], mostly in terms of acute exacerbations [39, 40]; 30-day mortality can increase to

18.8% [5]. These data suggest that when IPF is suspected, the benefits of diagnostic confirmation must be weighed against the potential risks of life-threatening complications [41]; in clinical practice, only 10–20% of fibrotic ILD patients undergo an SLB [42, 43].

The advent of TBLC has occurred over the previous decade, and it might soon be integrated in the routine diagnostic pathways [10, 41]. Current data have shown that this technique appears to be safer than SLB; however, its risks and benefits over VATS have yet to be completely elucidated. The primary objective of our study was to assess the DY and safety of TBLC in a large cohort of patients and to retrospectively compare these outcomes to those obtained from VATS in the diagnostic workup of DPLDs. As expected, the DY of SLB was slightly higher than that of TBLC, but the latter procedure offered significant advantages in terms of safety. Patients with DPLDs who underwent a TBLC had a significantly lower mortality rate following the procedure as compared to the



**Fig. 3.** DY by sedation/intubation. ES = Effect size.

patients undergoing VATS, and the overall mortality rate with this procedure among approximately 1,000 patients was at the very least negligible (0.1%). Our results are inconclusive with regard to BAL, maybe due to the selection of retrospective cases that underwent lung biopsy, thus including cases in which BAL was not diagnostic. However, it has recently been demonstrated that the addition of BAL to the clinicoradiological picture of patients with suspected ILD can change the diagnosis only in 8% of cases [44].

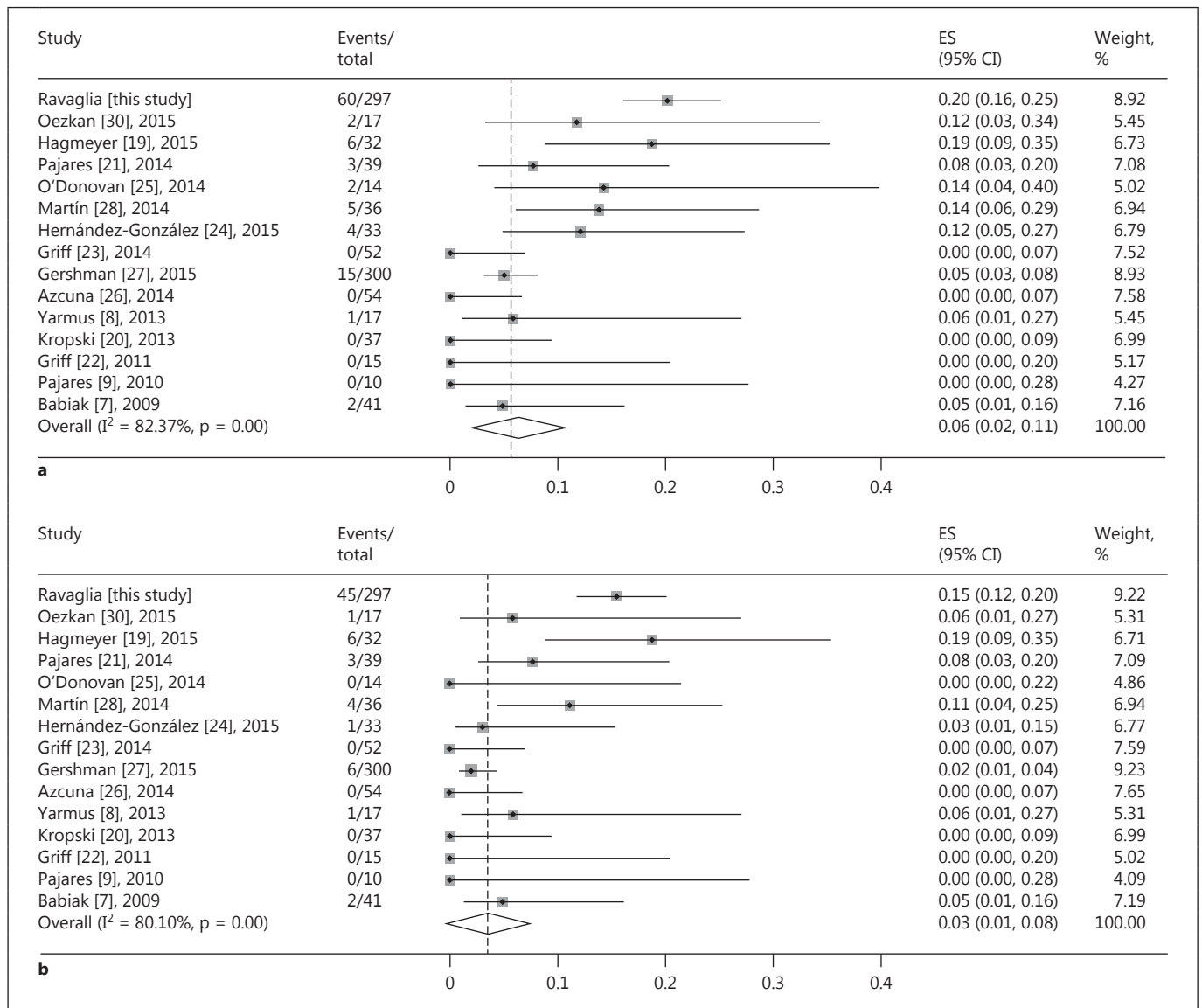
Regarding the length of hospitalization, the reported median time of hospitalization after the SLB procedure for any cause ranges between 4 and 8 days [43, 45], with elderly patients with ILDs being at higher risk of prolonged hospitalization [46]. Our data confirm that the time of hospitalization for cryobiopsy is usually shorter than the length of stay after SLB and could also be performed in an outpatient setting. On the other hand, it is striking that the time to the first adverse event after biopsy is much shorter with cryobiopsy than with VATS. This time to adverse events cannot be considered a re-

porting bias, as all patients of both groups had been seen at our center after biopsy, in particular patients undergoing cryobiopsy (even if they had been discharged earlier). The time of follow-up after cryobiopsy was 20.99 months, whereas that after VATS was 54.72 months.

In the Introduction, we also mentioned costs (SLB is associated with significant morbidity and mortality and also appreciable costs) [3–6]. Hernández-González et al. [24] demonstrated that systematic cryobiopsies could save between EUR 953.09 and 1,925.29 per patient in comparison to VATS in Spain.

Among the adverse events, pneumothorax represented the most important complication of TBLC, requiring chest tube drainage in 46 cases (15.50%); however, patient discomfort from incisional and/or chest tube site pain could be avoided, performing cryobiopsy instead of VATS, in 84.5% of the patients. When chest drainage was necessary, the time of drainage was similar in the two groups. The data on pneumothorax as a major complication were confirmed by the systematic review of the literature on safety profiles (100 out of 109 events). The het-





**Fig. 4.** Pneumothorax overall (**a**) and requiring a chest tube (**b**). ES = Effect size.

erogeneity between results was explored via subgroup analysis by procedural aspects; it showed a higher proportion of events among intubated patients undergoing the procedure under deep sedation compared to those under conscious sedation. This could partly be due to the differential prevalence of the UIP pattern between the subgroups, i.e. 25.5% in the first group and 14.4% in the second group, and partly due to the lower mean size of samples of patients under conscious sedation. Moreover, in our previous pilot study, we found that the risk of pneumothorax can increase when fragments of pleura are

present in the biopsy [10]. However, it was not possible to assess this in the meta-analysis, since data on pleural fragments in the samples were not available in the majority of studies included. At our center, the HRCT fibrosis score of the lower lung zones is significantly increased in patients with pneumothorax compared to those without pneumothorax; furthermore, the higher incidence of pneumothorax seems to correlate significantly with a histological UIP pattern and the bronchoscopist's learning curve [unpubl. data].

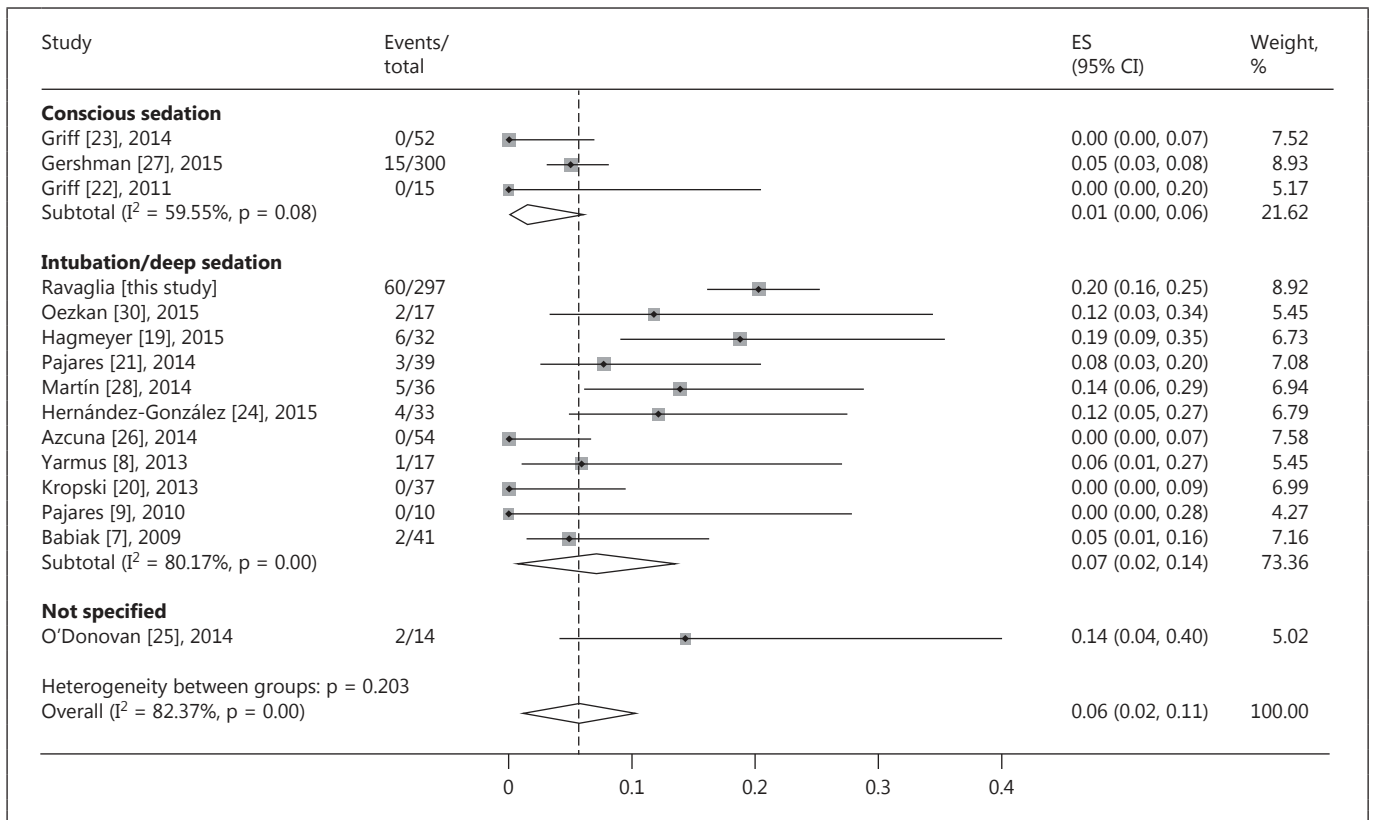


Fig. 5. Pneumothorax by sedation/intubation. ES = Effect size.

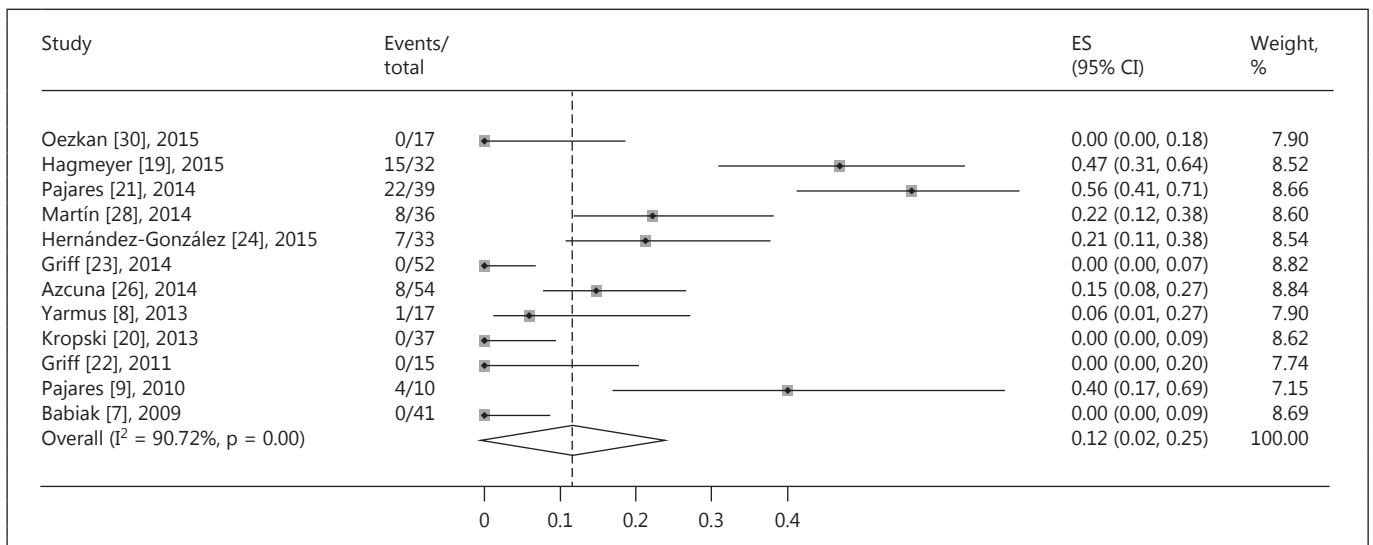
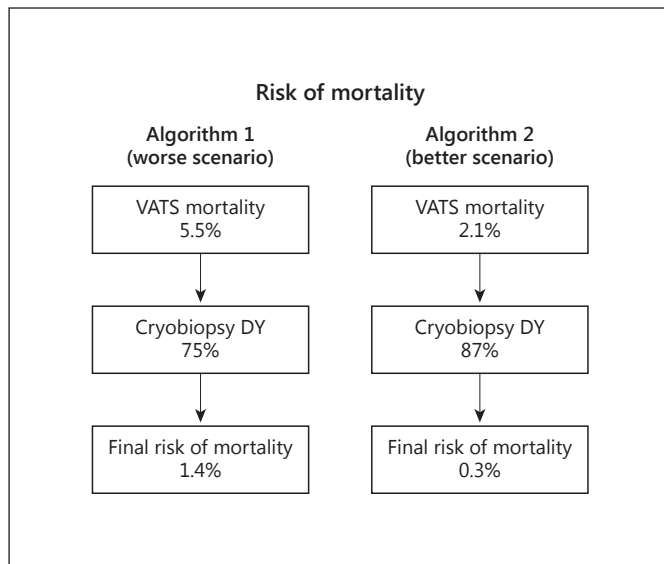


Fig. 6. Moderate bleeding. ES = Effect size.



**Fig. 7.** The ‘final’ risk of mortality, considering TBLC and VATS together, can vary from 0.3% (better scenario) to 1.4% (worse scenario).

No grade 2 and 3 bleeding occurred in our cohort, partly due to the preventive use of a Fogarty balloon, which is inflated immediately while the bronchoscope is being withdrawn from the airway to remove the biopsy specimen from the cryoprobe. Moreover, the hemostatic effects of cooling could probably have contributed to the low incidence of significant bleeding. Data from the systematic review again confirmed this result, since no severe bleeding was reported even in studies not employing the Fogarty balloon. However, a number of moderate bleedings were documented in 7 out of 12 studies reporting on this issue. The pooled estimate of 0.12, presented in figure 6, should be interpreted with caution, as the definition of ‘moderate’ bleeding was vastly different between the studies, making a reliable summary of the data difficult to accomplish. Moreover, the largest cohort studies were not included in this analysis, since Gershman et al. [27] did not distinguish between mild and moderate bleeding (overall rate 5.3%), while the preventive use of a Fogarty balloon in our study was considered a major ‘bias’ in the interpretation of the results. Anyhow, the fact that we did not experience any grade 2 bleeding does not mean that this is not a common and potentially serious adverse event related to the procedure; it rather suggests that using a prophylactic bronchial blocker is highly recommended in order to reduce and limit such a complication.

Prolonged postoperative air leaks were much more frequent in the VATS group (3.3 vs. 0.3%); this result is important, as air leaks lasting longer than 5 days could be associated with an increased rate of empyema [47] and other kinds of pulmonary complications such as atelectasis and pneumonia due to restricted ventilation [48], decreased mobility through chest tubes and related pain, as well as the necessity for pleurodesis, mechanical ventilation, and reoperation [49].

Until now, the identification and careful consideration of preoperative risk factors has been very important to limit the risk of complications associated with SLB for the diagnosis of ILDs. According to the current literature [6, 35], we observed that patients with a more severely impaired percentage predicted of forced vital capacity (FVC%) have a higher risk of developing adverse events after SLB, while complications after cryobiopsy seem to occur independently of lung function values. These results confirm that one of the advantages of cryobiopsy in the future might be that even patients not able to undergo VATS for functional reasons could be further diagnosed by cryobiopsy.

Although these overall results suggest a much better safety profile of TBLC compared to SLB, the DY of this novel technique should be at least comparable to that of the gold standard in order to be really considered a valid competitor. Due to the lack of studies directly comparing the two procedures, it is difficult to properly decide on this matter. However, our study and the pooled estimate from the literature showed a good DY independently of the criteria used for defining the final diagnosis and of the methods employed for sedation and airway control. Moreover, although a great heterogeneity between studies was observed in terms of design, sample size, and procedural aspects, the DY was  $\geq 0.70$  in most of the investigations. This is limited, however, considering the adverse events/mortality with TBLC and SLB taken separately, since in clinical practice the two procedures are not really used competitively; in fact, a patient might undergo TBLC and subsequently VATS if the first approach is not diagnostic. In this specific case, the overall mortality with SLB (3.6% according to the most recent review of the literature; 95% CI 2.1–5.5) [36] should not be applied to all patients (100%) but only to patients in whom cryobiopsy was not diagnostic and who are therefore candidates for VATS (overall cryobiopsy DY 81% according to our meta-analysis; 95% CI 75–87). Thereafter, we have two possible scenarios: (1) in the worse scenario, 25% of the patients undergo SLB because of a previous nondiagnostic cryobiopsy (higher mortality of 5.5%), and (2) in the better scenario, only 13%

of the patients undergo SLB because of a previous non-diagnostic cryobiopsy (lower mortality of 2.1%) (fig. 7). The 'final' risk of mortality, considering TBLC and VATS together, proves to be 0.3–1.4%, which is significantly lower than the overall mortality with VATS alone. Lastly, we acknowledge some limitations due to the fact that this is a retrospective and single-center study.

In conclusion, TBLC seems to be a safe procedure, with lower complication and mortality rates compared to

SLB. TBLC might, therefore, be considered the first diagnostic approach for obtaining tissue in DPLDs, reserving the surgical approach for only the minority of cases in which TBLC is not adequate or not diagnostic.

### Financial Disclosure and Conflicts of Interest

None of the authors have any conflicts of interest.

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