Transbronchial cryobiopsy increases diagnostic confidence in interstitial lung disease: a prospective multicentre trial

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Transbronchial cryobiopsy increases diagnostic likelihood of the first-choice diagnosis and confirms specified ILD diagnosis in a clinically relevant number of patients https://bit.ly/3hmd7HX

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ABSTRACT

Introduction: The accurate diagnosis of individual interstitial lung diseases (ILD) is often challenging, but is a critical determinant of appropriate management. If a diagnosis cannot be made after multidisciplinary team discussion (MDTD), surgical lung biopsy is the current recommended tissue sampling technique according to the most recent guidelines. Transbronchial lung cryobiopsy (TBLC) has been proposed as an alternative to surgical lung biopsy.

Methods: This prospective, multicentre, international study analysed the impact of TBLC on the diagnostic assessment of 128 patients with suspected idiopathic interstitial pneumonia by a central MDTD board (two clinicians, two radiologists, two pathologists). The level of confidence for the first-choice diagnoses were evaluated in four steps, as follows: 1) clinicoradiological data alone; 2) addition of bronchoalveolar lavage (BAL) findings; 3) addition of TBLC interpretation; and 4) surgical lung biopsy findings (if available). We evaluated the contribution of TBLC to the formulation of a confident first-choice MDTD diagnosis.

Results: TBLC led to a significant increase in the percentage of cases with confident diagnoses or provisional diagnoses with high confidence (likelihood ⩾70%) from 60.2% to 81.2%. In 32 out of 52 patients nondiagnostic after BAL, TBLC provided a diagnosis with a likelihood ⩾70%. The percentage of confident diagnoses (likelihood ⩾90%) increased from 22.7% after BAL to 53.9% after TBLC. Pneumothoraces occurred in 16.4% of patients, and moderate or severe bleeding in 15.7% of patients. No deaths were observed within 30 days.

Interpretation: TBLC increases diagnostic confidence in the majority of ILD patients with an uncertain noninvasive diagnosis, with manageable side-effects. These data support the integration of TBLC into the diagnostic algorithm for ILD.

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Introduction

The diagnostic process in a patient with interstitial lung disease (ILD) is challenging, but highly important due to its therapeutic and prognostic implications [1–4].

According to international guidelines [5–7] multidisciplinary team discussion (MDTD) is preferred over single-discipline decision making and is now the reference standard for ILD diagnosis [8–10]. The MDTD uses an approach proceeding from noninvasive to invasive diagnostic procedures. Flaherty *et al.* [8] introduced a methodology for MDTD which quantifies the diagnostic impact of additional information (*e.g.* clinicoradiological data, bronchoalveolar lavage (BAL), tissue sampling). MDTD with clinicoradiological discussion may provide a definite or confident provisional diagnosis, obviating tissue biopsy. When a first-choice diagnosis is made with low confidence (<70%) [11], biopsy is often necessary (unless contraindicated by age, disease severity or the presence of major comorbidities).

Historically, as the diagnostic yield of transbronchial lung forceps biopsy (TBLF) is limited, especially in patients with suspected idiopathic pulmonary fibrosis (IPF) [7], surgical lung biopsy (SLB) has been the reference standard tissue sampling technique. SLB leads to a histospecific diagnosis in 88.2% of cases [7], but is associated with significant side-effects: respiratory infection, procedure-associated acute exacerbation, bleeding, delayed wound healing, and procedure-related mortality of 1.7–1.9% for elective procedures [7, 12, 13]. The recent guideline summarised 23 studies which showed a mean overall mortality after SLB of 3.5% [7]. In an appreciable proportion of patients with an unclear diagnosis after clinicoradiological discussion in whom there is need for tissue sampling, a SLB is contraindicated because of its high periprocedural risk. Therefore, new and less-invasive approaches are needed.

Pajares *et al.* [14] and Griff *et al.* [15] reported that due to their relatively large size and lack of crush artifacts, transbronchial lung cryobiopsy (TBLC) specimens are superior to TBLF in overall diagnostic yield. Some mostly retrospective, single-centre studies [14, 16–20] have reported that TBLC adds substantial pathological information [7]. Moreover, TBLC may allow tissue acquisition in older patients and in those with advanced disease, not amenable to SLB [21]. However, due to the lack of adequate prospective trials addressing clinical decision making, the added diagnostic value of TBLC remains unclear. TBLC has a very low procedure-related mortality (0.2%), but peri-interventional bleeding has been reported to be as high as 56.4% [14, 22, 23] and pneumothoraces in up to 19.2% of cases [24]. Data from a recently published study indicate that mortality could be higher in patients with an acute decline and those with low baseline lung function and a bleeding complication [25]. Thus, the effect of TBLC on outcomes that are important to patients and its benefit–risk ratio are under debate.

We evaluated the contribution of TBLC to the diagnosis of ILD in an MDTD setting. To our knowledge, this is the first prospective international multicentre study to investigate the impact of TBLC on clinically important changes in diagnostic confidence and in the first-choice diagnosis by an independent central review board in a large study cohort.

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TABLE 1 Scheme of central multidisciplinary team discussion process with sequential steps adding additional information

Step	Information provided				Participants	Output
1	CR				Clinicians, radiologists	Consensus on diagnosis (yes/no) If yes, consensus on likelihood in %
2	CR	BAL			Clinicians, radiologists, pathologists	Consensus on diagnosis (yes/no) If yes, consensus on likelihood in %
3	CR	BAL	TBLC		Clinicians, radiologists, pathologists	Consensus on diagnosis (yes/no) If yes, consensus on likelihood in %
4	CR	BAL	TBLC	SLB	Clinicians, radiologists, pathologists	Consensus on diagnosis (yes/no) If yes, consensus on likelihood in %

CR: clinicoradiological data (patient characteristics: age, weight, height, smoking status, patient's history, patient's physical examination, serological testing for connective tissue disease and high-resolution computed tomography scan of thorax); BAL: bronchoalveolar lavage; TBLC: transbronchial lung cryobiopsy; SLB: surgical lung biopsy.

Methods

Patients with suspected idiopathic interstitial pneumonia (IIP) based on clinicoradiological criteria were included from five centres experienced in ILD. This prospective study was registered (NCT02563730), approved by the ethics committee at the University of Tübingen (035/2011MPG23), and confirmed by the ethics committees at the participating centres. The cases were prospectively collected based on predefined criteria by the central review board.

Patient selection and diagnostic procedures

The cohort consisted of consecutive patients aged >18 years with suspected IIP, considered by the local centre to need histopathological evaluation, due to diagnostic uncertainty following clinicoradiological evaluation. All patients who met inclusion and exclusion criteria underwent a bronchoscopy with BAL and TBLC (supplementary material). Exclusion criteria for study entry were age >80 years, a forced vital capacity <55% or a diffusion capacity for carbon monoxide <35%, bleeding disorders (international normalised ratio >1.3, partial thromboplastin time above normal range, thrombocytopenia <100 000 cells·μL^{-1} or treatment with acetylsalicylic acid or thienopyridines within the past 5 days), or a known systolic pulmonary arterial pressure >50 mmHg. All data were collected prospectively (supplementary material). It was up to each centre whether the BAL and TBLC were performed in one bronchoscopy or in two separate bronchoscopies.

Preparation of central MDTD

All clinical data were collected and standardised presentation was created. Radiological and pathological assessments were performed prior to the central MDTD (supplementary material).

Process of central MDTD

The central MDTD was performed using the methodology of Flaherty *et al.* [8, 17] with the stepwise provision of clinical data, high-resolution computed tomography (HRCT) interpretation by the radiologists, BAL data, discussion of TBLC findings by the pathologists, and finally, if available, discussion of SLB findings by the pathologists. HRCT images and illustrative histological sections were presented to the central MDTD, in order to replicate routine MDTD practice. After each step, central MDTD members defined the likelihood (censored at 5%) of their first-choice diagnosis (table 1). The likelihood level was assigned to the confidence of the diagnosis according to Ryerson *et al.* [26], currently the only standardised diagnostic likelihood ontology in ILD (table 2) (supplementary material).

TABLE 2 Likelihood of diagnosis of interstitial lung disease allocated to a confidence level of diagnosis according to Ryerson *et al.* [26].

	Confidence level of diagnosis
⩾90%	Confident diagnosis
70–89%	"Provisional diagnosis" with high confidence
<70%	"Provisional diagnosis" with low confidence (likelihood 51–69%) and unclassifiable (likelihood ⩽50%)
No consensus	

Primary and secondary end-points

The hypothesis of this study was that TBLC increases diagnostic confidence in ILD. Therefore, the primary end-point consisted of change in the percentage of cases with a first-choice diagnosis of ⩾70% (*i.e.* a definite diagnosis or a provisional diagnosis made with high confidence) [26], following the addition of cryobiopsy information. Secondary end-points consisted of 1) change in the percentage of cases with a first-choice diagnosis of ⩾90%; 2) change in diagnostic confidence with bronchoscopy (amalgamating BAL and TLBC data); 3) gaining a consensus MDTD diagnosis (if a consensus cannot be reached on clinicoradiological grounds); 4) revising a former clinicoradiological MDTD consensus diagnosis; and 5) the prevalence of bronchoscopy-associated side-effects.

The McNemar Chi-squared test was used to quantify changes in diagnostic confidence with the stepwise addition of data. A significance level of 5% was chosen. Patient characteristic and bronchoscopic parameters were given by mean and standard deviation or absolute and relative frequencies.

Results

At the five participating ILD centres, 139 patients were initially included in the study. 11 patients had to be excluded due to an incomplete diagnostic workup (figure 1), resulting in a final study population of 128 patients evaluated by the central MDTD group.

Data on patient characteristics and bronchoscopic procedures are shown in tables 3 and 4, respectively.

Change in diagnostic confidence level by the sequential diagnostic procedure

Figure 2 illustrates the confidence level for the first-choice consensus diagnosis after central MDTD for each diagnostic step (table 1).

In the central MDTD, consensus for a first-choice diagnosis could be reached after clinicoradiological discussion in 86.7%, after BAL in 89.5% (clinicoradiological *versus* BAL p=0.25) and after TBLC in 95.3% (BAL *versus* TBLC p=0.11; clinicoradiological *versus* TBLC p=0.005).

The percentage of cases with a diagnostic likelihood ⩾70% increased from 50.0% after clinicoradiological discussion to 60.2% after BAL and to 81.2% after TBLC (clinicoradiological *versus* BAL p=0.008; BAL *versus* TBLC p<0.0001; clinicoradiological *versus* TBLC p<0.0001; figure 2). A confident diagnosis (likelihood ⩾90%) was made in 11.7% of cases after clinicoradiological discussion, which significantly increased to 22.7% after BAL (p<0.0001), and to 53.9% after TBLC (p=0.001) (supplementary figure S1).

SLB was performed following local discussion in nine (7.0%) out of 128 cases (supplementary table S1). In six cases, SLB confirmed the TBLC diagnosis.

Figure 3 shows the allocation of cases with and without a definite or confident provisional diagnosis (defined by likelihood ⩾70% and likelihood <70%, respectively) following the stepwise addition of data.

With the addition of BAL data to clinicoradiological evaluation, the diagnostic likelihood increased to >70% in 31.3% of cases with likelihood <70% prior to bronchoscopy. In 10.9% of cases with a definite or confident provisional diagnosis after clinicoradiological evaluation, the diagnostic likelihood dropped below 70%. Overall, there was a nonsignificant increase in the prevalence of definite or confident provisional diagnoses with the addition of BAL (p=0.23).

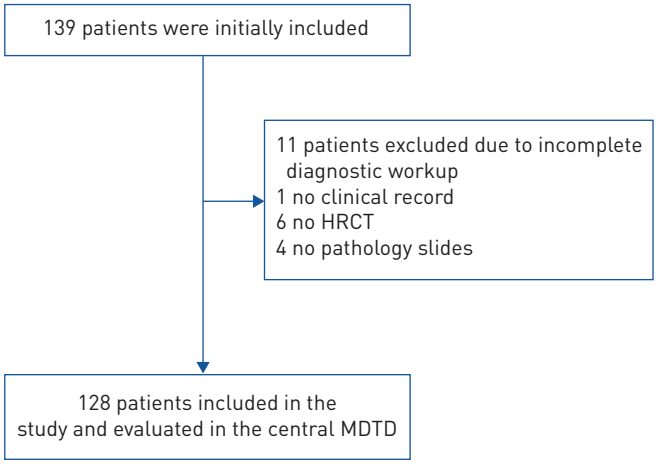

FIGURE 1 Study population. HRCT: high-resolution computed tomography; MDTD: multidisciplinary team discussion.

TABLE 3 Patient characteristics

Patients	128 (100)
Age years	62.6±12.2
⩾70	49 (38.3)
⩾75	16 (14.5)
Sex	
Female	56 (43.8)
Male	72 (56.2)
Weight kg	78.8±17.4
Height cm	167.8±9.6
Body mass index kg·m^{-2}	27.8±4.8
Symptoms	
Cough	89 (69.5)
Dyspnoea	101 (78.9)
Smoking status	
Nonsmoker	53 (41.4)
Ex-smoker	60 (46.9)
Current smoker	10 (7.8)
Smoking index pack-years	27.0±22.0
Updated Charlson score[#]	1.0
⩾2	36 (28.1)
History	
Familial ILD	7 (5.5)
Connective tissue disease a consideration	31 (24.2)
Exposure to drugs with potential of lung toxicity	20 (15.6)
Exposure to agents suspected to cause hypersensitivity pneumonitis	38 (29.7)
Pre-existing lung disease	18 (14.1)
Pre-existing tumour	12 (9.4)
Lung function	
TLC L/% pred	4.5±1.2/76.3±16.9
RV L/% pred	1.74±0.59/79.8±25.9
VC L/% pred	2.65±0.80/76.2±17.4
FEV_1 L/% pred	3.02±8.80/81.3±16.7
Specific resistance Pa·s^{-1}/% pred	0.60±0.31/67.0±26.6
D_{LCO} mmol·min^{-1}·kPa^{-1}/% pred	6.27±4.76/50.7±15.3
D_{LCO}/V_A mmol·min^{-1}·kPa^{-1}·L^{-1}/% pred	1.7±1.2/78.2±17.6
Serological testing elevated/normal	
Rheumatoid factor (reference <25 IU·mL^{-1})	9 (7.0)/79 (61.7)
ANA reference <1:80	66 (51.6)/57 (44.5)
ACA	0 (0)/26 (20.3)
ENA	12 (9.4)/89 (69.5)
CCP (reference <7 U·mL^{-1})	1 (0.8)/90 (70.3)
Scl-70	7 (5.5)/88 (68.8)
Coagulation profile	
Prothrombin time INR	1.00±0.08
Partial thromboplastin time s	24.5±2.2
Thrombocytes ×1000 cells·µL^{-1}	245±65.8
Acetylsalicylic acid treatment yes/no	27 (21.1)/82 (64.1)

Data are presented in n (%), mean±SD or median. Patient characteristics were unknown for body weight, height and body mass index in one case; smoking status was unknown in five cases; total lung capacity (TLC) (L) in 15 cases; TLC (% of reference) in 11 cases; residual volume (RV) (L) in 16 cases; RV (% of reference) in 15 cases; vital capacity (VC) (L) in three cases; forced expiratory volume in 1 s (FEV_1) (L) in four cases; FEV_1 (% of reference) in one case; specific resistance (Pa·s^{-1} and % of reference) in 34 cases; diffusing capacity of the lung for carbon monoxide (D_{LCO}) (mmol·min^{-1}·kPa^{-1}) in 13 cases; D_{LCO} (% of reference) in seven cases; D_{LCO} per alveolar volume (V_A) (mmol·min^{-1}·kPa^{-1}·L^{-1}) in 13 cases; D_{LCO}/V_A (% of reference) in 10 cases; and blood gas analyses in 28 cases. Serological testing was unknown for rheumatoid factor in 40 cases; for anti-nuclear antibodies (ANA) in four cases; for anti-centromere antibodies (ACA) in 102 cases; for autoantibodies to extractable nuclear antigen (ENA) in 27 cases; for autoantibodies to cyclic citrullinated peptide (CCP) in 37 cases; and for autoantibodies to anti-topoisomerase I (anti-Scl-70) in 33 cases. Coagulation profile was unknown in six cases. INR: international normalised ratio. [#]: according to QUAN *et al.* [27].

TABLE 4 Bronchoscopic intervention

Patients	128 (100)
TBLC	
Total biopsies	616
Biopsies per patient	4.8±1.3
TBLC procedures per patient	
<4	21 (16.4)
4	28 (21.9)
5	28 (21.9)
6	47 (36.7)
>6	4 (3.1)
Sedation	
General anaesthesia	100 (78.1)
Deep sedation	23 (18.0)
Intubation technique	
Rigid bronchoscopy	102 (79.7)
Flexible bronchoscopy	22 (17.2)
Size of cryoprobe	
Small 1.9 mm	91 (71.1)
Large 2.4 mm	36 (28.1)
Duration of TBLC min	11.7±5.7
Total duration of bronchoscopy min	27.2±9.2

Data are presented as n (%), n or mean±SD. Sedation was unknown in five patients; intubation technique was unknown in four patients; size of cryoprobe was unknown in one patient; duration of transbronchial lung cryobiopsy (TBLC) was unknown in 48 patients; and duration of bronchoscopy was unknown in 10 patients.

With the addition of TBLC data, the diagnostic likelihood increased to >70% in 62.7% of cases with likelihood <70% following BAL. In 6.5% of cases with a provisional diagnosis with high confidence or a confident diagnosis after BAL, the diagnostic likelihood dropped below 70%. Overall, there was a significant increase in the prevalence of definite or confident provisional diagnoses with the addition of TBLC ($p<0.0001$).

BAL and TBLC findings provided a definite diagnosis (diagnostic likelihood cutpoint of ⩾90%) in 47.8% of cases (supplementary figure S1).

After BAL, 51 patients lacked a consensus diagnosis or had a provisional diagnosis made with low confidence (likelihood <70%). In these cases, TBLC led to a definite or confident provisional diagnosis (likelihood ⩾70%) in 32 (62.7%) (figure 3).

Surgical lung biopsy

Based on local board decision SLB was performed in nine cases and confirmed the previous diagnosis in six cases. First-choice diagnosis changed in two cases. In one unclassifiable case after TBLC no consensus diagnosis could be achieved after SLB. The changes of confidence and/or diagnosis by surgical lung biopsy (n=9) are shown in figure 3 and supplementary figure S1 and table S1.

Subgroup analysis of the three most common first-choice diagnoses

The three most common first-choice diagnoses after clinoradiological evaluation were IPF, hypersensitivity pneumonitis and collagen vascular disease associated ILD. We analysed the development of the confidence and/or the change in the diagnosis for each of these subgroups, illustrated in supplementary figures S2–S4.

Final ILD diagnoses

Distribution of the final central MDTD-determined ILD diagnoses after TBLC, or after SLB if available, are shown in supplementary table S2.

TBLC-associated complications

TBLC-associated complications are summarised in table 5. No deaths occurred within 30 days.

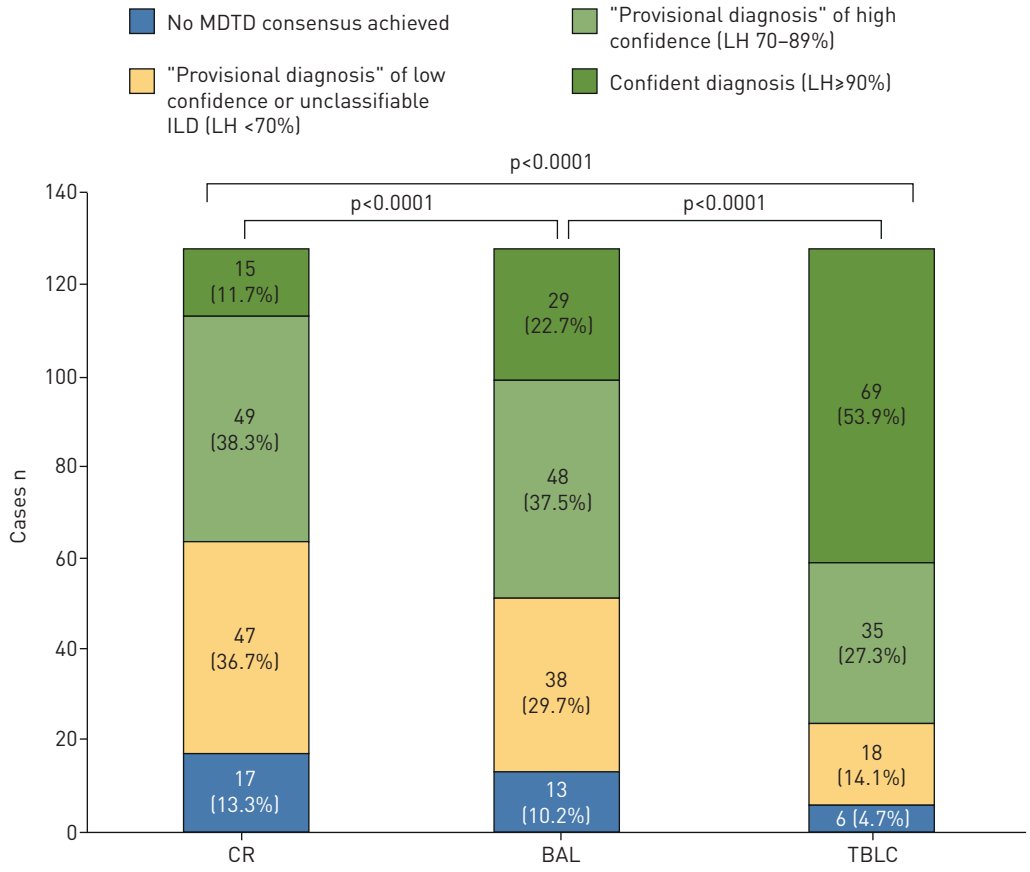

FIGURE 2 Change in diagnostic confidence level at sequential diagnostic steps. Data show central multidisciplinary team discussion (MDTD) consensus voting. Numbers show the absolute number of cases and the relative percentage in brackets. Clinicoradiological (CR) data: patient's history, physical examination, serological testing, lung function testing and thoracic high-resolution computed tomography. Additional bronchoalveolar lavage (BAL) was not performed in two patients; in these cases, the previous diagnostic likelihood (LH) of CR data was kept as the diagnostic likelihood for BAL. p-values were calculated using McNemar's test, comparing CR *versus* BAL, BAL *versus* TBLC and CR *versus* TBLC addressing achievement of consensus for a first-choice diagnosis.

Discussion

This prospective, multicentre, international study quantifies the value added by TBLC in ILD diagnosis and the acceptable side-effect profile. Although TBLC findings resulted in a change in the first-choice diagnosis in some cases, the major impact of the test was to increase the frequency with which definite or confident working diagnoses were made. As recently shown in the study by Walsh *et al.* [11], using the likelihood bands proposed by Ryerson *et al.* [26], the formulation of a confident working diagnosis of IPF (likelihood >70%) is a key threshold that impacts upon management (the use of antifibrotic therapy, a reduced need for surgical biopsy). Thus, our data indicate that TBLC data resulted, on average, in increased diagnostic confidence to a level likely to influence management.

In 81.2% of cases, a definite or confident provisional diagnosis was made by combining clinicoradiological evaluation and TBLC with BAL. In >60% of cases in whom diagnosis was neither definite nor made provisionally with high confidence prior to TBLC, the increase in diagnostic likelihood rose to ⩾70%. While there is currently no consensus on the exact level of diagnostic likelihood that obviates SLB, these data indicate that TBLC may reduce the need for SLB in many ILD patients with major pre-biopsy diagnostic uncertainty.

Based primarily on retrospective single-centre studies, TBLC has become an alternative, and in some institutions, a preferred procedure, to acquire lung tissue for histopathological evaluation [14–16, 18, 19, 21, 28–32].

In the recent American Thoracic Society/European Respiratory Society guideline, no recommendation was made (either for or against) for TBLC in patients with clinically suspected IPF and HRCT findings other than definite usual interstitial pneumonia as there was insufficient data available at the time the guideline were formulated. Specifically, the recent adequately powered study of Troy *et al.* [33], showing excellent

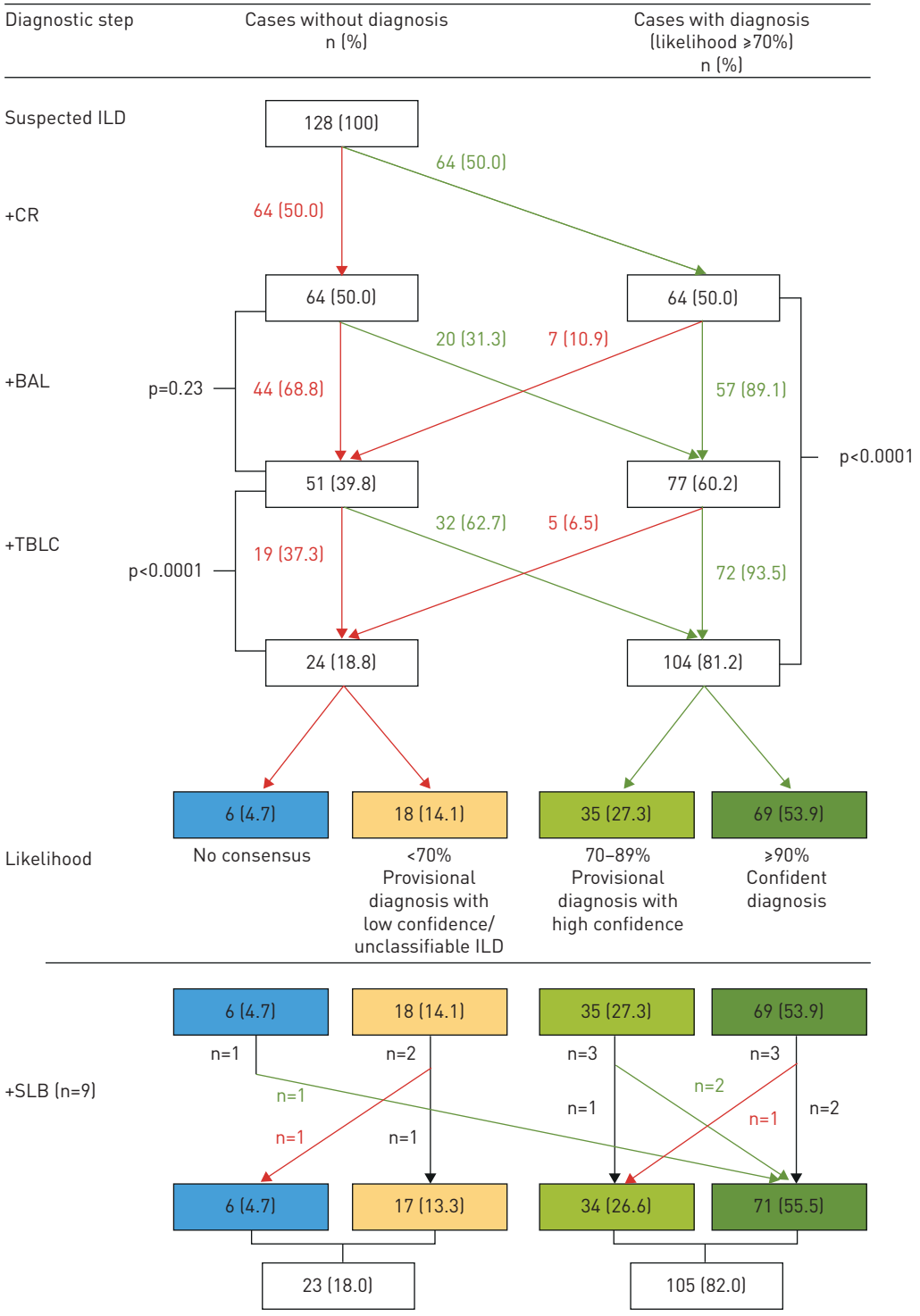

FIGURE 3 Allocation of cases with/without diagnosis (likelihood 70% as cut-off for "diagnosis") in the diagnostic workflow. The boxes on the left side show the remaining cases without diagnosis (likelihood <70% or no central multidisciplinary team discussion (MDTD) consensus). The boxes on the right side show the cases with diagnosis (likelihood ⩾70%) after the subsequent procedures, which are listed on the far left side. The boxes at the bottom summarise the diagnostic output of the diagnostic workflow with the diagnostic confidences. Bronchoalveolar lavage (BAL) had not been performed in two patients; in these cases, the previous diagnostic likelihood of clinicoradiological discussion was kept as diagnostic likelihood for BAL. Surgical lung biopsy (SLB) was performed in nine cases upon local centre's decision.

TABLE 5 Transbronchial lung cryobiopsy-associated complications

Patients	128 (100)
Bleeding	
No	37 (28.9)
Yes	90 (70.3)
Mild (suction alone)	70 (54.7)
Moderate (additional intervention)	19 (14.8)
Severe (prolonged monitoring or fatal)	1 (0.8)
Clinically relevant bleeding	
No (no bleeding or mild)	107 (84.3)
Yes (moderate or severe)	20 (15.7)
Intervention for bleeding control	
No	6 (4.7)
Yes	58 (45.3)
Suction alone	19 (14.8)
Cold saline	0 (0)
Vasoconstrictive drugs	0 (0)
Compression	28 (21.9)
Combination of interventions	11 (8.6)
Pneumothorax	
No	99 (77.3)
Yes	21 (16.4)
Insertion of/need for thoracic drainage	11 (8.6)

Data are presented as n (%). There was no information on peri-interventional bleeding in one case and no information on interventional bleeding control in 26 (20.3%) patients. Post-interventional pneumothorax was unknown in eight (6.3%) cases.

concordance (95%) between SLB and TBLC when TBLC findings are made with high confidence (in the majority of patients), was not available at the time of guideline formulation. We believe that this landmark study should prompt reconsideration of SLB, recommended in guidelines as the preferred tissue sampling technique despite a procedure-related mortality of 1.7–1.9% [7, 12, 13, 19, 34–36]. Our findings provide important complementary information on the impact of TBLC data on ILD multidisciplinary diagnostic confidence, an aspect not addressed by Troy *et al.* [33].

Our findings are highly relevant to the question of whether integration of TBLC in an ILD diagnostic algorithm can obviate the need for SLB, with its appreciable side-effects, in a sizeable proportion of cases. In this regard, the cardinal findings in our study were the significant increases in the frequencies of definite or confident working diagnoses (likelihood ⩾70%), from 50.0% to 60.2% with the addition of BAL data, and to 81.2% with the integration of TBLC information. It is not possible to quantify the exact impact of these findings in obviating SLB as the threshold for SLB varies between clinicians. However, in a recent survey of 404 clinicians examining the same clinical and computed tomography data, the majority of clinicians instituted antifibrotic therapy without the need for SLB when a confident working diagnosis of IPF (likelihood 70–90%) was made [11]. SLB was more often needed when IPF was diagnosed with low confidence. These data indicate that major increases in diagnostic confidence provided by TBLC, as seen in our study, must inevitably result in a parallel reduction in the need for SLB.

This consideration applies equally to the minority of clinicians, as in the study by Walsh *et al.* [11], who continue to recommend SLB unless a "definite" diagnosis (likelihood ⩾90%) has been made. In the current study, the frequencies of definite diagnoses (likelihood ⩾90%) increased from 11.7% to 22.7% with the addition of BAL data, and 53.9% with the integration of TBLC information (supplementary figure S1).

A change in the first-choice diagnosis after clinicoradiological discussion and TBLC was observed in 17 cases out of the 111 patients with a clinicoradiological consensus diagnosis (15.3%). Importantly, all 17 cases had a provisional diagnosis, made either with high confidence (n=5) or low confidence (n=12) after clinicoradiological discussion. None of the patients with a confident diagnosis after clinicoradiological discussion had a change in their diagnosis with addition of BAL and histological findings. The initial first-choice diagnosis "IPF" changed in eight (20.0%) out of 40 cases (supplementary figure S2), "hypersensitivity pneumonitis" in one (4.5%) out of 22 cases (supplementary figure S3) and "collagen vascular associated ILD" in three (16.7%) out of 18 cases after TBLC.

The most important side-effects of both biopsy techniques (TBLC and SLB) are the risks of infection, bleeding, pneumothorax, ILD exacerbation and the peri-interventional mortality.

A recent retrospective analysis by Pannu *et al.* [25] described a higher mortality after 30 and 90 days (five (2% and 2.5%, respectively) out of 197 patients); however, three patients already had a lung function decline pre-bronchoscopy, and the cause of death of the remaining two patients could not be clarified. Nevertheless, this highlights the need for careful patient selection and for follow-up >30 days after bronchoscopy with BAL and TBLC. SLB is associated with a 1.7% procedure-associated mortality [7, 12, 13, 22, 34, 36, 37]. In the present study no patient died within 30 days of the procedures. One patient died 5 weeks after the procedure, but was well for 3 weeks after an uncomplicated bronchoscopy, followed by an acute exacerbation. It should not be forgotten that the annual prevalence of acute exacerbations in IPF exceeds 5% and thus it is inevitable that acute exacerbations unrelated to bronchoscopic procedures will occur by chance in the succeeding months.

We observed clinically relevant bleeding in 20 (15.6%) patients. This corresponds to the bleeding rate in a prospective study of 359 patients using the same severity classification [38]. Bleeding severity was comparable to other previous data; however, there was a wide range [7, 14, 22, 23, 38]. These differences may be explained partially by different grading criteria which are dependent on subjective judgement of the bronchoscopist. Additionally, bleeding severity is influenced by the biopsy technique itself (how long and where to freeze, which cryoprobe was used) and whether an endobronchial balloon for bronchial blockage was placed prophylactically. Most importantly, there was no fatal bleeding after TBLC. Although bleeding is a frequent complication of TBLC, it is usually temporary and easily managed, whereas fatal bleeding is extremely rare. The incidence and severity of bleeding are favourably affected when safety recommendations are followed, especially intubation technique and prophylactic balloon placement. In 21 (16.4%) cases, a pneumothorax developed, which was higher than the 13.4% reported in other studies [7, 14, 22, 23]. However, only 11 (8.6%) of our cases required insertion of a chest tube.

It has been argued that a direct comparison of TBLC with SLB in the same patient is the only means of validating TBLC. This view may be appealing, but flawed when one considers that there is more to patient management than diagnostic yield alone. For both procedures, the value lies in the balance of benefit (yield) and risk. Yield can and should be compared between the two procedures and it is likely, based on accumulated data, that SLB will have an advantage in this regard. However, our study was not directed at this aspect. Romagnoli *et al.* [39] described in 21 patients a poor concordance between sequential TBLC and SLB. In contrast, in the multicentre trial of Troy *et al.* [33] in 65 patients, there was very good concordance between TBLC and SLB for both histopathological interpretation and final multidisciplinary diagnosis.

A limitation of our study is the fact that the prospective protocol did not specify rigorous criteria for the selection of patients 1) to undergo TBLC and 2) to undergo SLB if TBLC was inconclusive. In designing the protocol, we recognised that standardised patient selection offers major advantages in many contexts. However, the decision to undertake histological evaluation is based on the perception that the diagnosis is uncertain, and, as discussed earlier, there is no current consensus on whether biopsy is warranted if, for example, the likelihood of a diagnosis is 70–89% as opposed to <70%, and individual preferences at the local centres come into play. Therefore, our study design was based on the recommendation made by the Fleischner Society: that the decision to biopsy requires the integration of multidisciplinary discussion and individual patient wishes and is a case-by-case judgement at the local centre.

One limitation of the present study was the decision to standardise pre- and post-procedure diagnoses using expert group central review, as distinct from diagnoses made at participating centres. The use of expert central review is widespread in studies in ILD and this includes many IPF treatment studies (with central review of computed tomography and biopsy) as well as studies involving multidisciplinary evaluation, including the recent study by Troy *et al.* [33]. However, while this study design might improve the accuracy with which the added value of tests is defined against expert diagnostic evaluation, it did not allow a direct evaluation of the impact of BAL and TBLC upon diagnoses made in real-world practice.

The indication to include each patient in the study was based on the information provided by the clinicoradiological information; the results of the BAL were not considered here. In order to avoid a second bronchoscopy, BAL and transbronchial cryobiopsy were performed in one bronchoscopy in 81.3% of the cases. The combination of BAL and TBLC in one bronchoscopy corresponds to current practice in most centres. However, in order to analyse the influence of the respective diagnostic procedures, BAL and TBLC were considered separately.

To our knowledge, this is the first multicentre study to prospectively evaluate the impact of TBLC on diagnostic confidence in ILD. The findings highlight the potential increase in the benefit–risk balance of diagnostic evaluation when TBLC when is used as additional diagnostic tool prior to SLB in the diagnostic workup of suspected IIP in a MDTD setting. We stress that our study does not undermine the role of SLB in those cases in which a MDTD diagnosis cannot be made with high confidence following TBLC.

TBLC-associated side-effects exist, but they are manageable, especially in a standardised setting, with an experienced team and with prophylactic balloon placement.

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Authors' contribution: J. Hetzel, A.U. Wells, V. Poletti, U. Costabel and M. Häntschel designed the study. J. Hetzel, R. Musterle and M. Häntschel did the data analysis. A.U. Wells, T.V. Colby, U. Costabel and V. Poletti contributed to the data interpretation. R. Muche supervised the statistical analysis process. J. Hetzel, A.U. Wells, U. Costabel, T.V. Colby, R. Musterle, V. Poletti and M. Häntschel wrote the manuscript. A.U. Wells, U. Costabel, T.V. Colby, S.L.F. Walsh, J. Verschakelen, A. Cavazza, S. Tomassetti, C. Ravaglia and V. Poletti participated in the multidisciplinary team discussion or presented the data during the multidisciplinary team discussion. J. Hetzel, V. Poletti, R. Musterle and M. Häntschel presented the data during the multidisciplinary team discussion, S. Tomassetti and C. Ravaglia managed the data acquisition during the multidisciplinary team discussion. T.V. Colby and A. Cavazza did central evaluation of digitalised pathology data, S.L.F. Walsh and J. Verschakelen did central evaluation of the high-resolution computed tomography scans. J. Hetzel, S. Tomassetti, C. Ravaglia, M. Böckeler, W. Spengler, M. Kreuter, R. Eberhardt, K. Darwiche, A. Torrego, V. Poletti, V. Pajares and M. Häntschel performed the cryobiopsies at the participating centres. F. Fend, A. Warth, A. Dubini, D. Theegarten and E. Lerma did local pathology evaluation. M. Horger, C.P. Heußel, S. Piciucchi, T. Franquet did local evaluation of the high-resolution computed tomography scans.

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