CRIOBIOPSIE TRANSBRONCHIALI PARENCHIMALI E STADIATIVE

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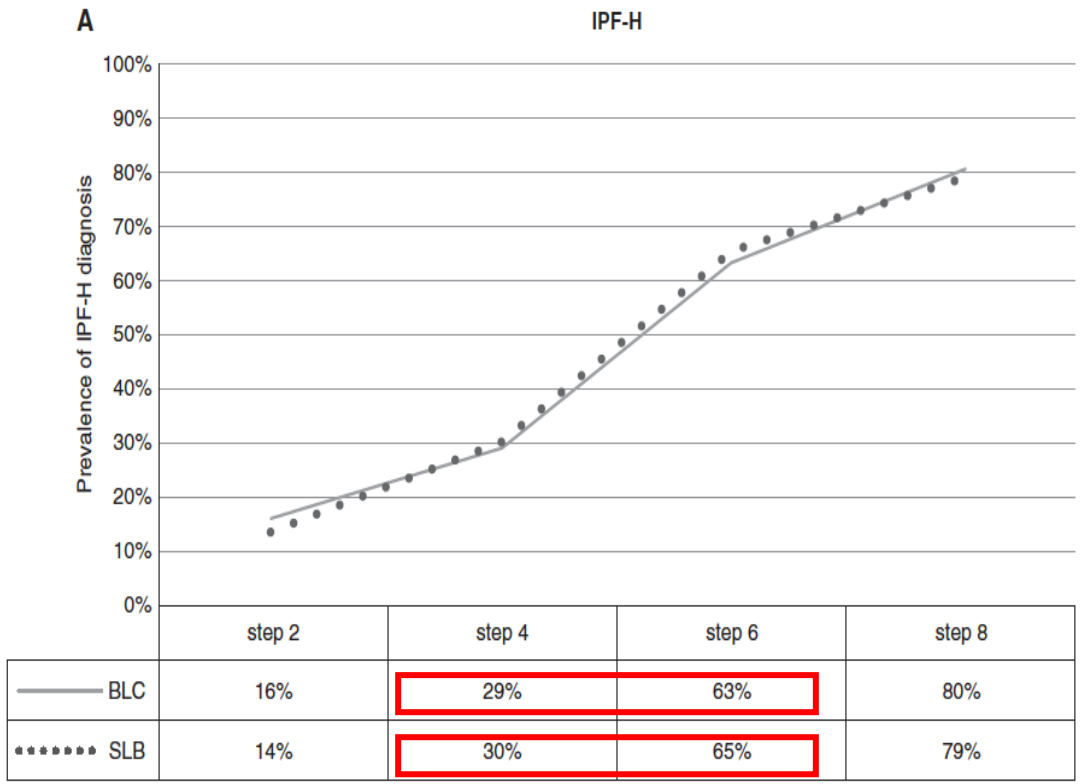
Summary

- Diagnostic accuracy and histopathological interpretation
- Identification of UIP pattern
- Prognostic validation
- Procedure – technical aspects
- Complications
- New perspectives

Diagnostic accuracy

STEP	DATA	PARTICIPANTS	DISCUSSION
1	Clinical-Radiological data	C + R	Individual
2			Group
3	BAL	C + R + P	Individual
4			Group
5	BIOPSY	C + R + P	Individual
6			Group
7	FOLLOW-UP data	C + R + P	Individual
8			Group

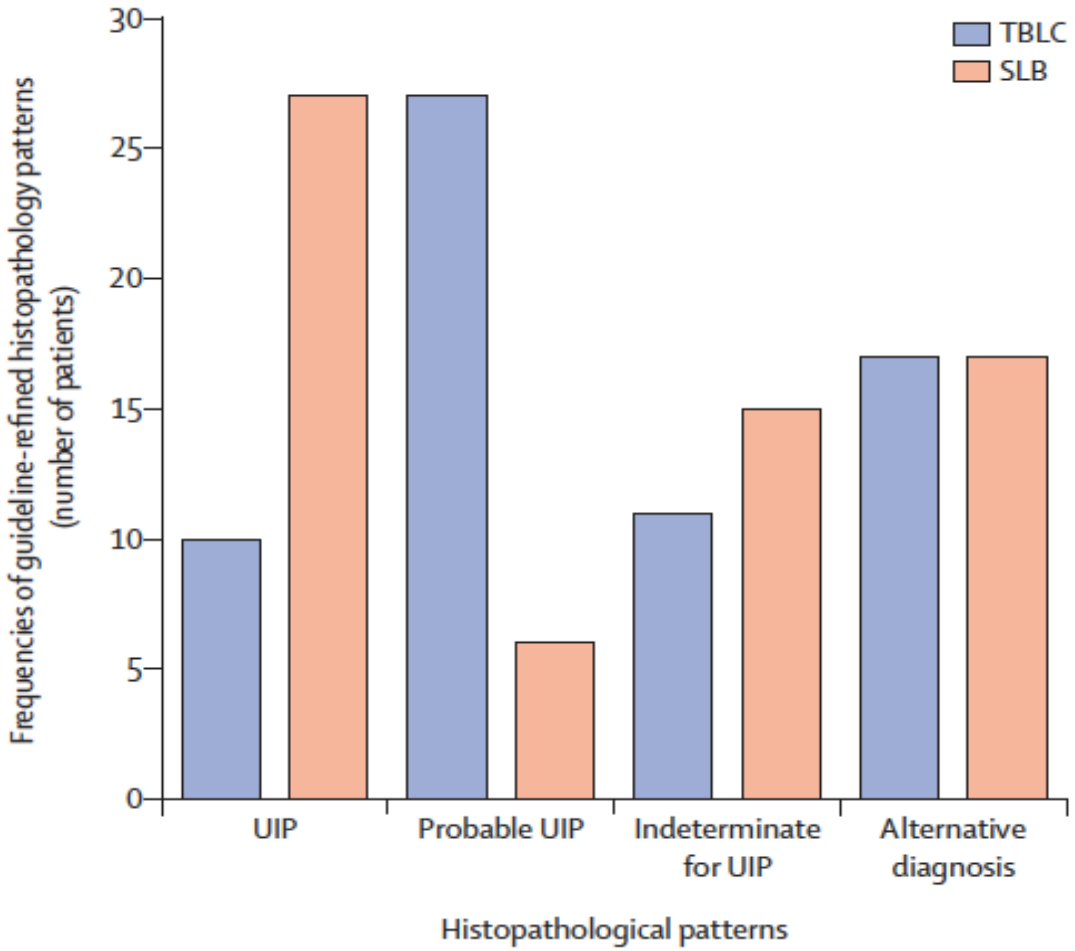


	step 2	step 4	step 6	step 8
BLC	16%	29%	63%	80%
SLB	14%	30%	65%	79%

58 cryobiopsy. 59 SLB. 2 clinicians, 2 radiologists, 2 pathologists

Tomassetti S. et al. AJRCCM 2016

COLDICE: agreement for histopathological diagnosis



Primary Endpoint

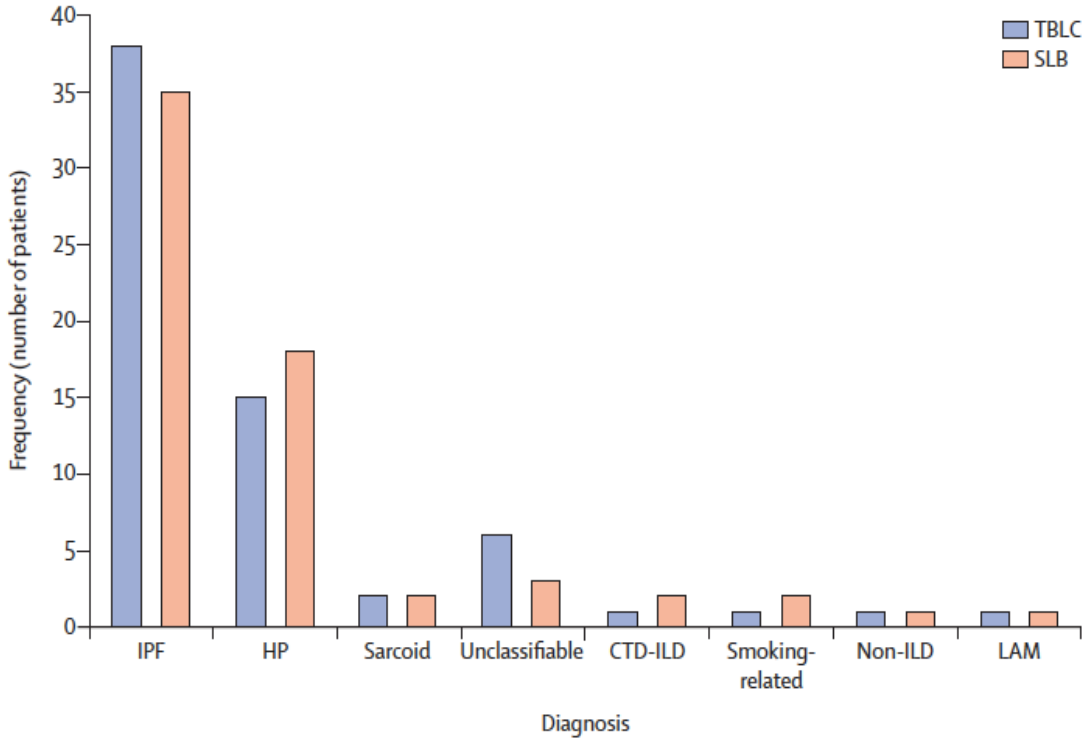
- Agreement with SLB performed concurrently in the same patients for histopathological diagnosis (2018 guideline-refined histopathology):
  Agreement 70.8%
  K 0.70 (95% CI, 0.55, 0.86)

Key Secondary Endpoint

- Inter-observer variability between individual pathologists (specific histopathology pattern):
  Agreement 69.2%
  K 0.47 (95% CI, 0.30, 0.64)

Troy LK, et al. Lancet Respir Med. 2019

COLDICE: agreement for histopathological diagnosis



Primary Endpoint

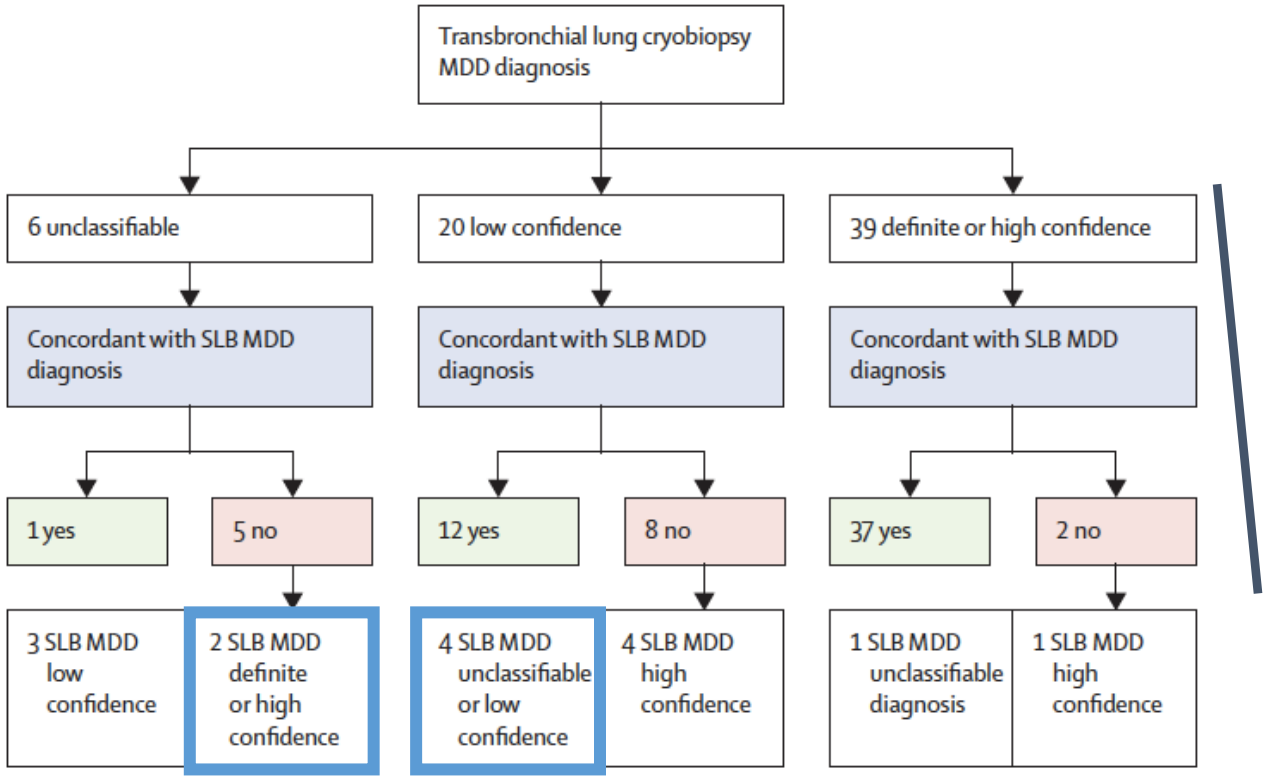
- Agreement with SLB performed concurrently in the same patients for MDD diagnosis (MDD consensus diagnosis):
  Agreement 76.9%
  K 0.62 (95% CI, 0.47, 0.78)

Key Secondary Endpoint

- Consensus diagnosis and level of diagnostic confidence after addition of either cryobiopsy or VATS samples (change in diagnostic confidence or unanticipated diagnosis)
  TBLC: 48/65 (74%) versus
  SLB: 50/65 (77%); (p=0.55)

Troy LK, et al. Lancet Respir Med. 2019

COLDICE: TBLC diagnosis concordance with SLB



For unclassifiable or low confidence TBLC MDD diagnoses, SLB provided a definite or high confidence diagnosis only in a minority!

High confidence TBLC were 95% concordant with SLB at MDD

Troy LK, et al. Lancet Respir Med. 2019

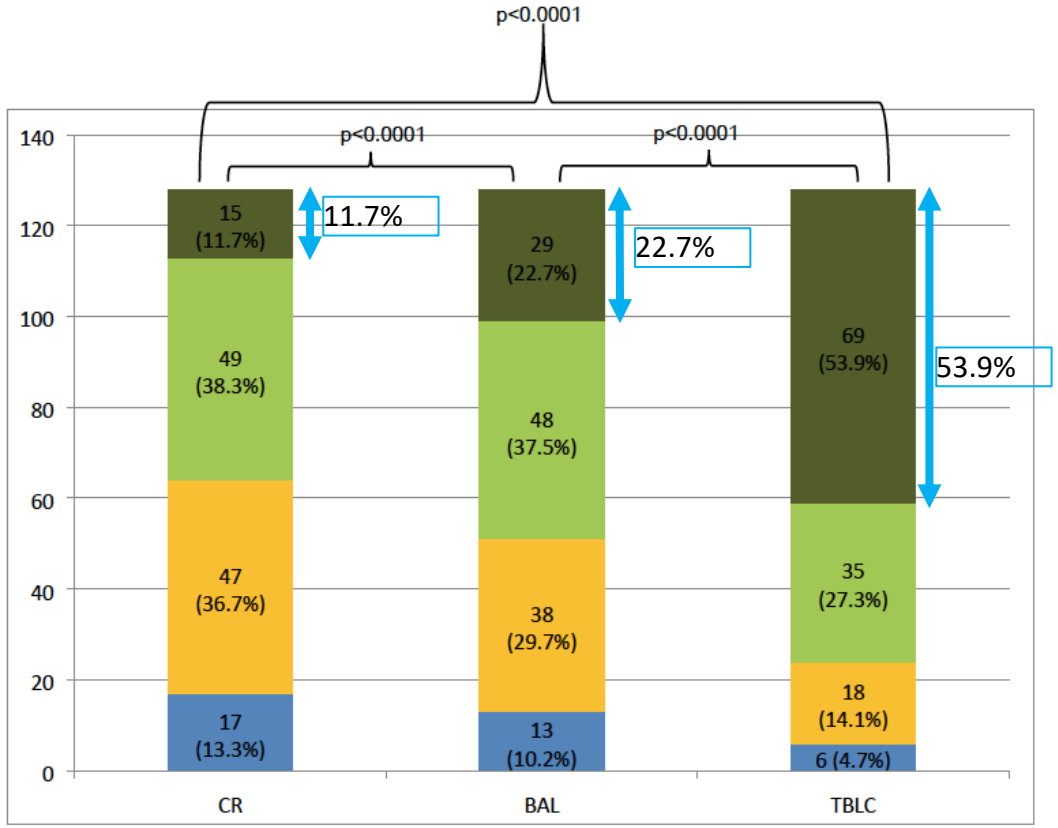
MDTD consensus (Likelihood > 90%)

CONFIDENT DIAGNOSIS

PROVISIONAL DIAGNOSIS HIGH CONFIDENCE

PROVISIONAL DIAGNOSIS LOW CONFIDENCE

NO CONSENSUS



Ryerson CJ, et al. AJRCCM 2017. Walsh SLF, et al. AJRCCM 2019. Hetzel J, et ERJ 2020

MDTD consensus (Likelihood > 70%)

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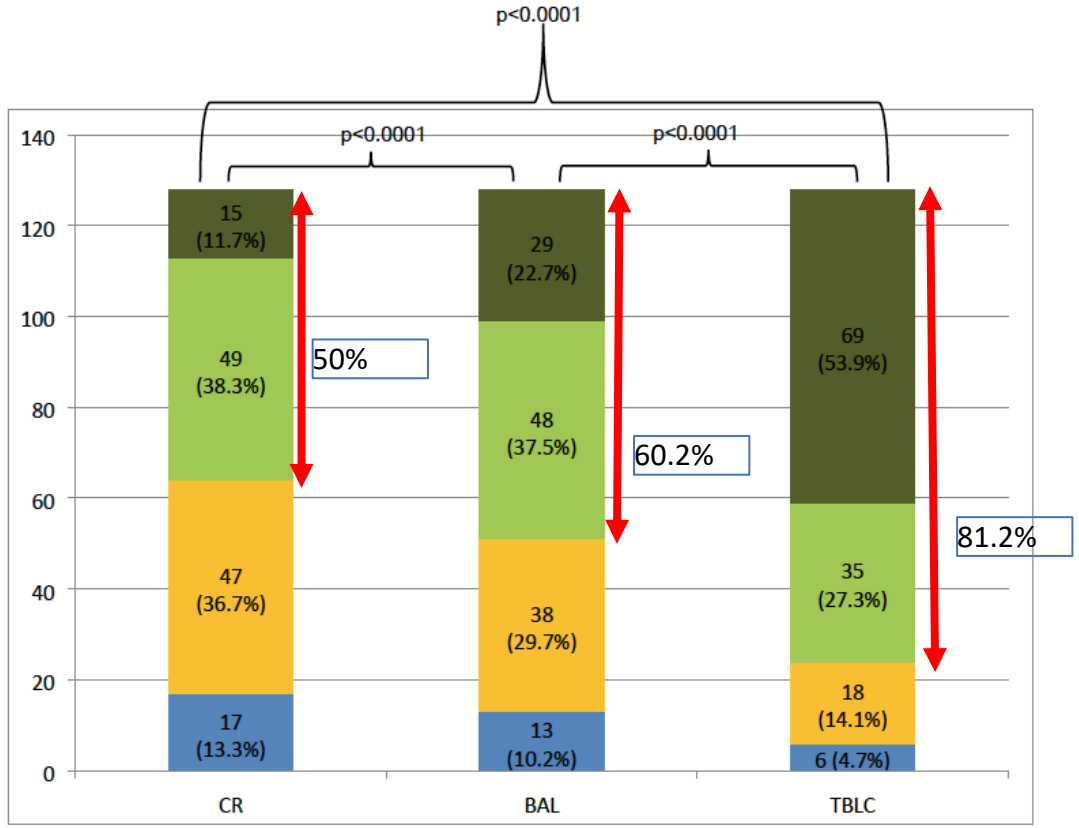
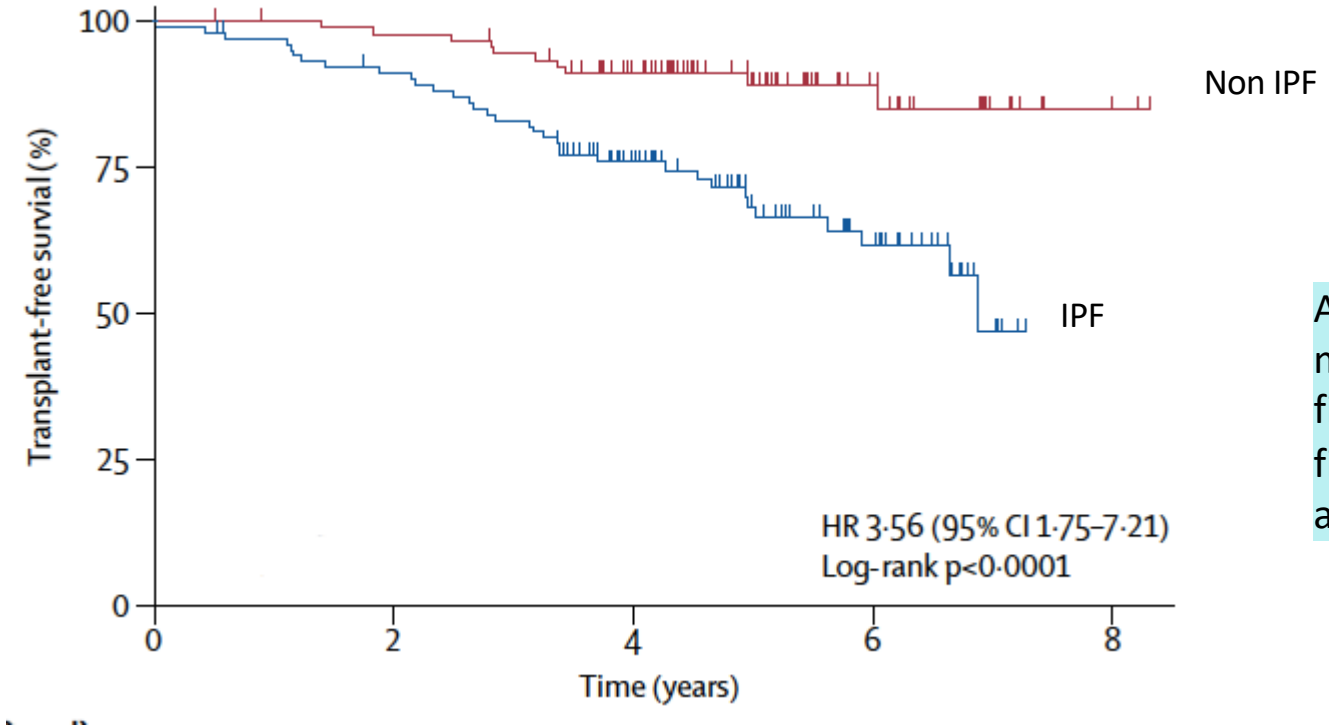


Ryerson CJ, et al. AJRCCM 2017. Walsh SLF, et al. AJRCCM 2019. Hetzel J, et ERJ 2020

Prognostic validation

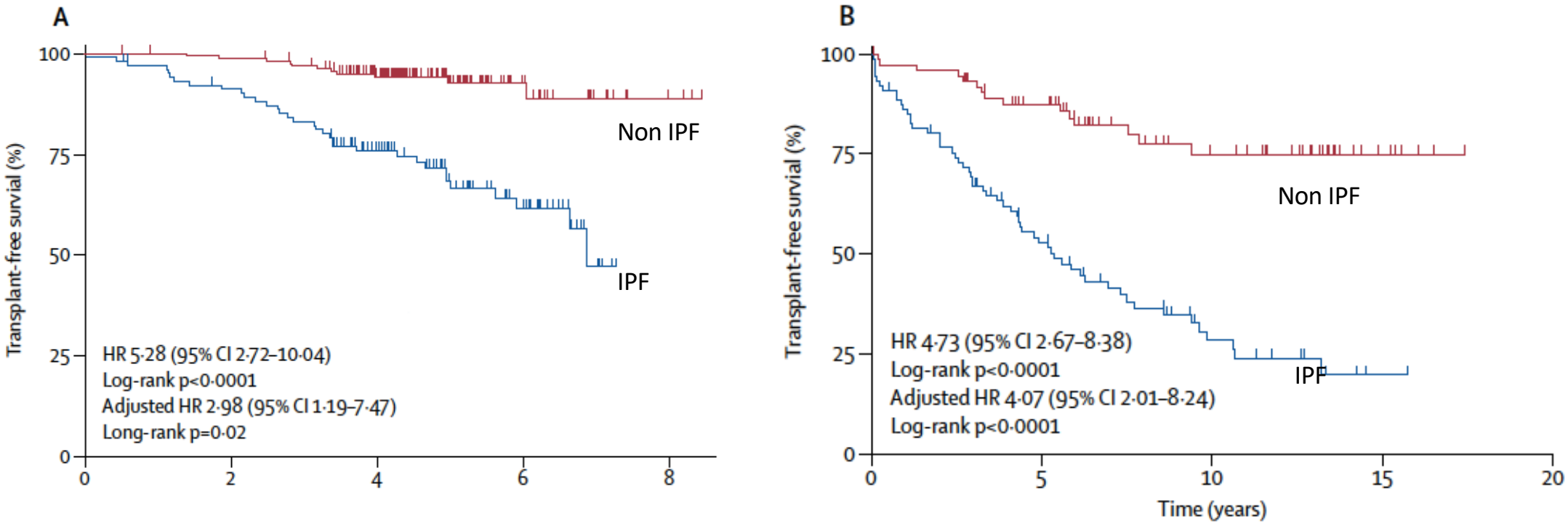
Prognostic validation of cryobiopsy



After exclusion of non-fibrotic ILDs, mortality was still higher in patients with final IPF diagnosis compared with other fibrotic non-IPF ILDs even in a multivariate analysis.

Tomassetti S. et al. LRM 2020

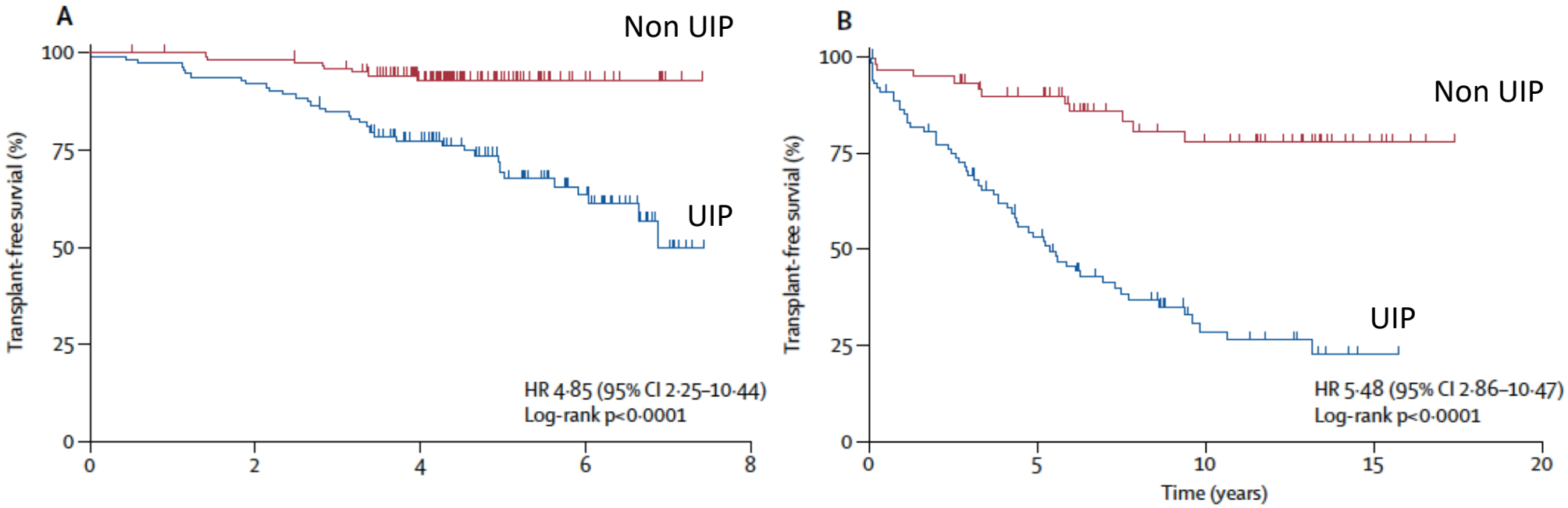
Prognostic validation of cryobiopsy



Cases diagnosed on cryobiopsy (A) and surgical lung biopsy (B)

Tomassetti S. et al. LRM 2020

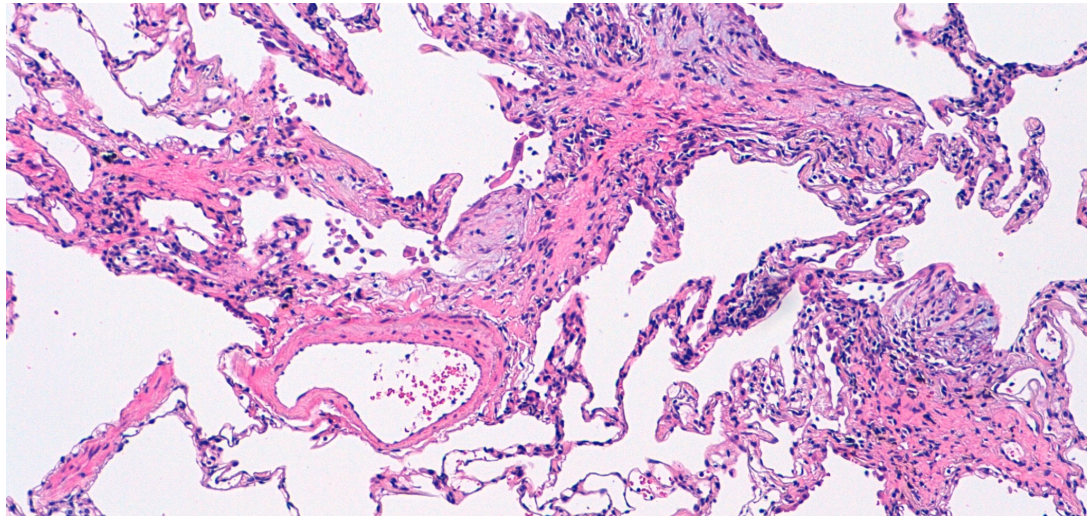
Prognostic validation of cryobiopsy



Cases diagnosed on cryobiopsy (A) and surgical lung biopsy (B)

Tomassetti S. et al. LRM 2020

Histopathological findings	TBLC	SLB
Guideline-refined patterns		
UIP	10 (15.4%)	27 (41.5%)
Probable UIP	27 (41.5%)	6 (9.2%)
Indeterminate for UIP	11 (16.9%)	15 (23.1%)
Alternative diagnosis	17 (26.2%)	17 (26.2%)



	TBLC	SLB
Pathological features		
Predominantly subpleural[†] or paraseptal fibrosis/ architectural distortion (eg honeycomb change)[‡]	8 (24.2%)	33 (100%)
Patchy fibrosis	33 (100%)	33 (100%)
Fibroblast foci	29 (87.9%)	33 (100%)
Absence of alternative diagnostic features	30 (90.9%)	31 (93.9%)
All four features observed	7 (21.2%)	31 (93.9%)
Three out of four features observed	21 (63.6%)	2 (6.1%)
Two out of four features observed	4 (12.1%)	0
One out of four features observed	1 (3.0%)	0

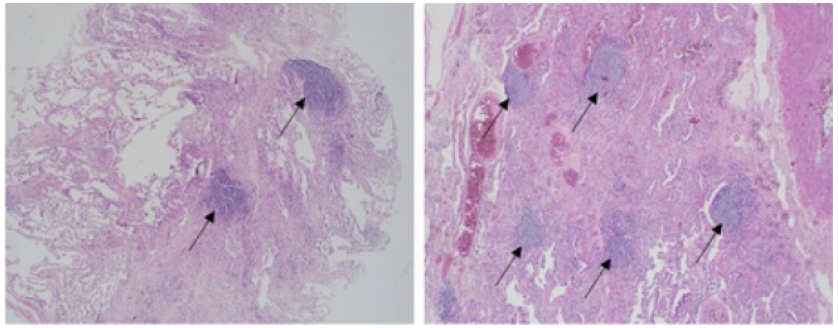
Cooper WA, et al. Am J Respir Crit Care Med 2021

Table 4: Predictors of cryobiopsy and surgical lung biopsy concordance

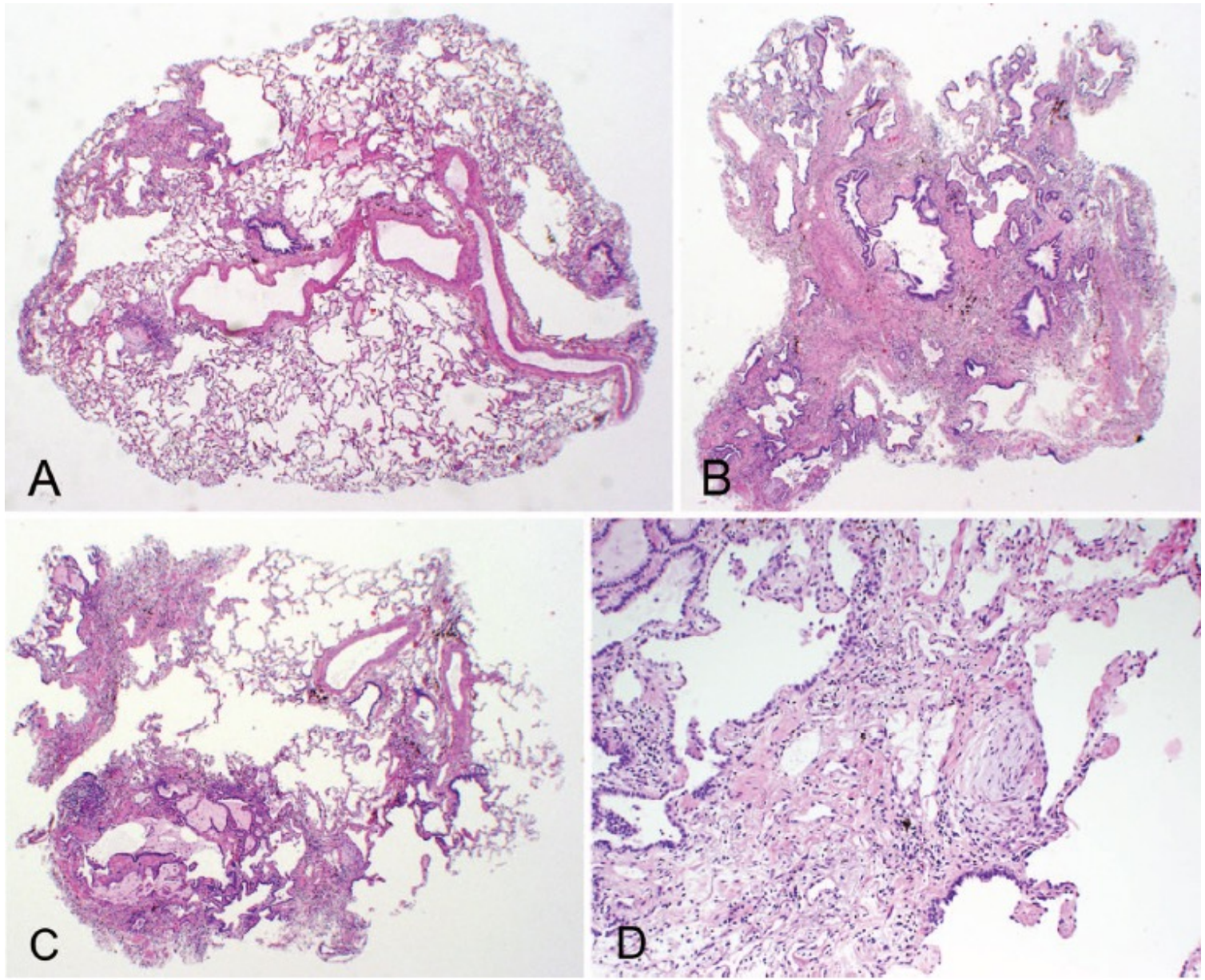
Variable	OR	95% CI	P-value
Clinical features			
Age, years	**0.86**	**0.77 – 0.96**	**0.006**
Gender	0.42	0.14 – 1.31	0.135
Family history of ILD	**0.15**	**0.03 – 0.69**	**0.02**
History of exposure*	**3.98**	**1.22 – 12.92**	**0.02**
Radiological features			
Asymmetry	**0.20**	**0.04 – 0.92**	**0.04**
Fibrotic changes	0.60	0.15 – 2.44	0.47
Ground glass opacities	1.24	0.21 – 7.39	0.82
Mosaicism	0.39	0.13 – 1.18	0.10
Cryobiopsy details			
Pleura present	2.70	0.30 – 24.10	0.374
Number samples	**1.80**	**1.08 – 3.01**	**0.03**
Size of samples†	1.06	0.79 – 1.43	0.68
Freeze time, secs	0.67	0.29 – 1.55	0.36

Probable UIP on cryobiopsy is strongly predictive of UIP at surgical biopsy

(OR 23.4, 95%CI 6.36-86.1, p<0.0001)



Cooper WA, et al. Am J Respir Crit Care Med 2021



Colby TV, et al. Arch Pathol Lab Med 2017

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

The committee concluded that the evolving use of TBLC merits commentary. Application of the histopathological criteria for UIP is more challenging with TBLC specimens because *1*) the subpleural predominance of pathologic changes may not be readily appreciated and *2*) the potential for sampling error results in less confident exclusion of features that may suggest an alternative diagnosis. Compared with surgical lung biopsy (SLB), TBLC is more likely to demonstrate a probable UIP pattern than a definite UIP pattern given the limited sampling of subpleural lung parenchyma in most cases (28). Nevertheless, a combination of patchy fibrosis, fibroblast foci, and the absence of features to suggest an alternative diagnosis is usually sufficient to establish a probable UIP pattern on TBLC (29). Combining UIP and probable UIP patterns in the context of multidisciplinary discussion (MDD) results in comparable rates of diagnostic agreement for SLB and TBLC in patients with IPF (28).

Evidence-based Recommendations for Diagnosis of IPF

We suggest that TBLC be regarded as an acceptable alternative to SLB for making a histopathological diagnosis in patients with ILD of undetermined type in medical centers with experience performing and interpreting TBLC (conditional recommendation, very low quality evidence).

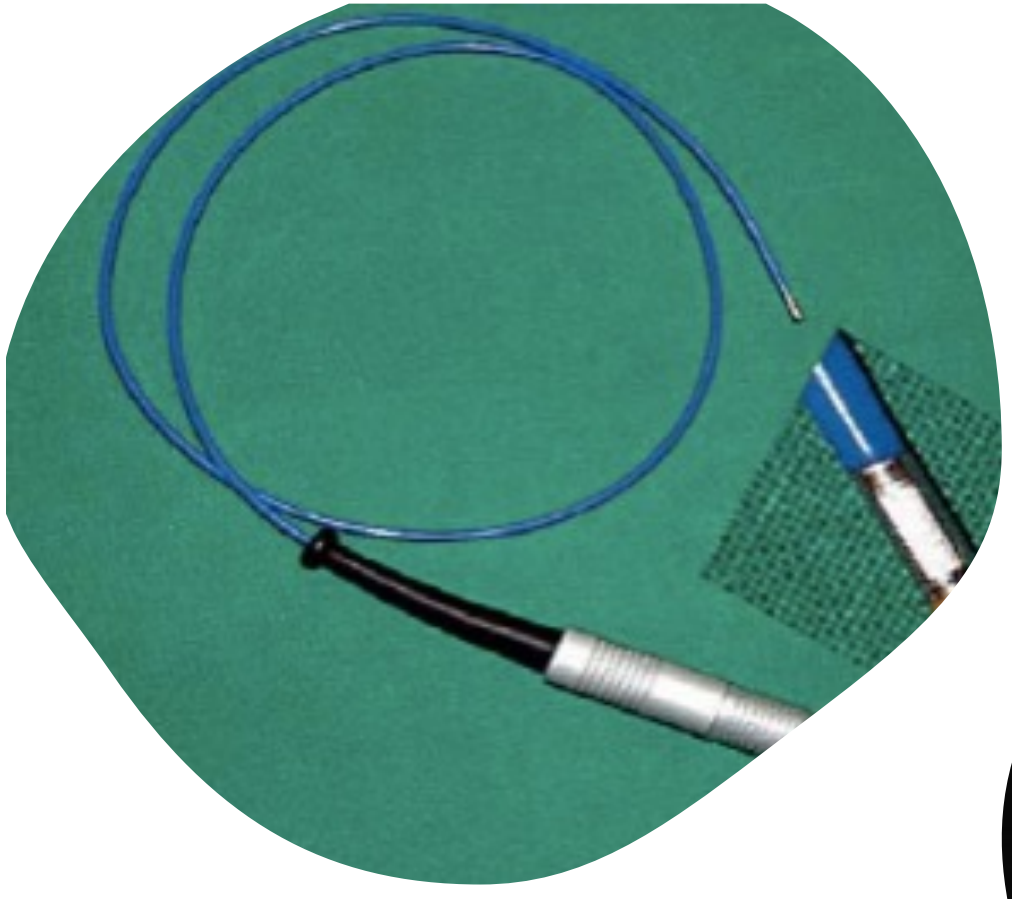
Background. The 2018 guidelines for diagnosis of IPF addressed TBLC in patients with ILD of undetermined type but failed to garner enough agreement to make a consensus recommendation for or against TBLC (2). Additional studies have been published since the previous guideline; therefore, the guideline committee decided to reconsider the evidence pertaining to TBLC. In contrast, the 2018 diagnosis of IPF

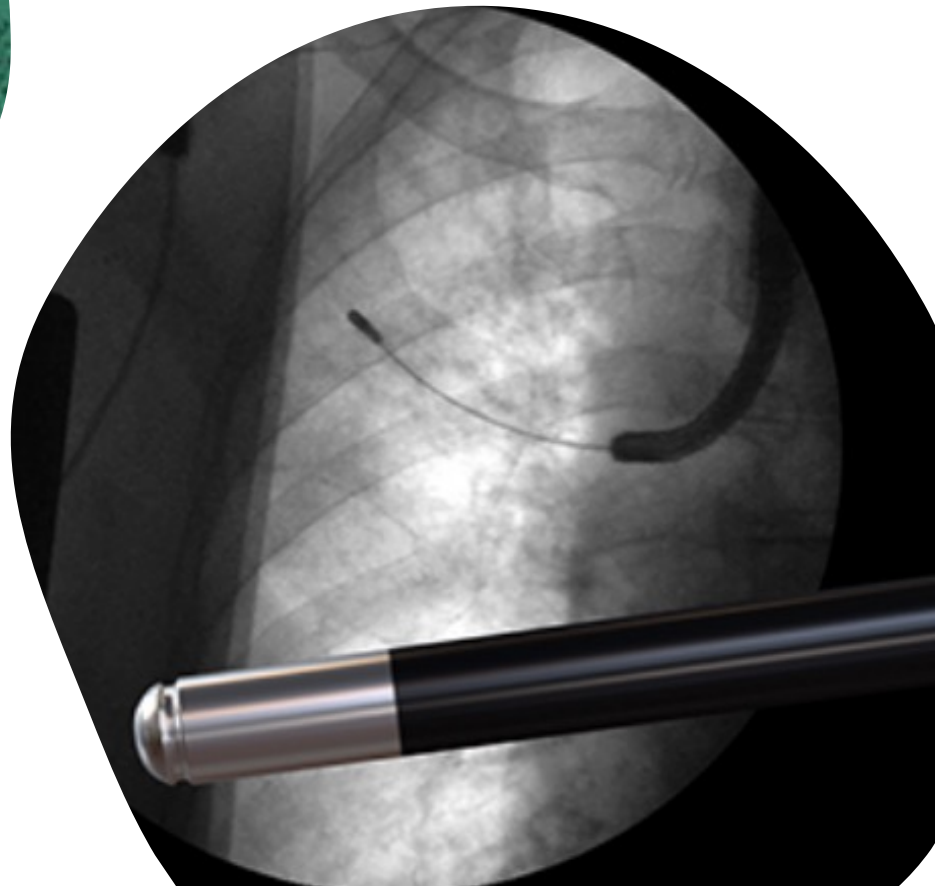
DIAGNOSTIC AGREEMENT. Two studies reported agreement between the diagnostic interpretation of TBLC samples and SLB samples (28, 60). The larger study demonstrated 70.8% agreement, which increased to 76.9% diagnostic agreement after MDD (28). *Post hoc* analysis suggested that agreement of TBLC with SLB improves by taking more samples (29). In contrast, the smaller study reported diagnostic agreement of only 38% (60).

COMPLICATIONS. Complications of TBLC included pneumothorax in 9% (28, 31, 33–35, 37, 39–43, 46, 48–50, 53–55, 60, 63, 68, 69) and any bleeding in 30% (28, 31, 33, 36, 39, 47, 50, 51, 55, 67–69). Severe bleeding, procedural mortality, exacerbations, respiratory infections, and persistent air leak were rare.

- ***Training important to achieve operator competency, as diagnostic yield increases and adverse events decrease with experience.***
- ***Introducing TBLC in less experienced centers may result in higher rates of complications***
- ***For other invasive procedures, it has been shown that formal training programs can increase operator competency***

Raghu G, et al. Am J Respir Crit Care Med 2022





Procedure – technical aspects

First author [Ref.]	OT	RB	LM	NI	GA + JV	GA/ DS	LA	Bronchial blocker	Cryoprobe size, mm	Freezing time, s
Babiak [16]	x					x		x	2.4	4
Pajares [20]	x					x		N	2.4	3
Griff [21]	x			x		x	x			
Kropski [22]	x					x			1.9	4
Yarmus [23]		x (10)	x (11)		x	x		Y	1.8	3
Fruchter [24]				x			x	N	2.4	4
Fruchter [25]				x			x	N	2.4	4
Fruchter [26]				x			x	N	2.4	4
Casoni [27]		x				x		Y	2.4	5/6
Pajares [28]	x					x		Y	2.4	3/4
Poletti [29]		x				x		Y	2.4	5/6
Griff [30]		x		x		x	x	N	1.9	3/5
Gershman [31]				x			x	N	2.4	4
Hagmeyer [32]	x	x			x			N	2.4	4/5
Hernández-González [33]	x					x		Y	1.9	3/4

Modified from [17]. OT, orotracheal tube; RB, rigid bronchoscope; LM, laryngeal mask; NI, no intubation; GA, general anesthesia; JV, jet ventilation; DS, deep sedation; LA, local anesthesia; Y, yes; N, no; x, method used.

Ravaglia C. Respiration 2016. Hetzel J. Respiration 201

Summary of recommendations

1. In patients with suspected interstitial lung disease (ILD), **we suggest that transbronchial cryobiopsy (TBC) can be used to provide histopathologic findings for multidisciplinary discussion diagnosis** (Weak Recommendation, Very Low-Quality Evidence).
2. In patients with suspected ILD undergoing TBC, **we suggest biopsy of at least two different sites** (either different segments in the same lobe or different lobes) (Weak Recommendation, Low-Quality Evidence).
3. In patients with suspected ILD undergoing TBC, **we suggest biopsy with the tip of the cryoprobe located 1 cm from the pleura** (Ungraded Consensus-Based Statement).
4. In patients with suspected ILD undergoing TBC, **we suggest the use of fluoroscopy** (Ungraded Consensus-Based Statement).
5. **In patients with suspected ILD undergoing TBC, we suggest that TBC be performed with a bronchial blocker either through an endotracheal tube or rigid bronchoscope (Ungraded Consensus-Based Statement).**
6. In patients with suspected ILD undergoing TBC, **we suggest the use of a small cryoprobe (1.9 mm) rather than a larger cryoprobe (2.4 mm)** (Ungraded Consensus-Based Statement).

The new ERS guidelines on CRYOBIOPSY are about to be released!!

Maldonado F, et al. Chest 2020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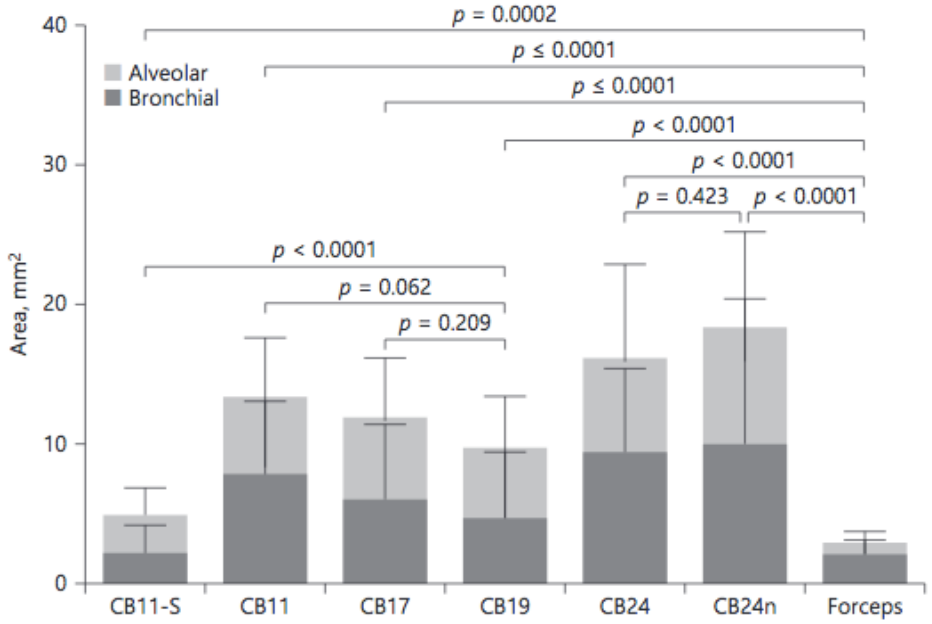

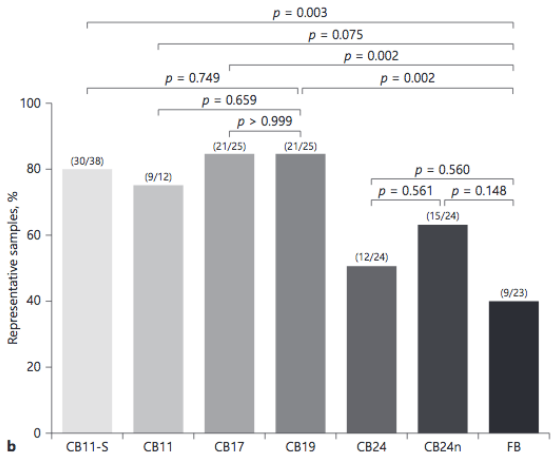

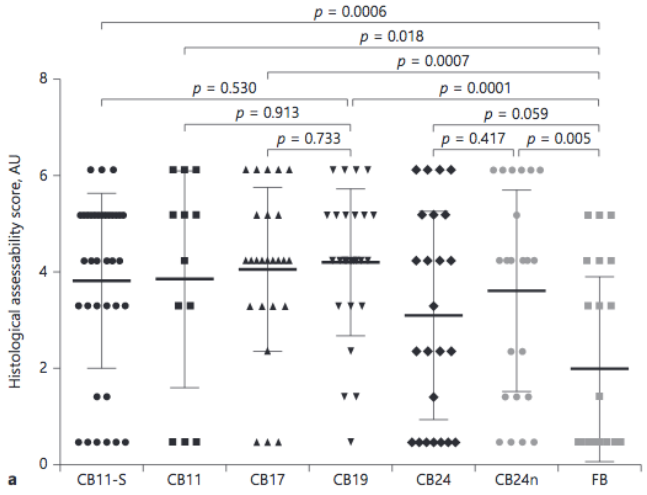

-The new disposable probes with 1.7 and 2.4 mm outer diameter yield similar biopsies compared to the standard cryoprobes

Hetzel J, et al. Respiration 2020

Summary of recommendations

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2. In patients with suspected ILD undergoing TBC, **we suggest biopsy of at least two different sites**

	1.9 probe	2.4 probe	Fisher's exact test
Pneumothorax	2/73 (2.7%)	130/613 (21.2%)	p < 0,0001
Bleeding	8/73 (10.9%)	78/611 (12.8%)	p 0,6460
Pathological diagnosis	62/73 (84.9%)	541/615 (87.9%)	p 0,4936
Multidisciplinary diagnosis	62/63 (84.9%)	557/615 (90.6%)	p 0,2014

Consensus-Based Statement).

5. In patients with suspected ILD undergoing TBC, **we suggest** that TBC be performed with a bronchial blocker either through an **endotracheal tube or rigid bronchoscope** (Ungraded Consensus-Based Statement).

6. In patients with suspected ILD undergoing TBC, **we suggest the use of a small cryoprobe (1.9 mm) rather than a larger cryoprobe (2.4 mm)** (Ungraded Consensus-Based Statement).

Ravaglia C, et al. BMC Pulm Med 2019

Maldonado F, et al. Chest 2020

Diagnostic yield of transbronchial lung cryobiopsy for diffuse parenchymal lung diseases diagnosis: 1.7 mm and 1.9 mm probe

Material and methods

- 60 consecutive patients
- Aim: to compare 1.9 and 1.7 mm probe (DY, adverse events, artifacts)
- Prospective, observational, monocentric study
- Consecutive patients undergoing TBC
- Suspected diffuse parenchymal lung diseases
- Randomized in two groups: A (1.7 mm probe) and B (1.9 mm probe)
- Data about biopsy characteristics, artifacts, DY, complications
- Switch of probe admitted and reported

In preparation

Biopsy characteristics	Group A (1.7 mm probe)	Group B (1.9 mm probe)	p
Samples	110	112	
Number of samples *n, range*	3.6 (1-5)	3.4 (2-5)	0.2116
Sample site			0.6843
One site *n, %*	3 (10)	4 (13.3)	
Two different lobes *n, %*	25 (83.3)	25 (83.3)	
Same lobe	16	13	
Different lobes	9	12	
Three different sites *n, %*	2 (6.7)	1 (3.4)	
Criobiopsy largest axis diameter *mm, sd, range*	5.50 (1.7) (2-10.7)	5.79 (1.66) (2.7-13.5)	0.5241
Criobiopsy smallest axis diameter *mm, sd, range*	3.87 (0.98) (1-6.2)	4.13 (0.84) (2-7.4)	
Sample surface area *mm2, sd, range*	16.3 (7.5) (2.27-36.75)	18.8 (9.78) (0.59-88.12)	
Pleural tissue present *n, %*	12 (40)	10 (33.3)	
Artefacts *n, %*	4 (13.3)	10 (33.3)	0.301
Freezing time *sec, sd, range*	7.7 (1.15) (4-9)	7.5 (0.83) (6-9)	0.532

Mean histopathologic DY: 93.3%

MDD: 98.3%
A → 100%
B → 93.6%

	Group A (1.7 mm probe)	Group B (1.9 mm probe)	p
Pathologic diagnostic yield *n, %*	29 (96.7)	27 (90)	0.718
High confidence diagnoses *%*	93.3	86.6	
UIP pattern *n, %*	10 (33)	11 (36.6)	

In preparation

No differences in Pneumothorax incidence (p 0.951)

No cases of severe bleeding

Switch from 1.7 to 1.9 mm was reported in 4 cases

Switch from 1.7 to 1.9 mm was reported in 1 case

MDD diagnoses	Group A (1.7 mm probe)	Group B (1.9 mm probe)
IPF *n, %*	10 (33.3)	8 (26.6)
Sporadic	10	7
Familial	0	1
HP *n, %*	5 (16.6)	2 (6.6)
CTD *n, %*	3 (10)	4 (13.3)
Sarcoidosis *n, %*	3 (10)	1 (3.3)
AFOP/COP *n, %*	4 (13.3)	3 (10)
IPAF *n, %*	0 (0)	2 (6.6)
iNSIP *n, %*	1 (3.3)	0 (0)
DIP/RB-ILD/SRIF *n, %*	2 (6.6)	2 (6.6)
Chronic eosinophilic pneumonia *n, %*	0 (0)	1 (3.3)
DIPNECH *n, %*	0 (0)	1 (3.3)
Amyloidosis *n, %*	1 (3.3)	0 (0)
Follicular/constrictive/cellular bronchiolitis *n, %*	0 (0)	1 (3.3)
Respiratory bronchiolitis *n, %*	0 (0)	1 (3.3)
PLCH *n, %*	0 (0)	1 (3.3)
Not specific NSIP/OP *n, %*	1 (3.3)	0 (0)
Suspected eosinophilic vasculitis *n, %*	0 (0)	1 (3.3)
Suspected constrictive bronchiolitis *n, %*	0 (0)	1 (3.3)
ND *n, %*	0 (0)	1 (3.3)
High confidence diagnoses *%*	90	83.3

In preparation

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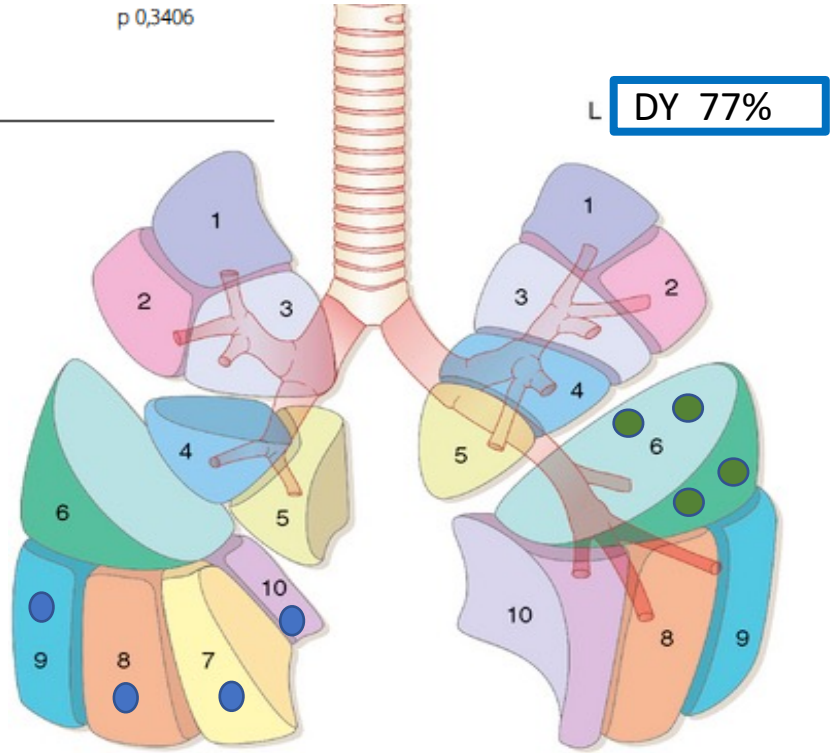
The new ERS guidelines on CRYOBIOPSY are about to be released!!

Maldonado F, et al. Chest 20

	Group A ($N = 22$ patients)	Group B ($N = 23$ patients)
Performing only 1 sample	23% not diagnostic (5/22)	39% not diagnostic (9/23)
Combining 2 samples (from the same segment)	9% not diagnostic (2/22)	35% not diagnostic (8/23)
Combining 2 samples (from different segments)		4% not diagnostic (1/23)

	1–2 samples			≥ 3 samples	Fisher's exact test
Pneumothorax	19/166 (11.4%)			115/532 (21.6%)	p 0,0009
Pathological diagnosis	145/168 (86.3%)			469/531 (88.3%)	p 0,5030
	1 sample	2 samples	p		
	23/34 (67.6%)	122/134 (91.0%)	0,0090		
Multidisciplinary diagnosis	20/168 (11.9%)			49/531 (9.2%)	p 0,3406
	1 sample	2 samples	p		
	23/34 (67.6%)	125/134 (87.0%)	0,0042		



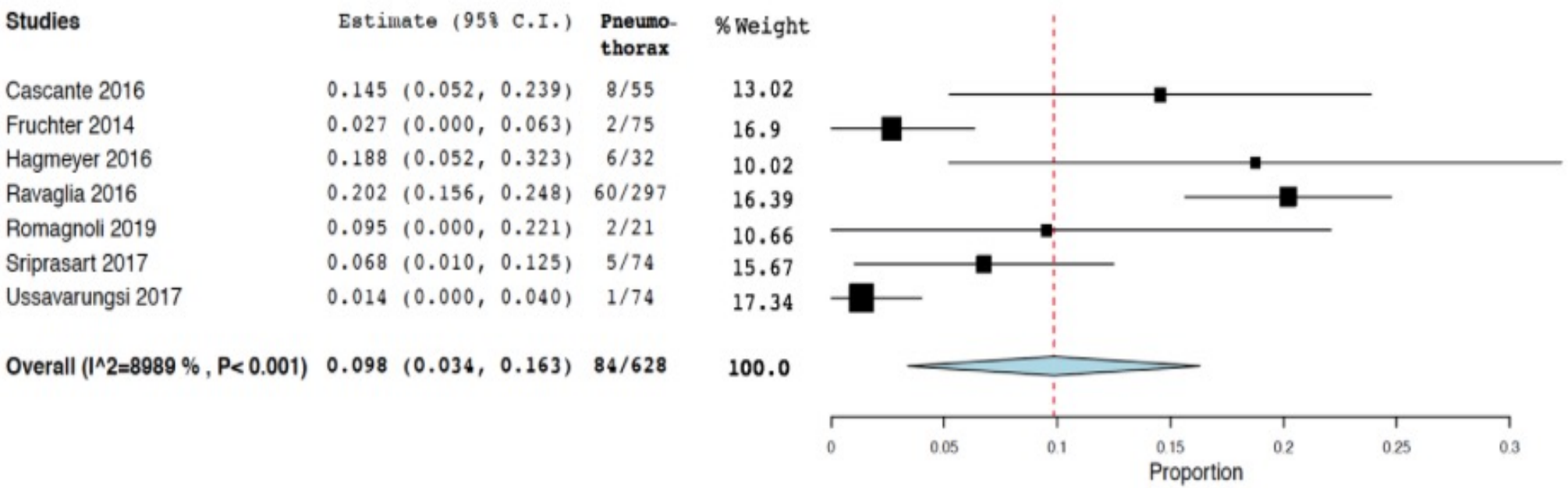
Maldonado F, et al. Chest 2020. Ravaglia C, et al. BMC Pulm Med 2019. Flaherty KR, et al. Am J Respir Crit Care Med 2001. Katzenstein AL, et al. Am J Surg Pathol 2002. Ravaglia C, et al. Respiration 2017

Complications

Complications

- **Pneumothorax**
- **Bleeding**
- Acute exacerbations
- Fever – pneumonia
- Respiratory failure
- Death
- Neurological complications
- Other

Complications: Pneumothorax Associated with cryobiopsy



The pneumothorax rate ranged from 1.4% to 20.2% with a median of 9.5%

Maldonado F, et al. Chest Guidelines 2020

Safety and DY - Biopsy strategy

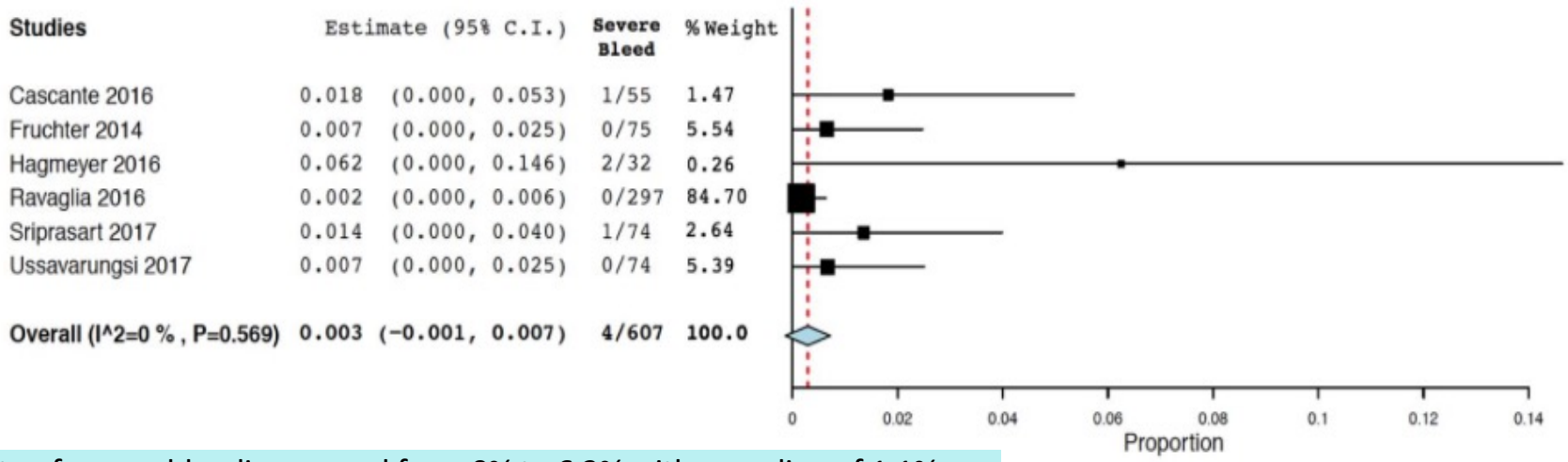
	Pathologic DIAGNOSTIC YIELD	PNX	BLEEDING
# SAMPLES (<3 → ≥3)	86% →88% (ns)	11% →21%	12% unchanged
# SEGMENTS lower lobes (1 →≥2)	85% →92.5%	15% →25%	12% unchanged
# LOBES (1 →≥2)	93% →91% (ns)	22% →29% (p=0.08)	11.4% → 13% (ns)
PROBE SIZE (1.9 →2.4)	85% →89% (ns)	3% → 21%	10% → 12.8% (ns)

PNX is also influenced by

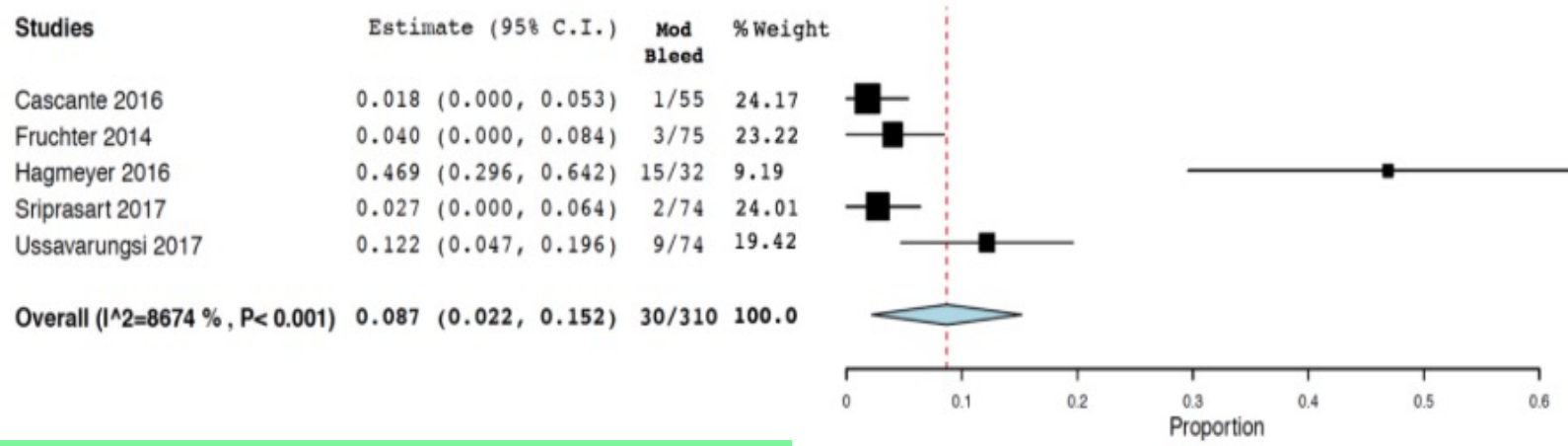
- **FUNCTIONAL IMPAIRMENT** FVC 81% vs 87% in cases without and with PNX , p=0,008; DLco 62% vs 58% in cases without and with PNX , p=0,03
- **FIBROTIC HRCT score** Median 280 (200-710) compared to 320 (200-749) in cases without and with PNX , respectively , p=0,04
- **UIP pattern**, p = 0.023

Ravaglia C, et al. BMC Pulm Med 2019

Complications: Bleeding Associated with cryobiopsy



Rate of severe bleeding ranged from 0% to 6.3% with a median of 1.1%

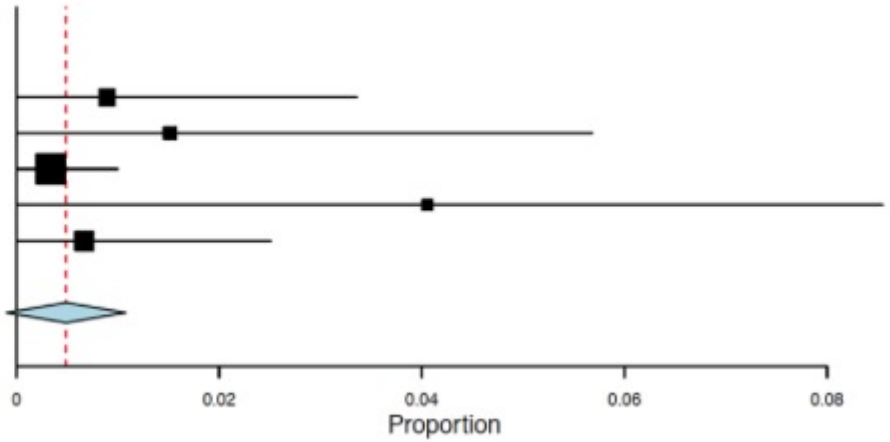


Rate of moderate bleeding ranged from 1.8% to 47%

Maldonado F, et al. Chest Guidelines 2020

Death Associated with cryobiopsy

Studies	Estimate (95% C.I.)	Deaths	% Weight
Cascante 2016	0.009 (0.000, 0.034)	0/55	5.74
Hagmeyer 2016	0.015 (0.000, 0.057)	0/32	2.01
Ravaglia 2016	0.003 (0.000, 0.010)	1/297	80.26
Sriprasart 2017	0.041 (0.000, 0.085)	3/74	1.73
Ussavarungsi 2017	0.007 (0.000, 0.025)	0/74	10.27
Overall (I^2=0 % , P=0.559)	**0.005 (−0.001, 0.011)**	**4/532**	**100.0**



Mortality rate is reported to be between 0% and 4.1% with a median of 0.3

Maldonado F, et al. Chest Guidelines 2020

Safety – patient selection

- Relative contraindications:
  - High bleeding risk
    - abnormal coagulation (trombocytopenia < 50x10^9/L)
    - use of clopidogrel, anticoagulant or new antiplatelet drugs
  - Pulmonary hypertension PAPs > 40mmHg
  - Poor lung function
    - FVC < 50%
    - DLCO < 35%
  - Respiratory failure (PaO2 < 55mmHg on room air)
  - Severe obesity (BMI > 35 Kg/m2)

Hetzel J, Maldonado F, Ravaglia C, et al. Respiration 2018. Lentz 2019. Ravaglia C 2019

	Variable	(Total)N N=197	Case 1	Case 2	Case 3	Case 4	Case 5
1.	Age at Procedure (years)	53.34 **(61.28)** 67.35	72	54	62	50	71
2.	Female	43.43% (86)	Yes	Yes	No	No	No
3.	BMI*	26.55 **(30.85)** 35.30	28	29.2	29.8	37.9	25.7
4.	Inpatient	4% (8)	Yes	Yes	No	No	No
5.	Smoking Never Current Former	 43% (83) 45% (86) 12% (24)	Never	Yes	Yes	Never	Never
6.	ASA* Class I II III IV V	 1% (1) 19% (36) 74% (140) 7% (11) 0	III	IV	IV	III	III
7.	ECOG* Performance Score 0 1 2 3	 9% (17) 56% (110) 25% (49) 10% (20)	3	3	1	1	4
8.	Charlson Comorbidity Index	1.0 (2.0) 3.5	3	1	5	1	1
9.	FEV1* (% predicted)	60 **(73.5)** 85.80	31	NA	60	101	85
10.	FVC* (% predicted)	58.0 **(71.0)** 82.0	24	NA	51	114	73
11.	DLCO* (% predicted)	43.00 **(57.00)** 67.00	NA	NA	36	29	43
12.	GAP* index	2.00 **(3.00)** 4.00	7	NA	4	1	5
13.	Pre-procedure oxygen requirement (Liters/minute)	0.00 **(0)** 12.00	6	2	0	3	0
13	Signs of recent decline pre procedure		Yes	Yes	No	Yes	No
14.	Intraprocedural bleeding		No	Yes	No	Yes	No
15.	Post-operative day of death		23	10	29	9	74

Multivariable analysis for predicting hospital admission.

	Early admission		Overall admission	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Charlson Comorbidity Index				
0	–		Reference	
1	–		3.56 (0.87 14.51)	0.076
≥2	–		3.58 (1.03, 12.49)	0.044
FVC				
≤50	5.58 (1.47, 21.17)	0.015	5.34 (1.37, 20.80)	**0.016**
>50	Reference		Reference	
Dyspnoea scale (mMRC)				
≤1	Reference		Reference	
≥2	4.20 (1.37, 12.84)	0.01	2.57 (1.02, 6.48)	0.045
AUC (95% CI)	0.72 (0.59, 0.84)		0.75 (0.65, 0.84)	
H-LT	0.76		0.71	

Table 9 Characteristic of patients with more compromised lung function (FVC < 50% predicted and/or DLCO < 35% predicted). Pre-test diagnosis was represented by NSIP (6 cases, 19%), IPF (6 cases, 19%), sarcoidosis (4 cases, 13%), diffuse neoplastic disease (4 cases, 13%), HP (3 cases, 10%), other (8 cases, 26%)

Patients characteristics (tot 31)	No. (% or SD)
Median age (SD), y	64 (7.8)
Male, No. (%)	22 (70.9)
Pathological diagnosis, No. (%)[a]	25 (80.6)
Multidisciplinary diagnosis, No. (%) [b]	26 (83.9)

Aburto M, et al. Respir Med 2020. Pannu J, et al. ERJ 2019. Ravaglia C, et al. BMC Pulmonary Medicine 2019

Diagnostic yield and risk/benefit analysis of trans-bronchial lung cryobiopsy in diffuse parenchymal lung diseases: a large cohort of 699 patients

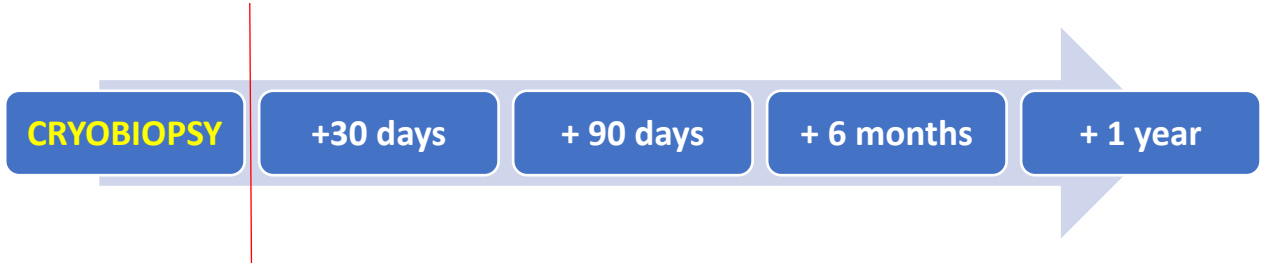
- Expert higher volume centers may view TBLC as reasonable option in some selected high-risk patients which would be excluded from surgery due to age, lung function tests, comorbidities
- TLCB has been performed safely in a wide age range of patients (21–87 years), with 56 patients (8%) over 75 years of age, with no complications, therefore no age limits should be suggested (giving much more importance to comorbidities and fitness for anesthesia).

Ravaglia C, et al. BMC Pulm Med 2019

Impact of Lung Biopsy on Lung Function in Idiopathic Pulmonary Fibrosis

Materials and methods

- Prospective, observational, monocentric study
- consecutive patients undergoing TBC
- Suspected diffuse parenchymal lung diseases
- LFTs collected (previous month and within the following month)



In preparation

Impact of Lung Biopsy on Lung Function in Idiopathic Pulmonary Fibrosis

Primary end-point

- changes in FVC from the last measurement performed before TBLC to the first measurement performed after TBLC

$$\frac{\text{pre-biopsy FVC} - \text{post-biopsy FVC}}{\text{pre-biopsy FVC}} \times 100$$

Secondary end-points:

- relative changes in FEV1, TLC, DLCO
- complications in the month and year following the biopsy
- AE/deaths occurring within the following month

In preparation

Impact of Lung Biopsy on Lung Function in Idiopathic Pulmonary Fibrosis

	Data	Diagnoses
Total number of patients	31	16 IPF (43%)
Age, years (range)	67 (56-79)	7 SR-ILD (29%)
Gender, n (%) male female	 22 (71%) 9 (29%)	4 cHP (13%) 2 NSIP (10%) 1 CTD-ILD (3%)
Smoking status, n (%) active smoker former smoker never smoker	 2 (6%) 21 (68%) 8 (26%)	1 sarcoidosis (3%)

Comparison of PFT between the last PFT before SLB and first PFT after the SLB				
	Pre-TBLC LFTs	Post-TBLC LFTs	Relative variation, %	P value
FVC, % pred	87.6%	89.4%	2.1%	0.931
DLCO, % pred	57.4%	58.0%	1.0%	0.734

Pending analysis in different sub-groups (IPF vs non-IPF diagnosis, treated vs non-treated, etc.)
Absence of control group

In preparation

Impact of Lung Biopsy on Lung Function in Idiopathic Pulmonary Fibrosis

	Preoperative PFT	Postoperative PFT	Relative variation, %	Absolute variation, L	*p* value
FVC, % pred	78.1±16.9	74.9±19.1	−4.8		<0.001
FVC, L	2.79±0.87	2.69±0.88		−0.156±0.386	<0.001
FEV1, % pred	81.7±18.2	78.2±19.3	−5.4		<0.001
FEV1, L	2.23±0.68	2.14±0.68		−0.138±0.312	<0.001
TLC, % pred	71.8±14.8	67.4±15.8	−6.1		<0.001
TLC, L	4.42±1.2	4.17±1.2		−0.282±0.616	<0.001
DLCO, % pred	53±16	48±17	−4.5		<0.001
Median PFT delay			185 days [61–691]		

	Patients *n* (%)	Complications at 1 month, *n* (%)	IPF exacerbation at 1 year, *n* (%)	Death at 1 year, *n* (%)
FVC before biopsy				
FVC ≥75%	69 (58.5)	9 (13)	0 (0)	1 (1.4)
FVC 60–74%	36 (30.5)	5 (14)	6 (16.7)	6 (16.7)
FVC 50–59%	4 (3.4)	0 (0)	0 (0)	0 (0)
FVC <50%	6 (5.1)	2 (33.3)	2 (33.3)	3 (50)
Missing data	3 (2.5)			
		$p = 0.47$	$p = 0.001$	$p = 0.001$
DLCO before biopsy				
DLCO ≥60%	24 (20.3)	2 (8.3)	0 (0)	1 (4.2)
DLCO 40–60%	51 (43.2)	11 (21.6)	3 (5.9)	5 (9.8)
DLCO <40%	14 (11.9)	2 (14.3)	1 (7.1)	0 (0)
Missing data	29 (24.6)			
		$p = 0.97$	$p = 0.36$	$p = 0.44$

Aussedat PH, et al Respiration 2020


New perspectives

Utility of a Molecular Classifier as a Complement to High-Resolution Computed Tomography to Identify Usual Interstitial Pneumonia

Table 1: Clinical demographics of the Envisia Genomic Classifier validation group

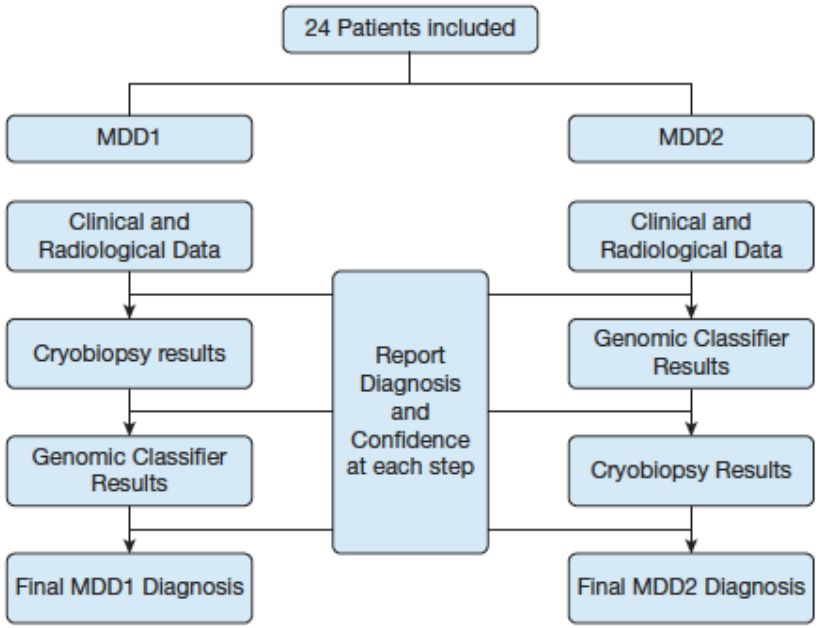
	Clinical Validation (N = 96)
Sex	
Women	41 (43%)
Men	55 (57%)
Age (years), mean (SD)	62.8 (12.1)
Smoker	
Yes	48 (50%)
No	48 (50%)
Study site type	
US academic	41 (43%)
US community	48 (50%)
European academic	7 (7%)
Biopsy Type	
Surgical	61 (64%)
TBBx	1 (1%)
Cryobiopsy	34 (35%)
UIP frequency in study	
By pathology	58 (60%)
By radiology	10/65 (15%)

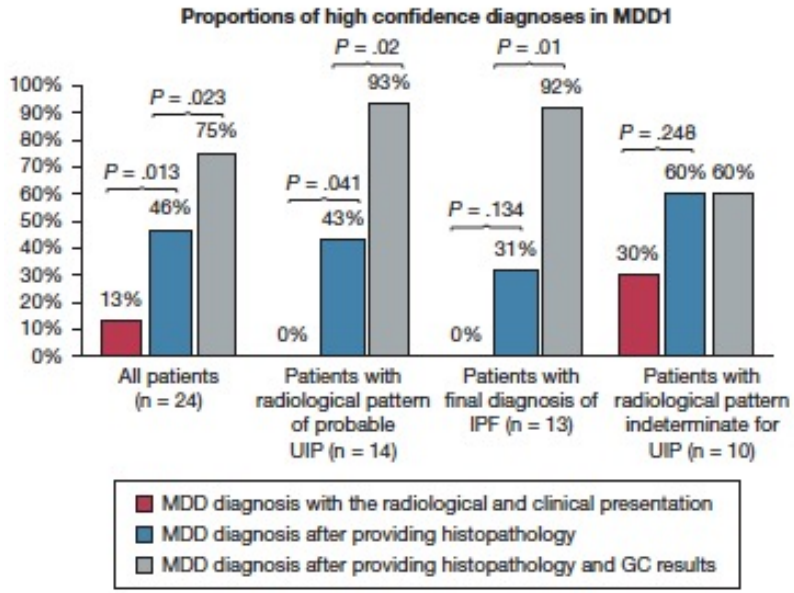
SD, Standard Deviation; TBBx, transbronchial biopsy; UIP, Usual Interstitial Pneumonia

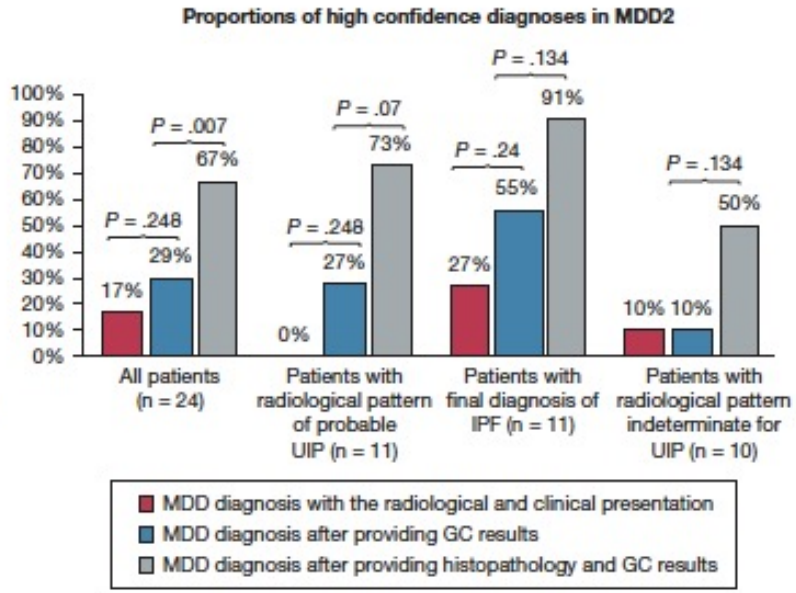
Table 4B. UIP diagnostic yield from local radiology in conjunction with Envisia Genomic Classifier testing

Local Radiology + Envisia Classifier	Pathology reference standard	
	UIP (N=53)	Non-UIP (N=32)
Definite/Probable UIP or Envisia Classifier UIP	42	3
Indeterminate for UIP/ Consistent with non-IPF and Envisia Classifier non-UIP	11	29
Sensitivity	79.2% [65.9 – 89.2]	
Specificity	90.6% [75.0 – 98.0]	
NPV	72.5% [56.1 – 85.4]	
PPV	93.3% [81.7 – 98.6]	
UIP prevalence	62.4%	

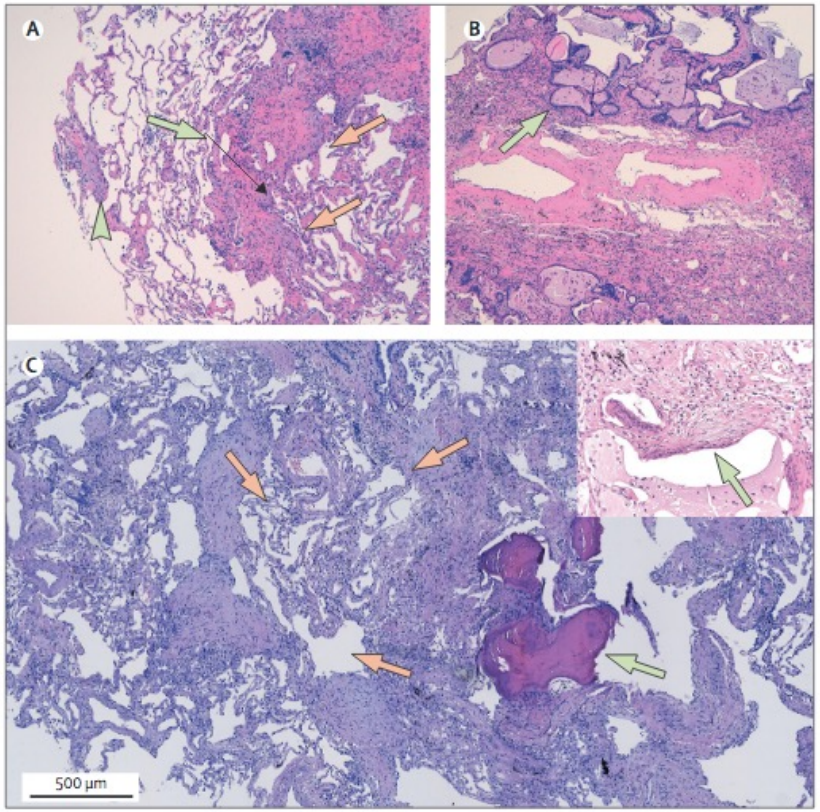
Richeldi L, et al. Am J Respir Crit Care Med 2021





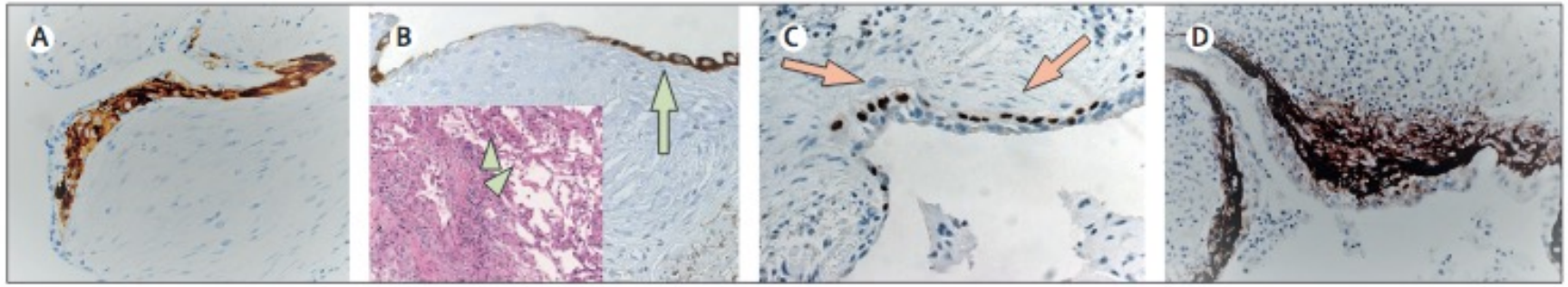


Kheir F, et al. Chest 2020



	Immunohistochemistry[65-69]	Clinical entities
UIP	Cells covering fibroblastic foci with bronchiolar basal cells phenotype (cytokeratin 5, ΔNp63, nuclear β catenin+, cyclin D1+, laminin-5γ2+, HSP27+, fascin+, MMP7+, autophagy markers [LC3, SIRT1, MAP1S, and pAMPKα]+), type 2 alveolar pneumocytes (A1 surfactant protein+, thyroid transcription factor 1+, p116 and p21+, autophagy markers+), spindle shaped cells embedded in extracellular matrix in fibroblastic foci (myofibroblasts; α-smooth muscle actin+, tenascin C+, p16+/− and p21+/−, and absence of Thy-1 expression), extracellular matrix (tenascin C+); sandwich fibroblastic foci*	IPF
Non-IPF UIP	Epithelioid or giant cells (cathepsin K+)	Fibrosing hypersensitivity pneumonitis
Fibrotic NSIP	Epithelioid or giant cells (cathepsin K+)	Fibrosing hypersensitivity pneumonitis
Organising pneumonia	Masson's bodies (tenascin C+)	Cryptogenic organising pneumonia
PPFE	Spindle cells in thickened pleura and subpleural fibroelastosis (α-smooth muscle actin+ and podoplanin+)	Idiopathic PPFE

IPF=idiopathic pulmonary fibrosis. NSIP=non-specific interstitial pneumonia. PPFE=pleuroparenchymal fibroelastosis. UIP=usual interstitial pneumonia. *Sandwich fibroblastic foci refers to the expression of HSP27, laminin-5γ2 and ΔNp63 in epithelial cells located between luminal bronchiolar cells (distinctive bronchiolar phenotype of basal epithelial cells) and myofibroblasts embedded in extracellular matrix rich in tenascin C. Sandwich fibroblastic foci are seen in UIP-IPF but not in non-IPF UIP or in fibrotic NSIP.[57]

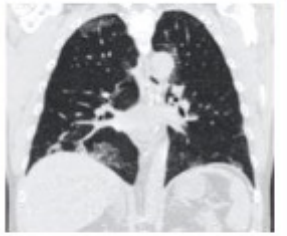


Renzoni EA, Poletti V, Mackintosh JA. Lancet 2021

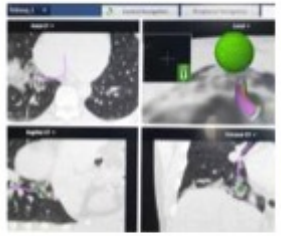
Table 2 Procedure related data and results.

	Aarhus cohortN=8	Florence cohortN=5	Total cohortN=13
Number of biopsies per patient (IQR)	4 [4-4]	4 [4-4]	4 [4-4]
Size of cryoprobe (1.7, 1.9)	1.7	1.9	
Seconds of freezing (median and IQR)	7 [7-8]	6 [6-6]	7 [6-7]
Size of biopsies (mm and IQR)	5 [4.6-7.5]	6.5 [5-8]	5 [5-8]
Site of biopsies			
-Right, Upper	3	0	3
-Right, middle	1	2	3
-Right, lower	3	3	6
-Left lower	1	0	1
Pneumothorax	1 (13%)	2 (40%)	3 (23%)
Hemorrhage			
-mild	1 (13%)	0	1 (8%)
-moderate	5 (63%)	1 (20%)	6 (46%)
Contribution to diagnosis (%)	7 (88%)	4 (80%)	11 (85%)
Diagnosis			
-Hypersensitivity pneumonitis	3	0	3
-Idiopathic pulmonary fibrosis	0	2	2
-Smoking related -ILD	1	1	2
-Cryptogenic organizing pneumonia	1	0	1
-Nonspecific interstitial pneumonia	1	0	1
-Scleroderma ILD	0	1	1
-Pulmonary alveolar proteinosis	1	0	1
-Unclassifiable ILD	1	1	2

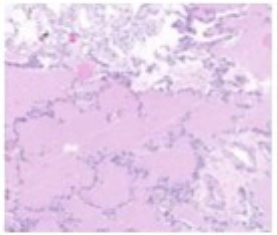
IQR: interquartile range, F: female, M: male, ILD: interstitial lung disease.



HRCT with localized crazy paving, difficult to reach by conventional fluoroscopy.



SD guided cryobiopsies.



Histology showing alveolar spaces filled with a granular, proteinaceous exudate and adjacent normal alveolar septa.

Kronborg-White S, et al. Pulmonology 2021

Cone Beam CT Guidance Improves Transbronchial Lung Cryobiopsy Safety

Bryan S Benn [1], Arthur Oliver Romero [2 3], Hasnain Bawaadam [2], Nathaniel Ivanick [2 4], Mendy Lum [5], Ganesh Krishna [2 6]

Introduction: Determining the cause of diffuse parenchymal lung disease (DPLD) is challenging. While surgical lung biopsy has been the standard approach, transbronchial lung cryobiopsy (TBLC) represents a minimally invasive alternative with an acceptable safety profile and reasonable accuracy. In this study, we prospectively assessed whether the use of cone beam CT (CBCT) coupled with a novel bronchoscope holder and prophylactic administration of vasoconstricting medications decreases potential complications and improves diagnostic accuracy when performing TBLC.

Methods: 33 patients presenting for evaluation of newly diagnosed DPLD were enrolled. Demographic data, pulmonary function values, chest imaging pattern, procedural information, and diagnosis were recorded.

Results: Mean patient age was 67, with the majority Caucasian (n = 26, 79%) and male (n = 20, 61%). Mean pulmonary function values revealed restrictive lung disease (76 ± 14% predicted) and diffusing capacity impairment (52 ± 16%). A non-usual interstitial pneumonia imaging pattern was commonly seen (n = 20, 61%). CBCT guided TBLC was performed in one lobe (n = 29, 88%) or two lobes (n = 4, 12%) with mean probe-to-pleura distance of 4.2 ± 1.3 mm. No peri or post procedural complications occurred. 32 patients (97%) received a histological diagnosis with a final multidisciplinary conference diagnosis possible for 32 (97%).

Conclusion: CBCT guided TBLC coupled with a novel articulating scope holder and prophylactic phenylephrine administration has the potential to increase safety and diagnostic yield for patients with newly identified DPLD. Future studies comparing different aspects of this approach in isolation and with other modalities have the potential to refine this procedure to improve patient care.

Benn BS, Lung. 2021

Using Cone Beam Computed Tomography when performing transbronchial cryobiopsy in interstitial lung diseases: A Case-Series Study

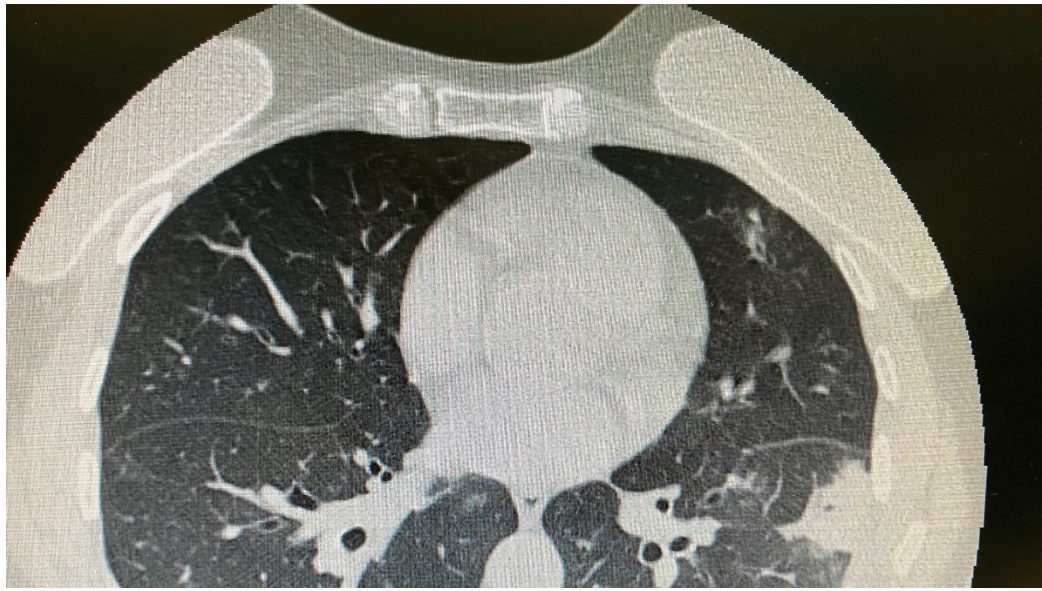
Background: Transbronchial lung cryobiopsy (TBLC) is a valuable technique for tissue sampling and is becoming a reasonable alternative to surgical lung biopsy (SLB) for making diagnosis in patients with interstitial lung diseases (ILDs). However, the positioning of cryoprobe is not accurate and probe-to-pleura distance is unclear.

Objective: Aim of the study was to find out the safety of Cone Beam 3D CT (CBCT) when performing TBLC in patients with ILDs.

Methods: The procedure was performed in patients with ILD at the high resolution computer tomography (HRCT), under general anesthesia, using a rigid bronchoscope. A 4/6 Fr Fogarty catheter was placed proximally to the target area. Through a flexible bronchoscope the cryoprobe (1.7mm) was advanced under fluoroscopic guide. Both the Fogarty catheter and the probe were secured to avoid misplacing during the CT. Once the exact placement of the probe was confirmed by CBCT, the cryobiopsy was performed, freezing the area for 7 seconds. All patients underwent post-procedure thorax radiography (Rx) to exclude complications.

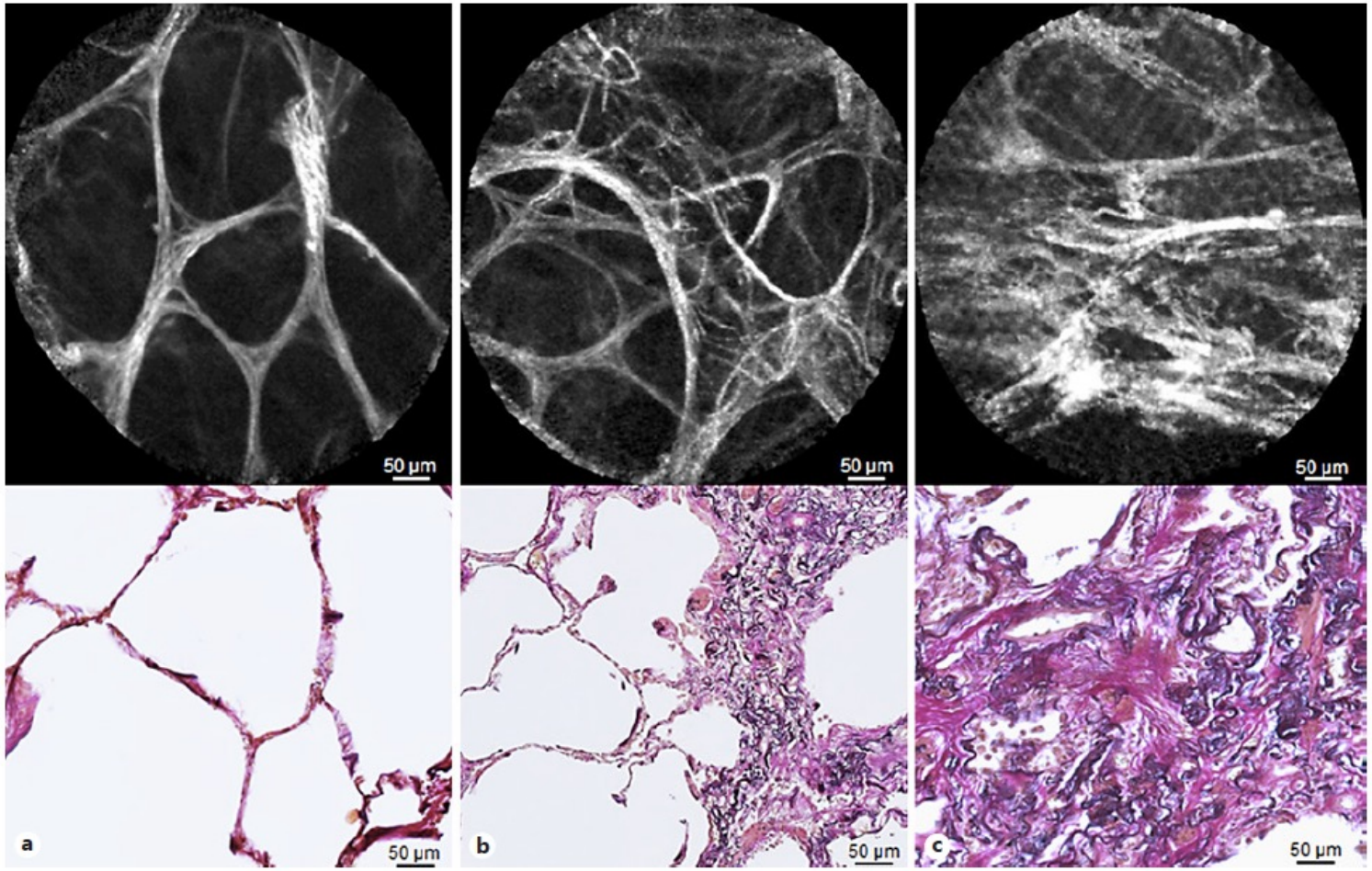
Results: A total of 8 patients were prospectively recruited in this study. All the biopsies were classified as adequate. TBLC diagnoses were obtained in 100% of cases. One patient (12,5%) had a mild bleeding that was rapidly controlled endoscopically with Fogarty catheters. One patient (12,5%) developed a pneumothorax. which required the positioning of a pleural drainage, revealed at the post procedural thorax Rx.

Conclusions: CBCT-guided TBLC in patients with ILDs is associated with a promising safety profile and diagnostic yield. A larger trial is necessary to validate the results and homogenize the technique between centers.



Submitted

Confocal Laser Endomicroscopy as a Guidance Tool for Transbronchial Lung Cryobiopsies in Interstitial Lung Disorder



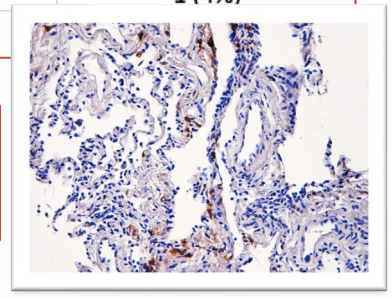
Wijmans L, et al. Respiration 2019

25 patients lung biopsy

N° Tot patients	28
Age (years), *mean ± SD*	63±15
M/F	17/11
Side: right/left	13/15

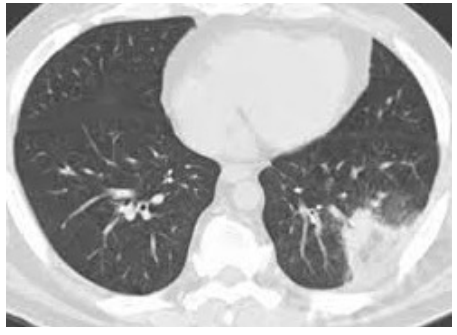
Hystopathological Diagnosis	n (%)
Aspecific chronic pleurisy	8 (29%)
Lung adenocarcinoma	5 (18%)
Other epithelial neoplasm	6 (21%)
Mesothelioma	4 (14%)
Lymphoma	2 (7%)
Tuberculosis	1 (4%)
Lymphangioleiomyomatosis	1 (4%)
CTD-ILD	1 (4%)

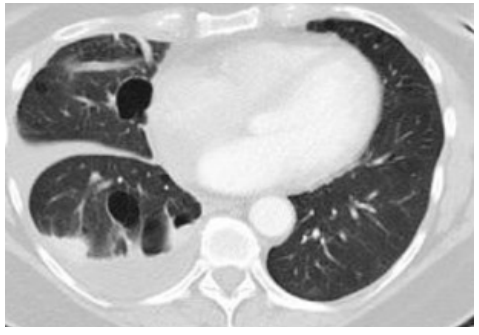
Biopsy, *n*	
Lung	23 (82%)
Pleura	3 (11%)
Lung and pleura	2 (7%)
Drainage days, *mean ± SD*	5±3
Chest tube suction, *n*	23 (82%)
Pleurodesis, *n*	13 (46%)
Hospitalization days, *mean ± SD*	7±3
Complications, *n*	4 (14%)
Fever	3 (10%)
Air leak and fever	1 (4%)



Cryobiopsy during medical thoracoscopy is feasible, safe and efficacious

Prospective trials are required for a better evaluation of its role as an alternative diagnostic tool to VATS in the hands of trained pulmonologists





In preparation

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Endobronchial ultrasound-guided transbronchial cryo-nodal biopsy: a novel approach for mediastinal lymph node sampling

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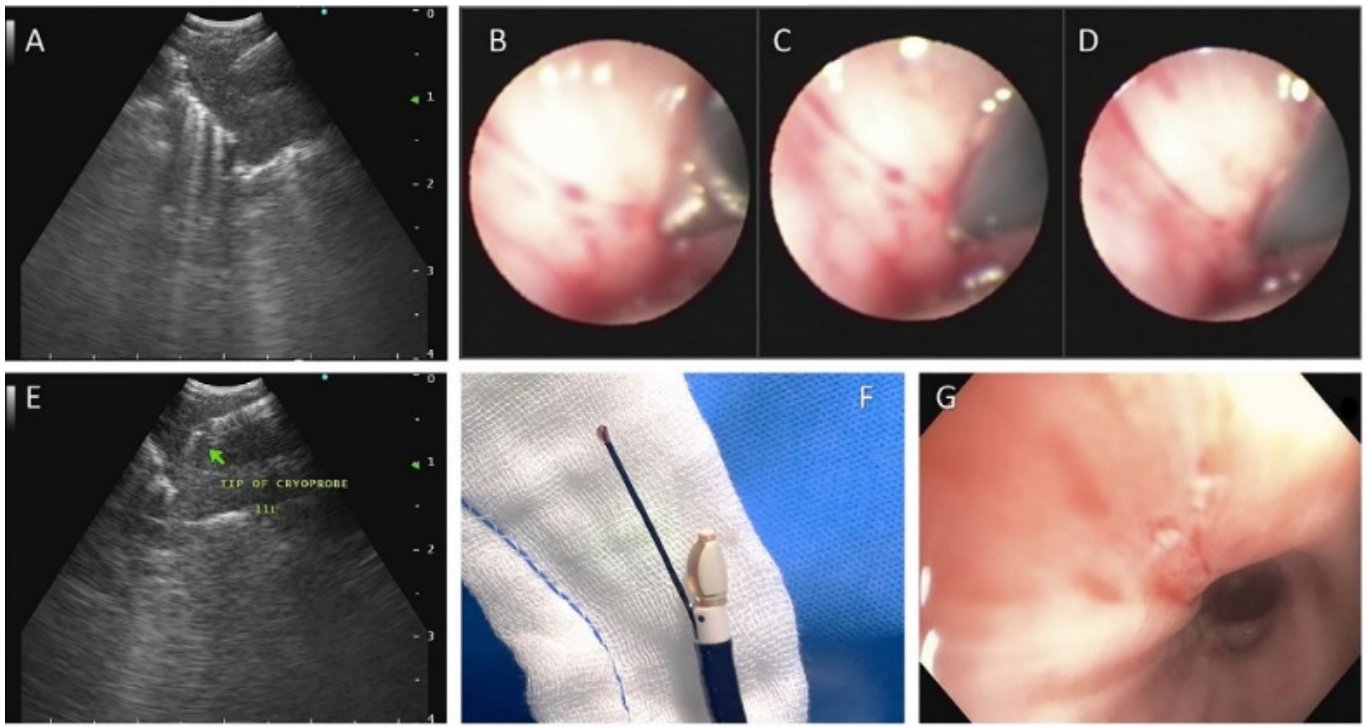

Gonununtla JK, Respirology Case Report. 2020

Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: a randomised trial

Jing Zhang[1], Jie-Ru Guo[1], Zan-Sheng Huang[1], Wan-Lei Fu[2], Xian-Li Wu[1], Na Wu[3], Wolfgang M. Kuebler[4], Felix J.F. Herth[5,6,7] and Ye Fan[1,7]

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Shareable abstract (@ERSpublications)

EBUS-guided transbronchial mediastinal cryobiopsy is a safe and promising novel diagnostic tool for mediastinal diseases that might allow for better histopathological evaluation and advanced testing https://bit.ly/3uiLkiD

Cite this article as: Zhang J, Guo J-R, Huang Z-S, *et al*. Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: a randomised trial. *Eur Respir J* 2021; 58: 2100055 [DOI: 10.1183/13993003.00055-2021].

Zhang J, Eur Respir J. 2021

Transbronchial mediastinal cryobiopsy in the diagnosis of mediastinal lesions: a randomised trial

TABLE 2 Diagnostic yields of TBNA and transbronchial mediastinal cryobiopsy

	Total	TBNA	Cryobiopsy	p-value
Subjects n	194	194	194	
Diagnostic yield n (%)				0.001
No	13 (6.7%)	39 (20.1%)	16 (8.2%)	
Yes	181 (93.3%)	155 (79.9%)	178 (91.8%)	
Common tumour n				
Lung, adenocarcinoma	75	68	72	
Lung, squamous cell	24	24	23	
Lung, large cell	3	3	3	
Lung, NSCLC (NOS)	7	6	5	
Lung, small cell	26	26	26	
Total n (%)	135 (69.6%)	127 (65.5%)	129 (66.5%)	0.58
Uncommon tumour n				
Lung, carcinoid	1	0	1	
Lung, sarcomatoid	1	1	1	
Lymphoma	8	1	7	
Seminoma	1	0	1	
Thymic carcinoma	1	1	1	
Total n (%)	12 (6.2%)	3 (1.5%)	11 (5.7%)	0.001
Benign disorder n				
Sarcoidosis	15	10	15	
Tuberculosis	16	8	16	
Pneumoconiosis	7	7	7	
Total n (%)	47 (24.2%)	25 (12.9%)	38 (19.6%)	0.004

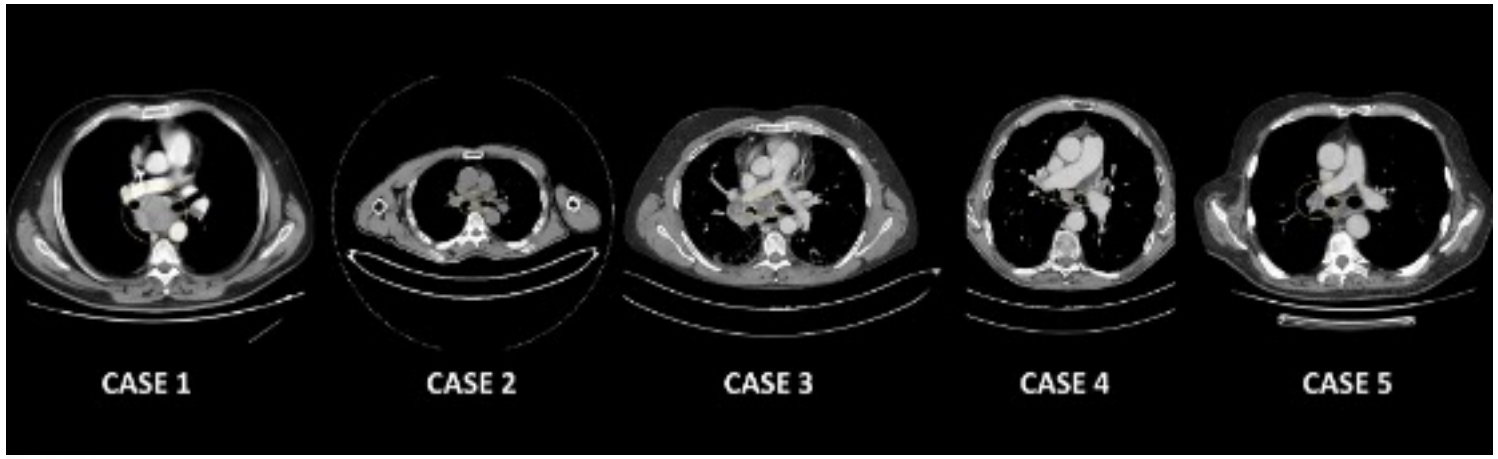
-97 patients were enrolled
-mediastinal lesion of⩾1 cm

-overall DY 91.8% vs 79.9%
-94.1% vs 95.6% (metastatic lymphadenopathy)
-91.7% vs 25.0% (uncommon tumors)
-80.9% vs 53.2% (for benign disorders)

-small incision in the wall (high-frequency needle-knife - Olympus KD-31C-1).

Zhang J, Eur Respir J. 2021

Potential application of cryobiopsy for histo-molecular characterization of mediastinal lymph nodes in patients with thoracic malignancies: a case presentation series and implications for future developments



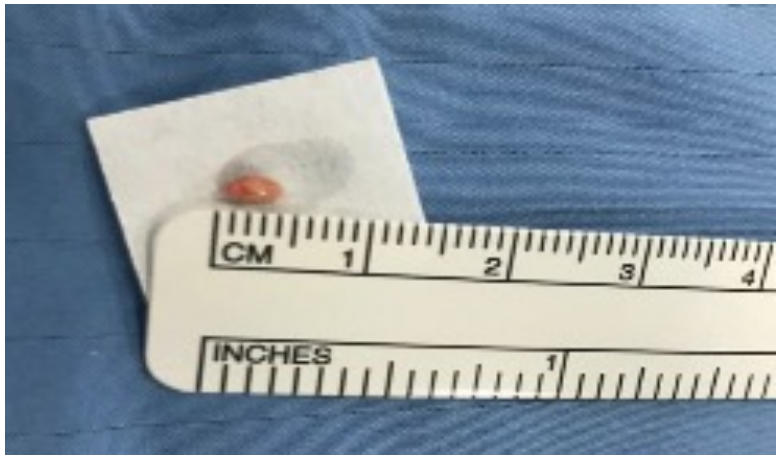


Table 1 Characteristics of the patients who underwent cryobiopsy of mediastinal lymph nodes within our Institution and findings at cryobiopsy and trans-bronchial needle aspiration (including cell block). All the patients were male. No post-procedural complications were observed

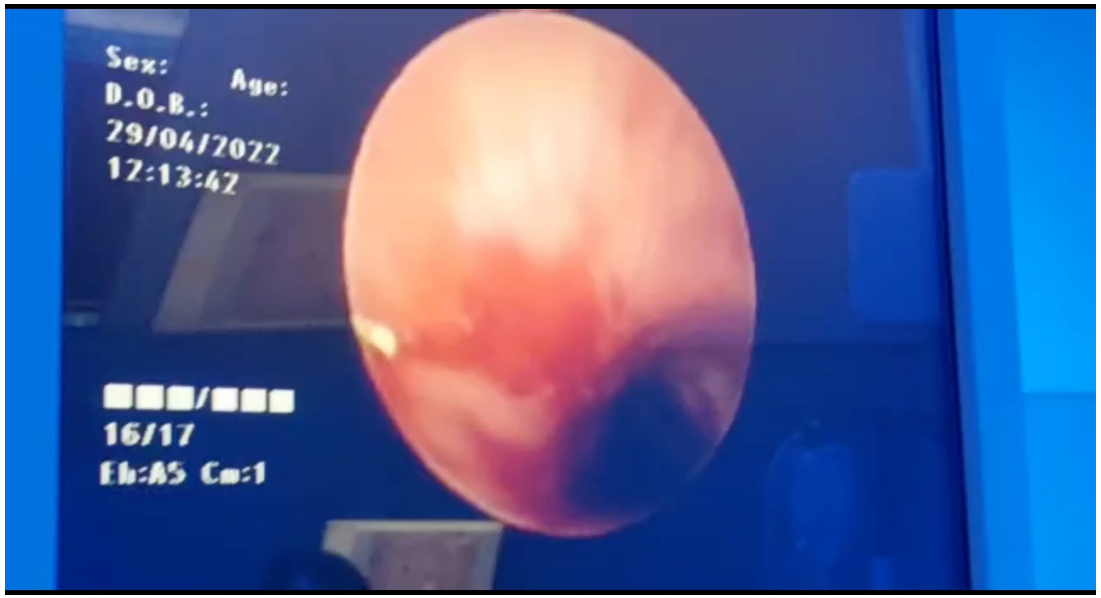
Patient	Age (years)	Smoking status	Reason for bronchoscopy	Disease stage at the time of bronchoscopy (if applicable)	Date of bronchoscopy	Target lymph node for cryobiopsy	Target lymph node for trans-bronchial needle aspiration	Outcome of cryobiopsy	Outcome of trans-bronchial needle aspiration / cell block	Concordance or discordance between cryobiopsy and cell block
Case 1	53	Never smoker	Characterization of progressive lymphoma	IV	July 7th, 2020	Station 7	Station 7	Positive for diffuse large B cell lymphoma	Positive for lymphoma cells	Concordance
Case 2	73	Former smoker	Diagnostic suspect of sarcoidosis	Not applicable	July 17th, 2020	Station 7	Station 4R; station 7	Negative for lymphatic elements (inadequate)	Negative for sarcoidosis or lymphoproliferative disorders	Not applicable*
Case 3	51	Former smoker	Characterization of lung cancer	IV	March 5th, 2021	Station 7	Station 4L; station 7	Positive for squamous cell lung cancer	Positive for exiguous amount of non-small cell lung cancer (possibly of squamous histology)	Concordance
Case 4	66	Current smoker	Mediastinal staging for squamous cell lung cancer	III	April 14th, 2021	Station 7	Station 4R; station 7	Negative for neoplastic cells	Negative for neoplastic cells	Concordance
Case 5	77	Current smoker	Characterization of mediastinal lymph nodes	IV	May 20th, 2021	Station 10R	stations 4R, 7, 10R and 11R	Negative for neoplastic cells	Positive for small cell lung cancer	Discordance

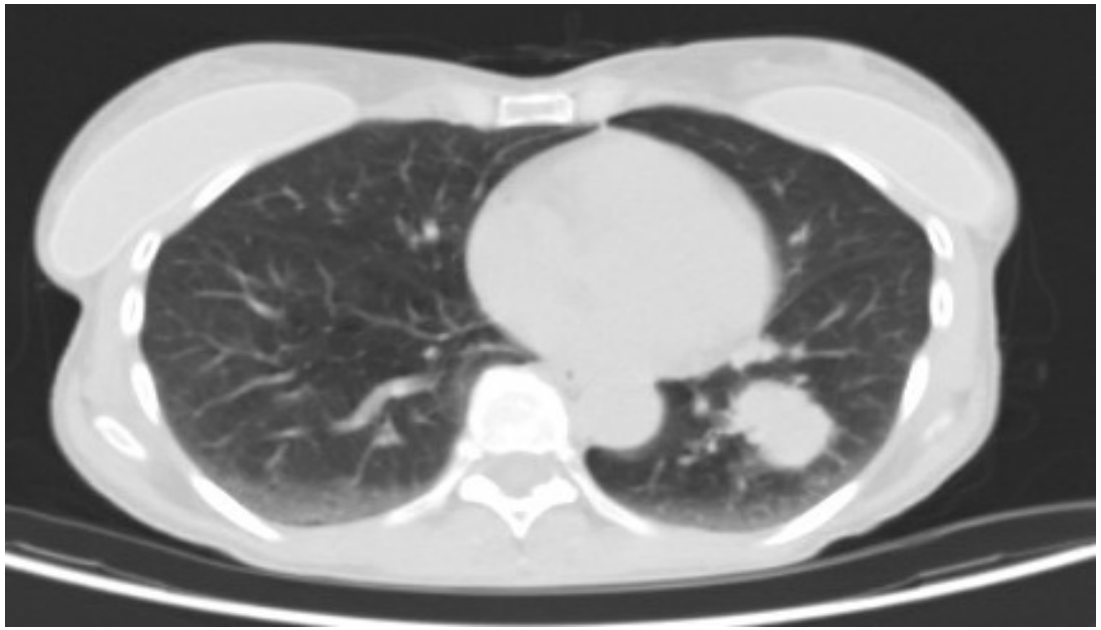
*In this case, concordance between cryobiopsy and EBUS TBNA was not ruled out because cryobiopsy was considered not diagnostic

-5 consecutive patients
-mediastinal lymph nodes for oncologic reasons
-both EBUS TBNA and EBUS-TBcryobiopsy
-same procedure
-no complications

Genova C, BMC Pulm Med. 2022

Patient	Genre	Age	EBUS-TBNA	EBUS-Cryo
1	F	42	Lymphocytes	**Lymphoma**
2	F	55	Lung ADK	Lung ADK
3	M	74	Lymphocytes	Lymphocytes
4	F	37	Pending	Pending
5	F	62	Lymphocytes	**Carcinoid**
6	M	46	Sarcoidosis	Sarcoidosis
7	M	67	Lung ADK	Lung ADK
8	M	74	Lung ADK	Lung ADK
9	M	37	Lymphocytes	**Sarcoidosis**
10	M	70	Amartoma	Amartoma



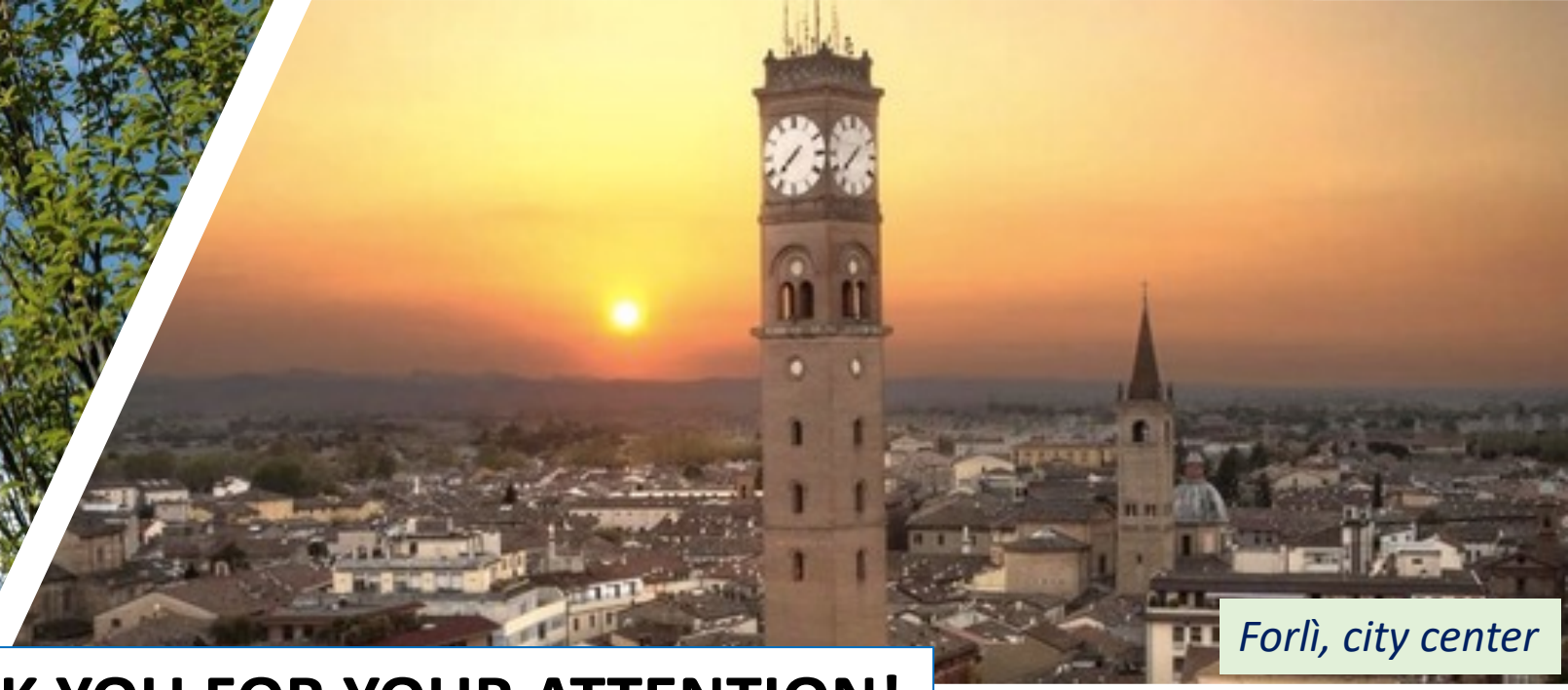


GB Morgagni data, Forlì

Conclusions

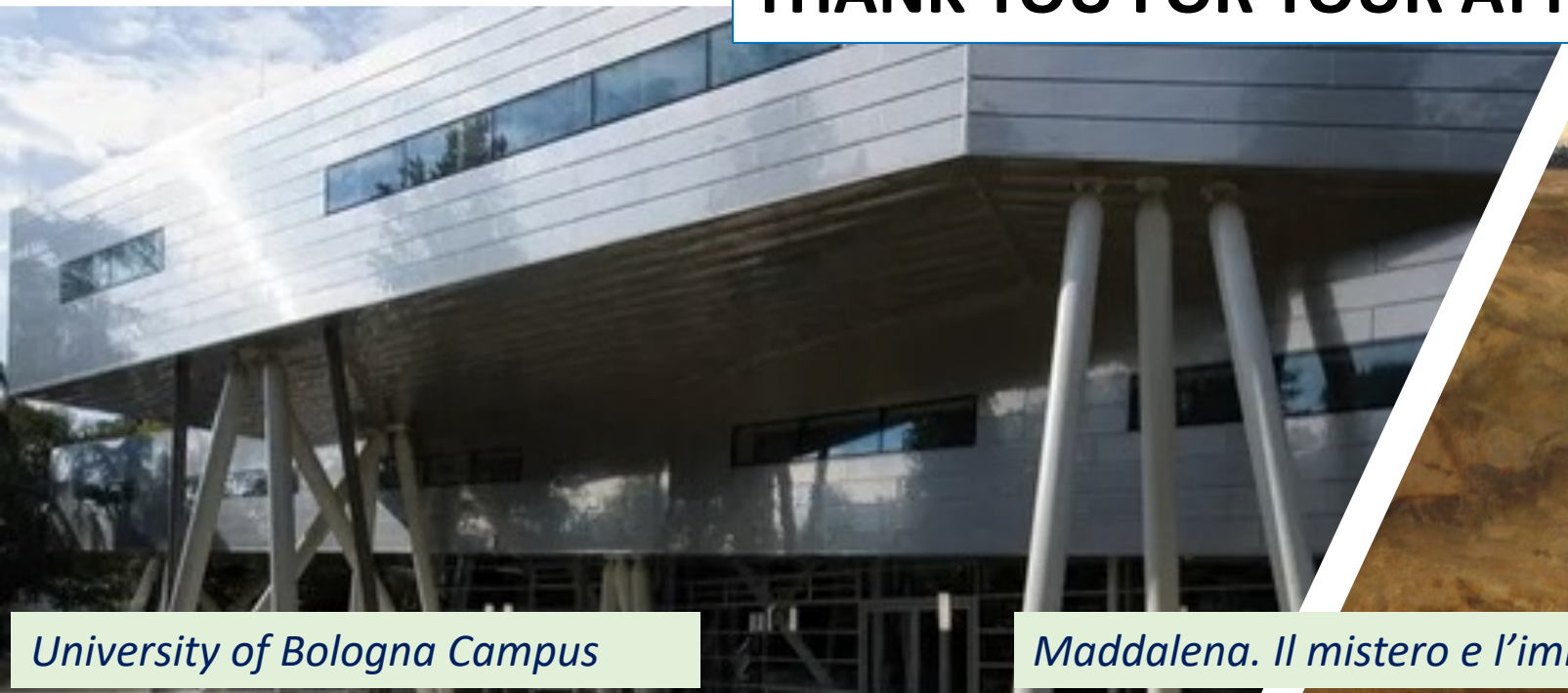
- Histopathological concordance and diagnostic agreement at multidisciplinary discussion between TBLC and surgical biopsy are good (70.8 and 76.9%, respectively).
- The combined findings generating the ‘probable’ UIP pattern (fibroblastic foci, patchy fibrosis and absence of features to suggest a non-UIP diagnosis) in cryobiopsy samples are strongly predictive of definite UIP in the corresponding SLB.
- IPF diagnosis made by multidisciplinary team on the basis of cryobiopsy is associated with higher mortality when compared with both other interstitial lung diseases and other fibrotic interstitial lung diseases; when a UIP pattern is found on cryobiopsy sample, this is associated with higher mortality compared with other histological patterns
- Cryobiopsy confirmed as **valid alternative to surgical lung biopsy** for making histopathological diagnosis in patients with suspected interstitial lung diseases in experienced centers
- New techniques for mediastinum sampling

GB Morgagni Hospital, Forlì Italy



Forlì, city center

THANK YOU FOR YOUR ATTENTION!



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Maddalena. Il mistero e l'immagine. Dal 27 marzo al 10 luglio 2022. Forlì