Supplementary Methods

Bronchoscopic procedure

Bronchoscopy was performed in all patients, depending on the operator's choice, either with intubation with a flexible tube or a rigid tracheoscope/ bronchoscope. In every patient, a bronchoalveolar lavage (BAL) was performed according to local standards and evaluated for differential cytology. After BAL TBLC was performed as previously described using cryoprobes of 1.9 or 2.4 mm diameter (Erbe Elektromedizin GmbH, Tuebingen, Germany) and a freezing time aiming 5 (2.4mm probe) and 7 seconds (1.9mm probe) [1]. The freezing time was modified according to the freezing power and the size of the already harvested biopsies. Up to 6 TBLC were taken on one side, the goal being biopsies in two different lobes. Biopsies were taken under fluoroscopic control, prophylactic balloon placement was not mandatory.

Primary histopathological evaluation of the TBLC was performed at the local pathological institute. Based on the result, the local center decided whether to proceed to SLB.

Bleeding severity was graded semi-quantitatively as "no bleeding", "mild" (managed by suction alone), "moderate" (additional intervention necessary) or "severe" (prolonged monitoring necessary or fatal outcome). Moderate and severe bleeding were regarded as clinically relevant.

Data collection

Demographic data were documented for all patients including age, sex, weight, height, smoking status patient's history with signs for hypersensitivity, connective tissue disease or drug toxicity and coagulation profile as well as current and previous medication. Lung function testing including diffusion capacity for carbon monoxide, and serological testing were performed within one month before study entry.

Radiological assessment

High-resolution computed tomography (HRCT) was performed in all patients not more than two months before study entry. The primary radiological evaluation, on which the further diagnostic process was based, was made independently at the respective participating center. Radiological datasets of all patients were subsequently collected at the study center in Tuebingen.

Subsequently two ILD expert radiologists (JV and SLFW) reevaluated all HRCTs independently of each other for the cMDTD.

Pathological assessment

The local pathological institutes performed the workup of BAL and TBLC. Along with the BAL report the histological slides of the TBLC and SLB were transferred to the study center in Tuebingen for the central reviewing process.

All slides were scanned using the 'NanoZoomer' (by Hamamatsu Photonics K.K., headquarters Hamamatsu City, Shizuoka, Japan), at the Department of Preclinical Imaging and Radiopharmacy of Tuebingen. Scanned slides were subsequently evaluated individually by two ILD expert pathologists independently (TVC, AC) using the 'NDP.view2' viewing software (also by Hamamatsu Photonics K.K.).

Neither the central reviewing radiologists nor the central reviewing pathologists had any clinical, or radiological or any other additional information prior to the cMDTD.

Central multidisciplinary team discussion (cMDTD)

In this study all cases were discussed one after the other by the same cMDTD team during four consecutive days. Predefined ILD diagnoses and percentage steps of diagnostic likelihood were recorded with an electronical documentation of the voting process.

The entire team consisted of major ILD experts: two clinicians (AW and UC), two radiologists (JV and SLFW) and two pathologists (TVC and AC). The case presentations and additional documentation of the discussion were performed by VP, ST, CR, MB, RM, MH, JH.

The cMDTD proceeded step by step analogous to the Flaherty methodology [2]: Clinical information with patient's history, including family history, signs of hypersensitivity, connective tissue disease or drug toxicity, physical examination, lung function testing, including diffusion capacity for carbon monoxide, blood gas analysis and autoimmunological serological testing, were provided and evaluated individually by cMDTD participants in combination with the HRCT scan by both, clinicians and radiologists. HRCT was visualized on a high-resolution screen and presented in a standardized procedure, repeatedly at the request of cMDTD participants.

After interdisciplinary discussion the panel members tried to reach consensus on the first-choice ILD diagnosis and its likelihood on a 5% step scale. If no agreement could be achieved non consensus was documented **(step 1)**.

Thereafter, additional information of differential cytology of BAL was provided and, in combination with the formerly provided information of step 1, revaluated **(step 2).**

In **step 3** both pathologists demonstrated their findings to the other cMDTD participants on a large screen monitor, using the digitalized high-resolution scanned slides of TBLC, followed by the 3rd consensus discussion.

In 9 cases the local MDTD of the respective centres performed a SLB thus providing additional information for the cMDTD. Presentation of the histology was done in the same way as for step 3, followed by consensus discussion **(step 4)**.

Statistical methods

Statistical evaluation was performed in cooperation with the Institute of Epidemiology and Medical Biometry at the University of Ulm. The avoidance of the need for SLB in 20% of the cases was considered as clinically relevant.

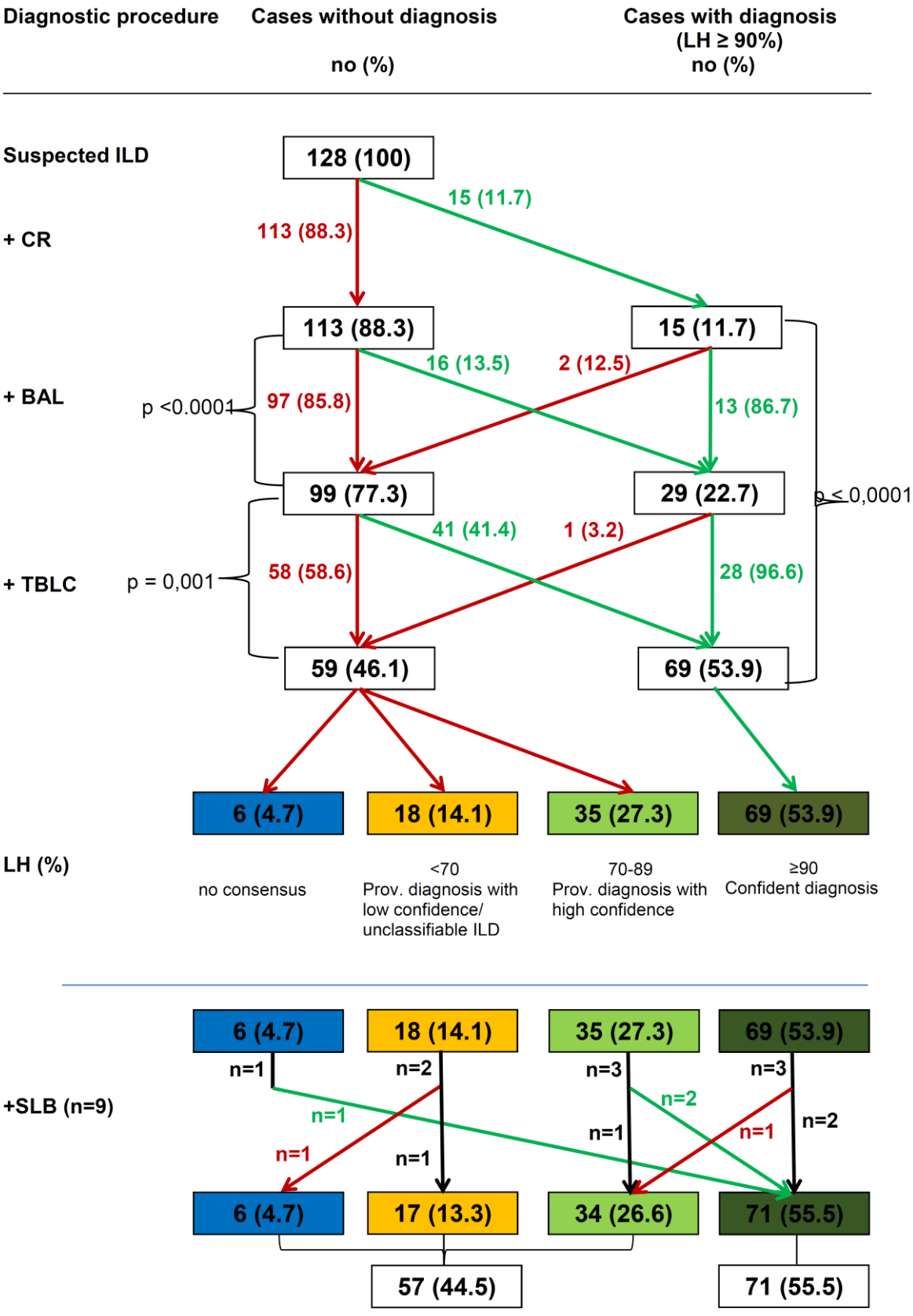
Supplementary Results

Supplement Table S1. Cases with SLB

Cases with SLB (n=9)				
Case	**Cons. diagn. after TBLC**	**LH (%)**	**Cons. diagn. after SLB**	**LH (%)**
1	No cons	-	DIP	100
2	IPF	70	IPF	100
3	unclassifiable	-	No cons	-
4	HP	75	HP	90
5	HP	100	HP	100
6	unclassifiable	-	unclassifiable	-
7	IPF	90	IPF	100
8	HP	90	HP	80
9	Familial IF	80	Drug related ILD	70

Cons. Diagn. – consensus diagnosis; DIP – desquamative interstitial pneumonia; Drug related ILD – drug related interstitial lung disease; HP – hypersensitivity pneumonitis; Familial IF – familiar idiopathic pneumonia; IPF – idiopathic pulmonary fibrosis; LH – diagnostic likelihood; No cons – no consensus diagnosis; SLB – surgical lung biopsy; TBLC – transbronchial lung cryobiopsy; Unclassifiable – unclassifiable ILD

Figure S1. Allocation of cases with/ without diagnosis (LH 90% as cut-off for "diagnosis") in the diagnostic workflow



The boxes on the left side show the remaining cases without diagnosis (LH <90% or no cMDTD consensus). The boxes on the right side show the cases with diagnosis (LH ≥ 90%) after the subsequent procedures, which are listed on the very left side.

The boxes at the bottom summarize the diagnostic output of the diagnostic workflow with the diagnostic confidences.

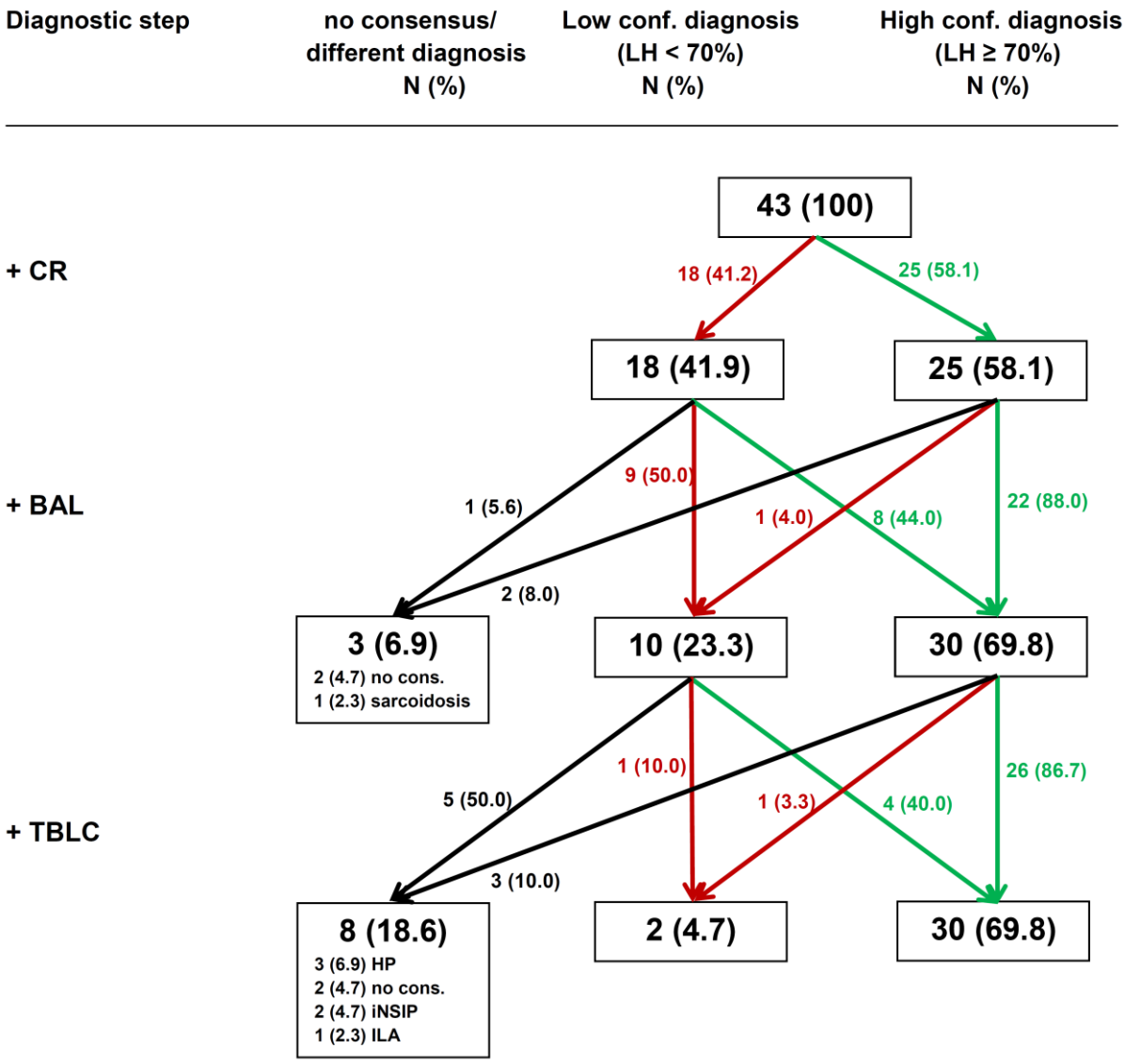
CR provided a definitive diagnosis in 15 cases. The entire process provided a definitive diagnosis in 69 patients. This means that BAL and TBLC lead to a definitive diagnosis in 69 – 15 = 54 patients. Out of 113 patients without a definitive diagnosis after CR this results in additional 54/ 113 (47.8%) cases with definitive diagnosis.

BAL was not performed in 2 patients. In these cases the previous diagnostic likelihood of CR was kept as diagnostic likelihood for BAL.

SLB was performed in 9 cases upon local center's decision.

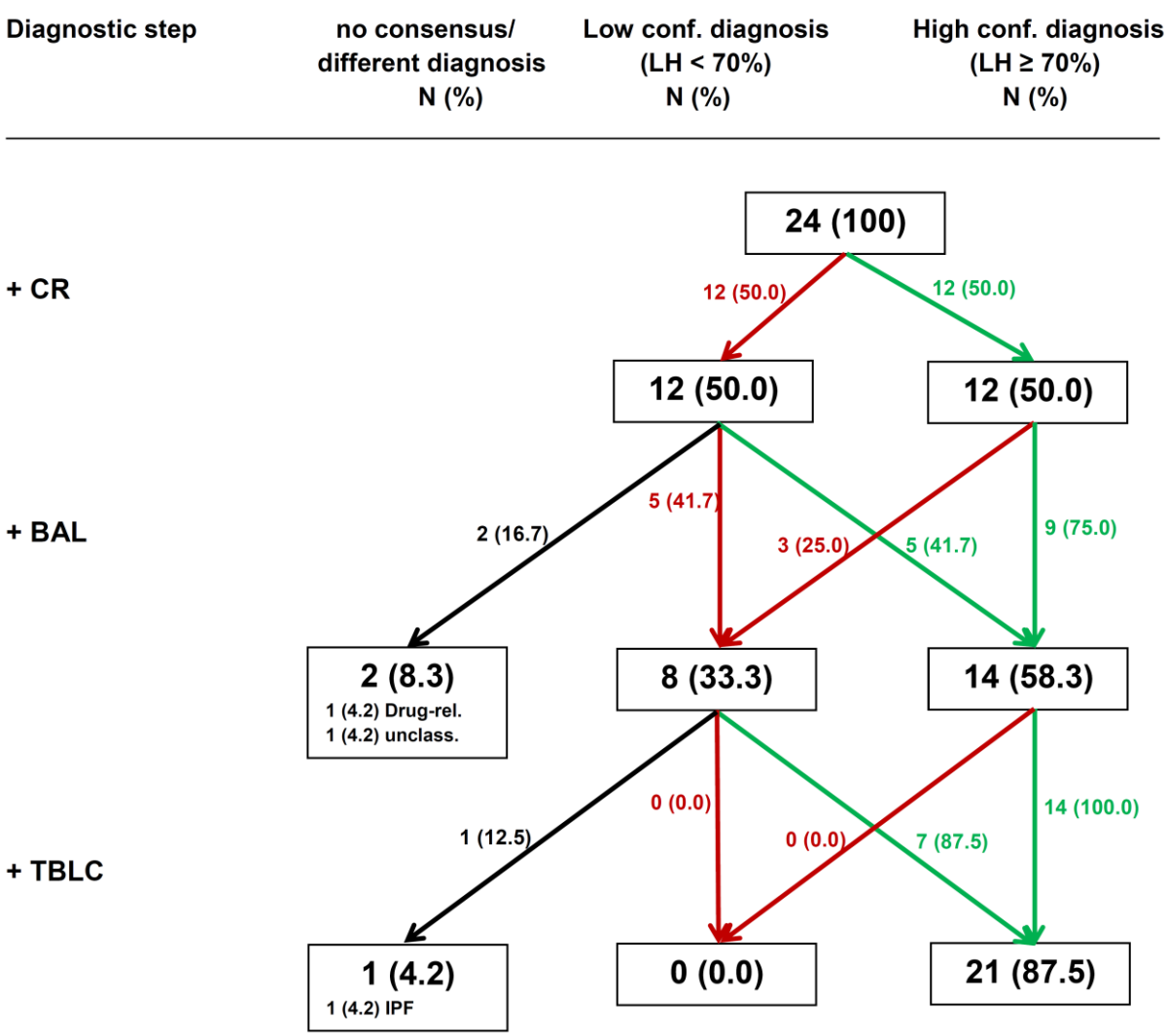
LH – likelihood; SLB – surgical lung biopsy; p-values were calculated by McNemar test, comparing CR vs BAL, BAL vs TBLC and CR vs TBLC addressing cases with and without diagnosis by using LH 90% as cut-off.

Figure S2. Development of the first-choice diagnosis after BAL and TBLC in patients having a first-choice diagnosis of IPF after clinicoradiological discussion



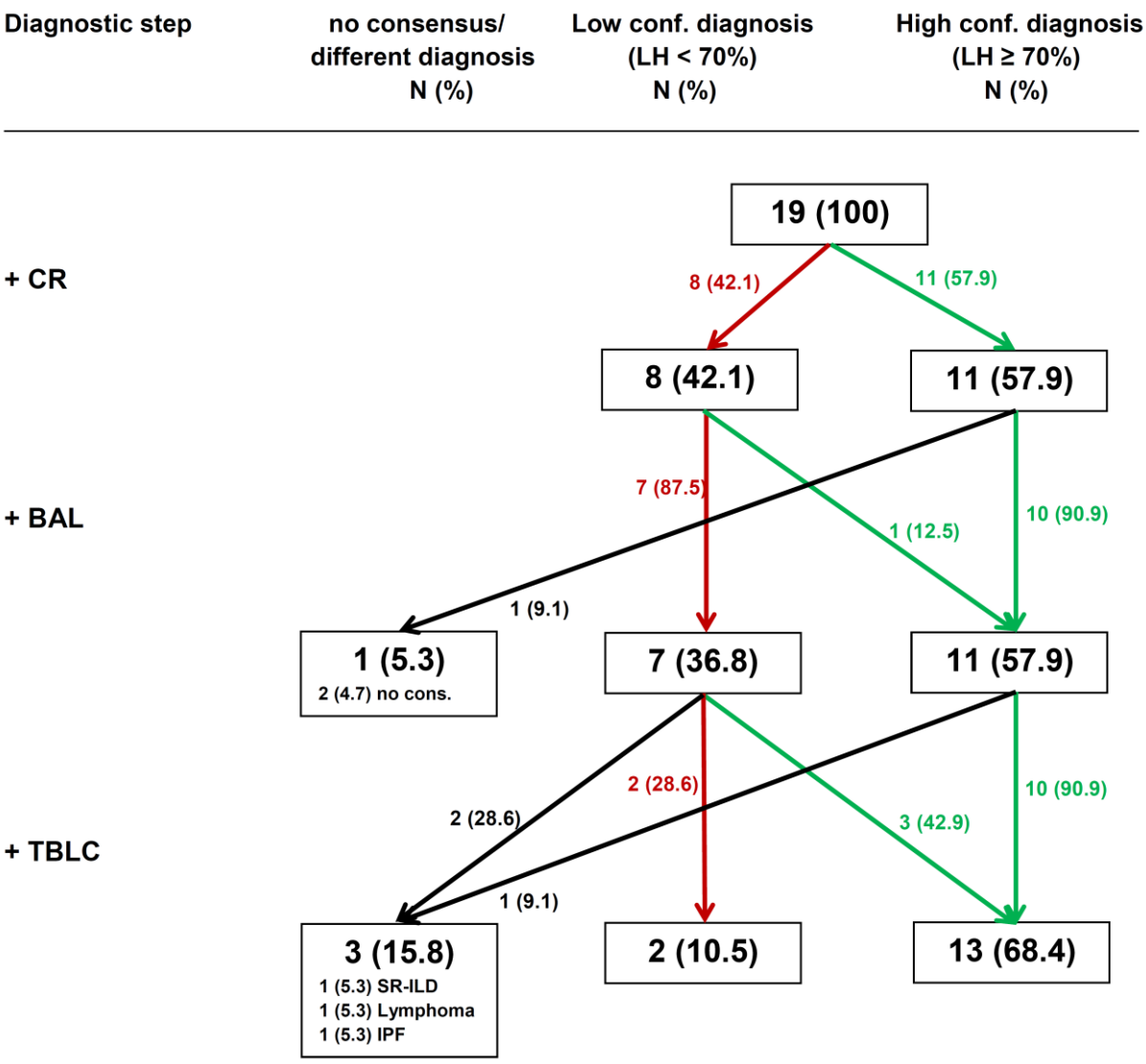
LH – likelihood; CR – clinicoradiological evaluation; BAL – bronchoalveolar lavage; TBLC – transbronchial lung cryobiopsy; no cons. – no consensus diagnosis; HP – hypersensitivity pneumonitis; iNSIP – idiopathic nonspecific interstitial pneumonia; ILA – interstitial lung abnormalities.

Figure S3. Development of the first-choice diagnosis after BAL and TBLC in patients having a first-choice diagnosis of hypersensitivity pneumonitis after clinicoradiological discussion



LH – likelihood; CR – clinicoradiological evaluation; BAL – bronchoalveolar lavage; TBLC – transbronchial lung cryobiopsy; Drug-rel. – drug-related interstitial lung disease; unclass. – unclassifiable interstitial lung disease; IPF – idiopathic pulmonary fibrosis

Figure S4. Development of the first-choice diagnosis after BAL and TBLC in patients having a first-choice diagnosis of collagen vascular disease associated ILD after clinicoradiological discussion



LH – likelihood; CR – clinicoradiological evaluation; BAL – bronchoalveolar lavage; TBLC – transbronchial lung cryobiopsy; no cons. – no consensus; SR-ILD – smoking related interstitial lung disease; IPF – idiopathic pulmonary fibrosis

Table S2. Distribution of first choice diagnosis

Distribution of first choice diagnosis	
Categories and Subcategories	**N= 128 (100%)**
Major IIPs	**52 (39.1)**
Idiopathic pulmonary fibrosis (IPF)	37 (28.9)
Idiopathic nonspecific interstitial pneumonia (iNSIP)	7 (5.5)
Respiratory bronchiolitis Interstitial lung disease (RB ILD)	4 (3.1)
Desquamative interstitial pneumonia (DIP)	1 (0.8)
Cryptogenic organizing pneumonia (COP)	3 (2.3)
Rare IIPs	**3 (2.3)**
Idiopathic lymphoid interstitial pneumonia (LIP)	1 (0.8)
Idiopathic pleuroparenchymal fibroelastosis (iPPFE)	1 (0.8)
Unclassifiable IIPs	**3 (2.3)**
Other ILDs	**57 (44.5)**
Hypersensitivity pneumonitis (HP)	27 (21.1)
Collagen vascular disease (CVD)	17 (13.3)
Familial interstitial pneumonia (Familial IF)	6 (4.7)
Coexisting Patterns	2 (1.6)
Drug related interstitial pneumonia (Drug related ILD)	5 (3.9)
Pulmonary Langerhans cell histiocytosis (PLCH)	1 (0.8)
Granulomatous lung disease	**3 (2.3)**
Sarcoidosis	2 (1.6)
Other granulomatosis	1 (0.8)
Others	**4 (3.1)**
Carcinomatous lymphangitis	1 (0.8)

Bronchiolitis (Infectious / respiratory - IB/ RB)	2 (1.6)
Unspecified Non-ILD	1 (0.8)
No consensus	**6 (4.7)**

The numbers indicate the absolute amount of cases. The cases are categorized in accordance with Travis et al.[3] as major idiopathic interstitial pneumonias (Major IIPs), rare idiopathic interstitial pneumonias (Rare IIPs), unclassifiable idiopathic interstitial pneumonias (Unclass. IIPs), other interstitial lung disease (other ILDs), granulomatous lung diseases, other non-pulmonary differential diagnoses (Others) and no consensus.

IIP – idiopathic interstitial pneumonias; IPF – idiopathic pulmonary fibrosis; iNSIP – idiopathic nonspecific interstitial pneumonia; RB ILD – respiratory bronchiolitis interstitial lung disease; DIP – desquamative interstitial pneumonia; COP – cryptogenic organizing pneumonia; LIP – idiopathic lymphoid interstitial pneumonia; iPPFE – idiopathic pleuroparenchymal fibroelastosis; HP – hypersensitivity pneumonitis; CVD – collagen vascular disease; Familiar IF – Familiar interstitial pneumonia; Coex. Patterns – coexisting patterns; Drug rel. ILD – Drug related interstitial lung disease; PLCH – pulmonary Langerhans cell histiocytosis; Other gran. – other granulomatosis; Car. Lymph. – Carcinomatous Lymphangitis; IB/ RB – infectious bronchiolitis/ respiratory bronchiolitis.

Supplementary References

1. Babiak A, Hetzel J, Krishna G, Fritz P, Moeller P, Balli T, Hetzel M. Transbronchial cryobiopsy: a new tool for lung biopsies. *Respiration; international review of thoracic diseases* 2009: 78(2): 203-208.
2. Flaherty KR, King TE, Jr., Raghu G, Lynch JP, 3rd, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q, Murray S, Lama VN, Gay SE, Martinez FJ. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *American journal of respiratory and critical care medicine* 2004: 170(8): 904-910.
3. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, Ryerson CJ, Ryu JH, Selman M, Wells AU, Behr J, Bouros D, Brown KK, Colby TV, Collard HR, Cordeiro CR, Cottin V, Crestani B, Drent M, Dudden RF, Egan J, Flaherty K, Hogaboam C, Inoue Y, Johkoh T, Kim DS, Kitaichi M, Loyd J, Martinez FJ, Myers J, Protzko S, Raghu G, Richeldi L, Sverzellati N, Swigris J, Valeyre D. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *American journal of respiratory and critical care medicine* 2013: 188(6): 733-748.