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Original Research

Risk factors of clinically significant complications in transbronchial lung cryobiopsy: A prospective multi-center study

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ABSTRACT

Background: The use of a transbronchial lung cryobiopsy (TBLC) is increasing as a diagnostic method of interstitial lung diseases (ILD). This study aimed to evaluate risk factors associated with clinically significant complications of TBLC in ILD patients.

Methods: Patients referred to Kuopio or Tampere university hospitals, in Finland, for a suspected ILD were included. The TBLC was performed in an outpatient setting for 100 patients. Patients were mechanically ventilated in general anesthesia. Fluoroscopy guidance and prophylactic bronchial balloon were used. Complications, such as bleeding, pneumothorax, infections, and mortality were recorded. Moderate or serious bleeding, pneumothorax, or death ≤90 days were defined as clinically significant complications. A multivariable model was created to assess clinically significant complications.

Results: The extent of traction bronchiectasis (Odds ratio [OR] 1.30, Confidence interval [CI] 1.03–1.65, p = 0.027) and young age (OR 7.96, CI 2.32–27.3, p = 0.001) were associated with the risk of clinically significant complications whereas the use of oral corticosteroids ≤30 days before the TBLC (OR 3.65, CI 0.911–14.6, p = 0.068) did not quite reach statistical significance. A history of serious cough was associated with the risk of pneumothorax (OR 4.18, CI 1.10–16.0, p = 0.036). Procedure associated mortality ≤90 days was 1%.

Conclusion: The extent of traction bronchiectasis on HRCT and young age were associated with the risk of clinically significant complications whereas oral corticosteroid use did not quite reach statistical significance. A history of serious cough was associated with the risk of clinically significant pneumothorax.

1. Introduction

The diagnosis of an interstitial lung disease (ILD) is important to achieve since the management options of different disease types are evolving [1]. Surgical lung biopsy (SLB) is a part of the diagnosis in a minority of patients. The use of a transbronchial lung cryobiopsy (TBLC) is increasing as a diagnostic method of ILDs since it has been reported to be safer and more cost effective than the SLB and to achieve a better diagnostic yield than a traditional forceps transbronchial biopsy [2,3]. The latest international guideline and expert panel report concluded that TBLC can be used in the diagnosis of ILD [4].

Several studies have described the procedure, diagnostic yield, and complications in TBLC, but the evaluation of risk factors associated with complications has been scarce [5–11]. The prevalence of bleeding and pneumothorax have revealed large variations (6–70% and 0–20%, respectively), whereas diagnostic yield has been reported as 66–86%,

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and procedure associated mortality has been low 0–3% [5–17]. Only few of the studies have reported differences between patients with and without complications [12–15] and even fewer have evaluated the risk factors of procedural complications in a multivariable model [16–18].

More knowledge of the risk factors of complications associated with the TBLC is needed. The aim of this study was to evaluate the preoperative risk factors of clinically significant complications of TBLC in ILD patients. We created multivariable models using all the feasible biological associations available to achieve a real-life model. In addition, we describe the Finnish TBLC procedure for the first time and report complication rates and diagnostic yield.

2. Methods

2.1. Patient selection and data collection

The patients of this study were prospectively recruited from Kuopio University Hospital (KUH) and Tampere University Hospital (TAUH) pulmonology clinics between January 2015 and December 2019. Inclusion criteria included a referral to a tertiary university hospital (KUH or TAUH) for a suspected ILD and a requirement of a histological investigation in the diagnosis of ILD. A written informed consent was obtained from all participants. Exclusion criteria included acute myocardial infarct, acute and untreated heart disease, active tuberculosis, anticoagulation treatment that could not be withheld, abnormal bleeding history or bleeding parameters (thrombocytes, international normalized ratio [INR], activated partial thromboplastin time [APTT]), forced expiratory volume in 1 s (FEV1) < 50%, total lung capacity <50%, diffusion capacity to carbon monoxide (DLCO) < 50%, mean pulmonary artery pressure >55 mmHg in echocardiogram (ECHO), irreparable hypoxia (arterial pressure of oxygen <8 kPa). Patients with body mass index (BMI) > 30 kg/m^2 were excluded if the mean pulmonary artery pressure in ECHO was >55 mmHg. Anticoagulants and antiplatelets (except for acetyl salicylic acid [ASA]) were withheld at the time of biopsy [19].

All 100 patients had computed tomography (CT) scans and a Leicester Cough Questionnaire (LCQ) obtained before the TBLC [20]. Patient data, comorbidities, medication (Supplementary Tables S1 and S2), pulmonary function tests, acute exacerbations of ILD, and 30-day and 90-day mortality rates were collected from the electronic medical records of the hospitals. Exacerbation was defined according to Collard et al. [21]. The use of oral corticosteroids was recorded within 30 days before the TBLC. The indications for oral corticosteroid use were suspected ILD, cough, drug induced lung reaction, or dyspnea after liver biopsy. The oral corticosteroids used were prednisolone and methylprednisolone, daily dose ranging from 5 mg to 40 mg. The diagnosis was concluded according to the international guidelines at the time and handled in a meeting of multidisciplinary discussion (MDD). In 2015–2018 diagnoses for idiopathic pulmonary fibrosis (IPF) were made according to the 2011 international ATS/ERS guideline [22] and after 2018 according to the 2018 international ATS/ERS guideline [23]. In addition, idiopathic interstitial pneumonias (IIP) were diagnosed according to available international guideline [24]. The study protocol was approved by the Research Ethics Committee of the Northern Savo Hospital District (statement 80/2014) and Tampere University Hospital (R15149), and the study was conducted in compliance with the Declaration of Helsinki (as revised in 2013).

2.2. The cryobiopsy protocol

All the study subjects had TBLC and bronchoalveolar lavage (BAL) performed in an operating room in an outpatient setting. Altogether two operators in KUH and four in TAUH performed the TBLC. Due to a long distance, 42% of patients were admitted to the hospital on the previous evening. The TBLC was conducted on intubated patients in general anesthesia using mechanical ventilation, according to the current guideline and expert panel report [4]. A flexible therapeutic bronchoscope with a 2.8 mm working channel and a 6.2 mm outer diameter (Olympus BF-1T180 Evis Exera II) was used to obtain BAL. Preferred biopsy site was previously decided by the operator according to the CT findings. A deflated balloon blocker (Fogarty® balloon) was inserted through the endotracheal tube's side port just above the preferred biopsy site and a multiple use cryoprobe (KUH 2.4 mm; TAUH 1.9 mm; ERBE, Tübingen, Germany) through the operating channel of the flexible bronchoscope. Fluoroscopy guidance was used to reassure 1–2 cm distance from the pleura. The cryoprobe was cooled for approximately 5 s and the sample was extracted along with the bronchoscope and thawed in saline at a room temperature. Simultaneously, the balloon blocker was inflated prophylactically to prevent bleeding. The blocker remained inflated until re-insertion of the bronchoscope. In the absence of bleeding the blocker was slowly deflated. Up to six biopsies (aim of 5 biopsies [mean 5, range 1–6]) were obtained in different segments of one or two lobes. A chest x-ray was taken approximately 30–60 min after the procedure to exclude post-operative pneumothorax. Patients were monitored in the recovery ward until fully awake and discharged at the same day unless complications or a long distance to home required otherwise. Lung tissue samples were transferred from saline to 10% formalin within 10 min. All tissue slides were stained by Hematoxylin-eosin. The pathologists of each hospital analyzed the samples as routine clinical diagnostics.

Complications, such as bleeding, pneumothorax, and infections, were recorded. The bleeding and pneumothorax classifications were adapted from previous publications [7,25–27] (Supplementary Appendix). Moderate and severe bleeding or pneumothorax were defined as clinically significant bleeding or pneumothorax, respectively. Further, the presence of either clinically significant bleeding or pneumothorax, or both, or an admittance to intensive care unit (ICU), or death within 90 days after the TBLC were defined as clinically significant complications. Infection was diagnosed by clinical and radiological findings. Two out of the three patients with infection also had moderate bleeding. The third infection complication did not prolong the TBLC procedure or hospitalization after the TBLC and was not included in the clinically significant complication.

2.3. The CT imaging

The extent of several specific high-resolution CT (HRCT) patterns was assessed separately in three zones of each lung as described previously [28]. In addition, two radiologists agreed on a consensus of the HRCT scans according to the 2018 international statement as a definite usual interstitial pneumonia (UIP), probable UIP, indeterminate with UIP, and alternative diagnosis [23]. The inter-observer agreement between the two radiologists was moderate to good regarding the different HRCT patterns (honeycombing 0.655, emphysema 0.697, and traction bronchiectasis 0.440).

2.4. Statistical analyses

Data were expressed as means and standard deviations (SD) or frequencies with percentages for categorical variables. Independent-samples T-test was used for normally distributed parameters and Mann-Whitney U tests for not normally distributed continuous variables, and Chi-square test was used for distribution counts when appropriate. LCQ total score, glomerular filtration rate (GFR), and age cut-off values were determined with greatest sensitivity and specificity (Youden index). Variables for the multivariable models of clinically significant complications in TBLC were selected using expert evaluation and literature [29]. The variables with a plausible association to the complication (bleeding, pneumothorax) were selected (Table 1). A backward stepwise logistic regression model was used. A receiver operating characteristic (ROC) curve was created to present the model's ability to evaluate clinically significant complications. Inter-observer agreements

Table 1
Characteristics of the study subjects.

Variable	Total (N = 100)	No or mild complication (N = 68)	Clinically significant complication (N = 32)
Gender (male)	60 (60)	45 (66)	15 (47)
Age[#] (years)	66.1 (9.07)	67.9 (6.84)	62.1 (11.7)
BMI[#] (kg/m^2)	28.5 (4.51)	28.5 (4.56)	28.4 (4.49)
FVC%[#]	81.0 (14.6)	81.9 (13.6)	79.1 (16.6)
DLCO%[#]	61.4 (14.1) 99/100	61.0 (13.4)	62.3 (15.5) 31/32
LCQ total score[#]	15.7 (3.82)	16.3 (3.48)	14.4 (4.27)
GFR[#]	80.9 (16.5)	78.0 (15.3)	87.3 (17.3)
ASA	20 (20)	17 (25)	3 (9)
Oral corticosteroids	15 (15)	6 (9)	9 (28)
PH	1 (1)	–	1 (1)
Reticulation score[#]	8.87 (3.19) 88/100	8.57 (3.04) 62/68	9.60 (3.48) 26/32
Emphysema score[#]	1.08 (2.37) 97/100	1.13 (2.35) 67/68	0.950 (2.45) 30/32
Traction bronchiectasis score[#]	3.23 (2.38) 97/100	2.84 (2.06) 67/68	4.10 (2.82) 30/32
Center, KUH/ TAUH	47 (47)/ 53 (53)	39 (57)/29 (43)	8 (25)/24 (75)
Upper-medium lobe/lower lobe	6 (6)/94 (94)	2 (3)/67 (97)	4 (13)/28 (88)

Numbers are presented as N (%) or mean (standard deviation, SD)[#]. BMI = body mass index, FVC% = forced vital capacity percent predicted, DLCO% = diffusion capacity to carbon monoxide percent predicted, LCQ = Leicester Cough Questionnaire, GFR = glomerular filtration rate, ASA = acetyl salicylic acid, PH = pulmonary hypertension, KUH = Kuopio university hospital, TAUH = Tampere university hospital. Note: DLCO% and pulmonary hypertension were not included in the multivariable model.

of the HRCT patterns are presented as a kappa (κ) value: good agreement κ = 0.61–0.80, moderate agreement κ = 0.41–0.60 and fair agreement κ = 0.21–0.40. P-values < 0.05 were considered statistically significant. IBM statistics SPSS software, version 27.0, was used in the statistical analysis.

3. Results

3.1. Patient characteristics

The clinical characteristics of the 100 TBLC patients are presented in Table 1. The mean FEV1 of the study population was 82.6% (SD 13.5).

3.2. The occurrence of complications

Thirteen out of the 18 patients with pneumothorax (72%) needed intervention, of which two were thoracoscopic operations (Table 2). Thirty-nine percent of the patients were discharged on the same day and 49% on the next day of the procedure. None of the patients died within 30 days after the TBLC, whereas two patients died within 90 days after the TBLC. One of them (non-specific interstitial pneumonia, NSIP) had a suspicion of an acute exacerbation of ILD after the procedure. The other (IPF) died due to an acute cardiac arrest which had no connection to the TBLC operation. Thus, the procedure related mortality was 1%.

Table 2
The number of patients with complications.

Complication	N (%)
Bleeding	
no	59 (59)
mild	22 (22)
moderate	19 (19)
severe	0
clinically significant (moderate + severe)	19 (19)
Pneumothorax	
no	82 (82)
mild	5 (5)
moderate	11 (11)
severe	2 (2)
clinically significant (moderate + severe)	13 (13)
Clinically significant complication[a]	32 (32)[b]
Infection	3 (3)
Subcutaneous emphysema	1 (1)
ICU ≤ 90 days	2 (2)
Death ≤ 90 days	2 (2)

[a] Includes clinically significant bleeding, clinically significant pneumothorax, patients admitted to ICU within 90 days or died within 90 days.
[b] Note that same patient may have had both bleeding and pneumothorax, or admitted to ICU due to bleeding/pneumothorax, or had a complication and died for another reason. Therefore, the numbers do not add up. ICU = intensive care unit.

3.3. The risk factors in multivariable analysis

The main factors associated with the risk of clinically significant complications were the extent of traction bronchiectasis on HRCT and young age whereas oral corticosteroid use did not quite reach statistical significance (Table 3, Fig. 1). The use of oral corticosteroids and the site of the procedure were the main factors associated with the risk of clinically significant bleeding. The use of ASA was not associated with the risk of bleeding. The factors associated with the risk of clinically significant pneumothorax were lower LCQ total score and young age (Table 3). Emphysema or the extent of fibrosis on HRCT were not associated with the risk of pneumothorax.

3.4. Final diagnosis and diagnostic yield

Histopathological pattern was obtained from 87 out of the 100 patients, diagnostic yield being 87%. The radiological re-assessment was made according to the 2018 international ATS/ERS guideline [23] for this study and histopathological diagnoses were those from the original routine diagnostics (Table 4).

Table 3
The multivariable models.

Variable	Odds ratio	95% Confidence interval	P-value
The risk factors of clinically significant complications			
Oral corticosteroids	3.65	0.911–14.6	0.068
Traction bronchiectasis score	1.30	1.03–1.65	0.027
Age ≤ 59.5 years	7.96	2.32–27.3	0.001
Center, KUH reference			
TAUH	2.97	1.00–8.77	0.050
The risk factors of clinically significant bleeding			
Oral corticosteroids	3.55	1.00–12.6	0.050
Lobe, lower	0.106	0.017–0.678	0.018
Center, KUH reference			
TAUH	3.11	0.900–10.7	0.073
The risk factors of clinically significant pneumothorax			
Age ≤ 59.5 years	7.56	2.06–27.8	0.002
LCQ total score ≤ 14.6	4.18	1.10–16.0	0.036

KUH = Kuopio University Hospital, TAUH = Tampere University Hospital, LCQ = Leicester Cough Questionnaire.

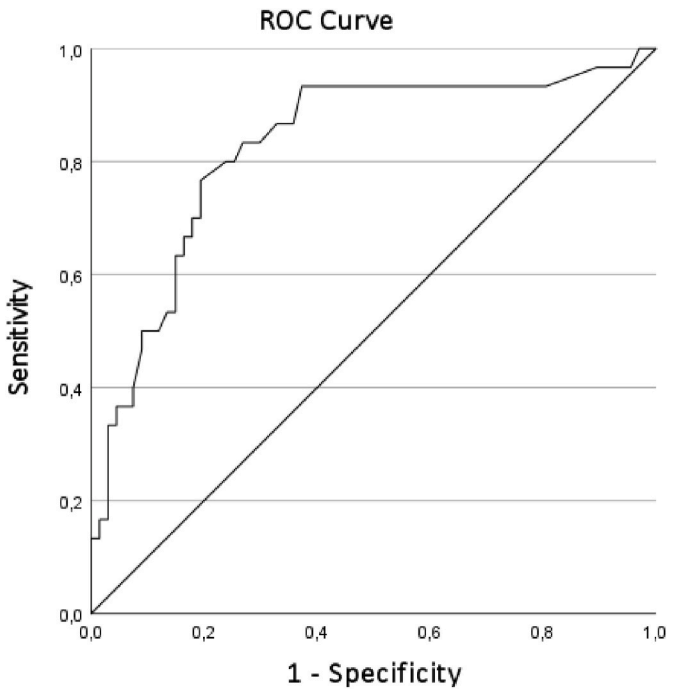

Fig. 1. A ROC curve that represents the multivariable models' ability to evaluate clinically significant complications in transbronchial cryobiopsy of the lung (AUC = 0.827). ROC = receiver operating characteristic, AUC = area under curve.

Table 4
Diagnoses.

Radiological re-assessment[a]	N (%)	Histopathological pattern[b]	N (%)	MDD-diagnosis	N (%)
Definite UIP	5 (5)	UIP	16 (16)	IPF	62 (62)
Probable UIP	29 (29)	Probable UIP	6 (6)	INSIP	15 (15)
Indeterminate with UIP	37 (37)	Possible UIP	36 (36)	HP	10 (10)
Alternative diagnosis	29 (29)	NSIP	12 (12)	Asbestosis	1 (1)
		HP	10 (10)	CTD-ILD	1 (1)
		Other	7 (7)	RB-ILD	1 (1)
		Not diagnostic	13 (13)	COP	1 (1)
				Unclassified fibrosis	6 (6)
				Other	3 (3)

MDD-diagnosis = the diagnosis after multidisciplinary discussions, UIP = usual interstitial pneumonia, NSIP = non-specific interstitial pneumonia, HP = hypersensitivity pneumonia, IPF = idiopathic pulmonary fibrosis, INSIP = idiopathic non-specific interstitial pneumonia, CTD-ILD = connective tissue disease associated interstitial lung disease, RB-ILD = respiratory bronchiolitis associated interstitial lung disease, COP = cryptogenic organizing pneumonia.

[a] According to the 2018 international ATS/ERS statement, re-assessed for this study.

[b] Diagnoses obtained from the original pathology reports. During 2015–2017 the 2011 international ATS/ERS statement was used, 2018 onwards the 2018 ATS/ERS statement, thus both the possible and probable UIP are present [22,23].

4. Discussion

In this study, the main factors associated with the risk of clinically significant complications were the extent of traction bronchiectasis on HRCT and young age whereas the use of oral corticosteroids within 30 days before the TBLC did not quite reach statistical significance. In addition, a history of severe cough measured as a LCQ total score was associated with the risk of clinically significant pneumothorax.

The association between oral corticosteroid use and the risk of complications in TBLC has not been reported before. In a study of plastic surgery complications, long term corticosteroid use increased major bleeding complications [30]. Another study reported that intravenous corticosteroid administered on the day of the tonsillectomy increased the risk of a reoperation for hemostasis in children (≤15 years) but not in adults (>15 years) [31]. Instead, a study of non-cardiac surgical patients did not find any increased intraoperative bleeding in patients with preoperative prolonged corticosteroid use [32]. In the PANTHER-IPF study, IPF-patients treated with prednisone, azathioprine and *N*-acetylcysteine had increased risk of death and hospitalization [33]. Considering our results, further investigations in the association between oral corticosteroid use and the risk of clinically significant complications of TBLC are warranted.

The LCQ has not been reported in TBLC patients previously. The LCQ is a validated symptom specific health measure for patients with chronic cough, where lower total score (range 3–21) indicates more severe impairment in the cough-related quality of life [20]. Cough is a common symptom in IPF with an association with disease progression and survival [34]. In addition, cough rates were observed to be higher in IPF-patients than in healthy subjects or asthma patients, and the LCQ correlated strongly with the objectively measured cough frequency [35]. In our study, the TBLC was performed in general anesthesia and therefore, coughing during the procedure was rare. However, those with an enhanced coughing tendency may have coughed more after the procedure, thus increasing the risk of pneumothorax. Similarly, the authors of a recent study pondered the relevance of coughing during extubation in the risk of pneumothorax occurrence [36]. The association between low LCQ score and the risk of pneumothorax could theoretically be explained in two ways. First, a low LCQ score increases the risk of peri- or postoperative coughing and second, a low LCQ score represents a more severe disease. Since the multivariable models also included other variables describing the disease severity that were not associated with the risk of pneumothorax, we propose that the former explanation is more probable.

The extent of traction bronchiectasis on HRCT was associated with the risk of clinically significant complications in this study. Instead, the extent of fibrosis or emphysema were not associated with the risk of pneumothorax. In a previous study, fibrotic score on HRCT increased the risk of pneumothorax [15], whereas another study did not find an association between the risk of pneumothorax and HRCT findings [16]. In our study population, the extent of honeycombing was low since a histological investigation is rarely necessary with high extent of honeycombing on HRCT, which usually indicates a definite UIP pattern, and an IPF diagnosis can be made without a histological investigation. Therefore, we chose traction bronchiectasis and reticulation to represent fibrosis on HRCT.

The study center was significantly associated with the risk of complications in this study. There were more complications in the center with more operators suggesting a slower accrual of experience per operator, a finding that is in line with the learning curve described in the TBLC [37]. In addition, a recent study demonstrated that higher hospital SLB volume was associated with lower 30-day post-operative mortality [38]. Obtaining sufficient number of samples in the TBLC is a constant balance between the risk of complications and an adequate biopsy sample. This study population had largely minor ILD changes with subpleural distribution in the HCRT, which forces the operator to reach areas near to the pleura to obtain an adequate biopsy sample, thus

increasing the risk of pneumothorax. The amount of non-diagnostic biopsies was lower in the center with higher complication rate although the difference was not statistically significant.

One patient died possibly due to an acute exacerbation within 90 days after the TBLC. Previous studies have reported mortality rates in 30-day [7–9,15,18], 60-day [13], or 90-day [18,36,39] intervals. Several studies have not reported any time interval for their 0% mortality rates [5,6,10,11,14,16]. We used both 30-day and 90-day procedural mortality. While the complication rates and mortality in this study are comparable to previous studies the results of our models can be considered reliable.

Due to a small population, gathering study subjects was time consuming and the study population was rather small, which can be considered as a limitation of this study. Nevertheless, we achieved low complication rates that were comparable to international results. Due to the nature of real-life studies, few of the HRCTs were other comparable CTs rather than volume HRCTs. This study was unvalidated and thus, the results should be considered as pilot data requiring further studies. Furthermore, the statistical analysis (backward stepwise elimination) can be considered as hypothesis-generating which limits the conclusions drawn from the study. However, the covariates in the model were carefully selected before the logistic regression analysis was used to increase the reliability of the model and to reduce the number of noise variables.

5. Conclusion

Higher extent of traction bronchiectasis on HRCT and younger age were associated with the risk of clinically significant complications in TBLC whereas the use of oral corticosteroids within 30 days before the TBLC did not quite reach statistical significance. A history of severe cough was associated with the risk of clinically significant pneumothorax. It might be wise to investigate severe cough before the TBLC is considered.

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Declaration of interest

MM: personal consulting fee, congress travel costs and a lecture fee from Boehringer Ingelheim, congress travel cost from Roche, outside the submitted work. ES: personal consulting fee and congress travel cost from Boehringer Ingelheim, congress travel cost from Novartis Finland and Orion Pharma, owns personal stocks from Orion LTD, outside the submitted work. SS: owns personal stocks from Merck & Co, Faron Pharmaceuticals, CRISPR Theraupeutics, and 3M Co. outside the submitted work. HN: personal lecture fees from Boehringer Ingelheim and Roche, congress travel cost from Boehringer Ingelheim, Sanofi-Genzyme, and Chiesi, outside the submitted work. HK: owns personal stocks from Orion LTD, outside the submitted work. RK: personal consulting and lecture fees, advisory board member from Boehringer Ingelheim, lecture fee from Roche, virtual congress travel cost from Roche and Novartis, advisory board member MSD, outside the submitted work. MP: personal lecture fee, congress travel cost and advisory board member Boehringer Ingelheim, lecture fee Roche, congress travel cost Orion Pharma, outside the submitted work. HH, H-PK, JR, JL, and TU declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

CRediT authorship contribution statement

Minna Mononen: Conceptualization, Data curation, Formal analysis, and, interpretation, Methodology, Investigation, Writing – original draft, Visualization, Funding acquisition, Final draft approval. **Eeva Saari:** Conceptualization, Data curation, Investigation, Writing – review & editing, Funding acquisition, Final draft approval. **Hannele Hasala:** Data curation, Investigation, Writing – review & editing, Final draft approval. **Hannu-Pekka Kettunen:** Data curation, Investigation, Writing – review & editing, Final draft approval. **Sanna Suoranta:** Data curation, Investigation, Writing – review & editing, Final draft approval. **Hanna Nurmi:** Data curation, Investigation, Writing – review & editing, Final draft approval. **Jukka Randell:** Data curation, Writing – review & editing, Final draft approval. **Jari Laurikka:** Data curation, Writing – review & editing, Final draft approval. **Toomas Uibu:** Data curation, Writing – review & editing, Final draft approval. **Heikki Koskela:** Conceptualization, Formal analysis and interpretation, Methodology, Writing – review & editing, Final draft approval. **Riitta Kaarteenaho:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition, Final draft approval. **Minna Purokivi:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Resources, Funding acquisition, Final draft approval.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2022.106922.

Abbreviations

APTT	activated partial thromboplastin time
ASA	acetyl salicylic acid
ATS	American Thoracic Society
AUC	Area under curve
BAL	Bronchoalveolar lavage
BMI	Body mass index
COP	Cryptogenic organizing pneumonia
CTD-ILD	Connective tissue disease associated interstitial lung disease
DLCO	Diffusion capacity to carbon monoxide
ECHO	Echocardiogram
ERS	European Respiratory Society
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
GFR	Glomerular filtration rate
HRCT	High-resolution computed tomography
HP	Hypersensitivity pneumonia
ICU	Intensive care unit
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
INR	international normalized ratio
IPF	Idiopathic pulmonary fibrosis
KUH	Kuopio University Hospital
LCQ	Leicester Cough Questionnaire
MDD	Multidisciplinary discussion
NSIP	nonspecific idiopathic pneumonia
RB-ILD	Respiratory bronchiolitis associated interstitial lung disease
ROC	Receiver operating characteristic
SLB	Surgical lung biopsy

TAUH	Tampere University Hospital
TBLC	Transbronchial lung cryobiopsy
UIP	Usual interstitial pneumonia

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