Original Article

Inflammatory myositis-associated interstitial lung disease can be distinguished from that associated with other connective tissue diseases

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Background: Acute onset of interstitial lung disease (ILD) has been described in patients with idiopathic inflammatory myositis (IIM), but controlled studies about this issue are sparse. The aim of this study was to compare disease onset, demographics, and high-resolution computed tomography (HRCT) patterns in IIM-ILD and other connective tissue disease (CTD)-ILDs.

Methods: Clinical and radiological data of 22 IIM-ILD and 132 other CTD-ILD patients was retrospectively gathered from hospital registries between January 2000 and November 2019. Data was re-assessed and compared using a multivariate analysis.

Results: Compared to other CTD-ILDs, the patients with IIM-ILD were younger (59.7 *vs.* 68.0 years, P=0.023), more often non-smokers (71.4% *vs.* 45.7%, P=0.029) and displayed radiological nonspecific interstitial pneumonia/organizing pneumonia (NSIP/OP) overlap pattern more frequently (27.3% *vs.* 1.5%, P<0.001). The onset of ILD was acute with patients needing intensive care significantly more often in IIM-ILD than in other CTD-ILDs (22.7% *vs.* 2.3%, P<0.001). In most patients ILD was diagnosed before or simultaneously with IIM presentation unlike in other CTD-ILDs (90.9% *vs.* 47.7%, P<0.001). In multivariate analysis, NSIP/OP overlap pattern, acute onset disease treated in intensive care unit and ILD preceding or being diagnosed simultaneously with CTD were significantly associated with IIM-ILD. The multivariate model, supplemented with age, had excellent diagnostic performance identifying IIM-ILD [area under curve (AUC) 0.845].

Conclusions: Unlike other CTD-ILDs, IIM-ILD often develops acutely, simultaneously with the systemic disease. Therefore, clinicians should consider IIM-ILD as an option of differential diagnosis in patients with acute ILD and promptly test muscle enzymes as well as comprehensive autoantibody tests.

Keywords: Interstitial lung disease (ILD); high-resolution computed tomography (HRCT); connective tissue disease (CTD); idiopathic inflammatory myositis (IIM)

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Introduction

Interstitial lung disease (ILD) increases the morbidity and mortality of the patients with connective tissue diseases (CTD), such as rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), Sjögren's syndrome (SjS) and idiopathic inflammatory myopathies (IIM) (1).

IIM are a heterogeneous group of disorders characterized by muscle inflammation and weakness. The most common IIM in adults are dermatomyositis (DM) including clinically amyopathic dermatomyositis (CADM), polymyositis (PM) and inclusion body myositis (2). The antisynthetase syndrome (ASyS) is a distinct condition, which nowadays is also included in the IIM group (3).

The clinical presentation of any CTD-ILD can vary from an indolent disease course to an acute respiratory failure (4). Several cohorts have revealed that a high proportion of patients with IIM-associated ILD (IIM-ILD) presented an acute onset of disease (3,5-7), particularly in those patients with CADM and/or anti-melanoma differentiation-associated gene-5 (MDA5) positivity (7-9) and ASyS (10). However, a rapid disease onset has been described in other CTD-ILDs as well (11-13). More importantly, the IIM-ILD studies reporting high frequency of acute disease onset have lacked a control group consisting of other CTD-ILDs. Thus, it is unclear whether IIM-ILD has a distinct clinical presentation among CTD-ILDs.

Controlled comparative studies regarding to radiological findings and demographic data of IIM-ILD are also limited. One study has compared high-resolution computed tomography (HRCT) patterns of IIM-ILD and other ILDs, but the control group mostly consisted of idiopathic ILDs and less of CTD-ILDs (14). Thus, it is also unknown whether the radiological findings of IIM-ILD differ from other CTD-ILDs.

The aim of this study was to compare the clinical presentation and radiological findings between IIM-ILD and other CTD-ILDs. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1219/rc).

Highlight box

Key findings

- Idiopathic inflammatory myositis-associated interstitial lung disease (IIM-ILD) can be distinguished from other connective tissue disease-associated ILDs (CTD-ILDs) by clinical and radiological presentation.

What is known and what is new?

- Uncontrolled studies have suggested that a high proportion of IIM-ILD patients present an acute onset of the disease.
- We compared IIM-ILD with other CTD-ILDs and observed that an acute disease onset was particularly associated with IIM-ILD.
- Radiological nonspecific interstitial lung pneumonia/organizing pneumonia (NSIP/OP) overlap pattern, the simultaneous onset of both ILD and CTD symptoms, and younger age were also associated with IIM-ILD.

What is the implication, and what should change now?

- In acute respiratory failure with lung infiltrates a clinician should evaluate the possibility of IIM-ILD.

Methods

Data sources and search

The study cohort consists of patients treated in the Kuopio University Hospital (KUH) pulmonology clinic between 1.1.2000–20.11.2019. The subjects for the study were searched from the KUH database using following International Classification of Diseases (ICD-10) codes: M05.X/M06.X/J99.0*M05.1 for RA, M32.X/J99.1*M32.1 for SLE, M33.X/J99.1*M33.9/J99.1*M33.2 for IIM, M34.X/J99.1*M34.8 for SSc, M35.0/J99.1*M35.0 for SjS, M35.1 for MCTD and M35.8/M35.9 for undifferentiated connective tissue disease (UCTD). We have previously published three studies of RA-ILD, in which the patient search reached to December 2014 (15-17). These patients are included in the present study cohort and the RA searches were further extended to 20.11.2019.

Altogether 2202 new patients were identified. First the patients were screened (HMN, VAEK, HMIJ) based on medical records and HRCT or other comparable computed tomography (CT) reports. If those did not suggest a presence of ILD, the patient was excluded, as were the cases for whom a proper CT scan allowing reliable analysis

of the lung parenchyma was not available. The remaining 121 patients with suspected CTD-ILD, as well as our previous RA-ILD cohort of 60 patients, were further analyzed by an experienced rheumatologist (PKE) and two radiologists (HPK, SKS).

Re-analysis of the CTD diagnoses

A rheumatologist independently evaluated laboratory findings, clinico-radiological data and other necessary examinations and re-assessed the CTD diagnoses. Patients were included in the IIM subgroup if they fulfilled either (I) the probable or definite European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and their Major Subgroups (2), or (II) the Connor's criteria for ASyS (18). Other CTD diagnoses were confirmed by using the current International classification criteria of each disease (19-27). Eight patients with dry eyes, dry mouth, and Sjögren's-syndrome-related antigen A/B (SSA/SSB) antibodies were included to SjS subgroup as highly probable SjS, without objective tests for dryness of mouth or eyes, but with multiple signs and symptoms supporting the diagnosis. Twenty-three patients with autoantibodies or clinical features of CTD without meeting the criteria for any specific autoimmune disease were included as UCTD (28).

Radiological re-analysis

Two radiologists independently re-assessed the baseline HRCT scans according to the 2018 international statement as a definite usual interstitial pneumonia (UIP), probable UIP, indeterminate with UIP, or alternative diagnosis (29). In cases with alternative diagnosis, the 2013 idiopathic interstitial pneumonias (IIP) classification was applied to diagnose patients as having nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), desquamative interstitial pneumonia (DIP), diffuse alveolar damage (DAD) or unspecific radiological patterns (30). Some patients displayed NSIP/OP overlap pattern, as described in the previous literature (31). In 106 patients with available follow-up HRCTs, the final radiological diagnosis was determined based on the analysis of both CTs. In case of a disagreement, the final radiological categorization was reached via discussion between the investigators (HMN, HPK, SKS).

Gathering of demographic information

After the re-analysis of rheumatological and radiological diagnoses, 27 patients were excluded for not having confirmed CTD-ILD. Clinical information and laboratory test results (Table S1) were gathered from the patient records of KUH. The results of pulmonary function tests were gathered at baseline ± three months.

The order of CTD/ILD presentation was determined from the medical records. If the patient revealed both CTD- and ILD- related symptoms, signs, or findings on the first contact to either rheumatologist or pulmonologist, the disease onset was defined as simultaneous.

The disease onset was defined as acute if the patient needed hospitalization at the onset of ILD. These patients were further divided into those who were admitted to intensive care and those admitted to pulmonology ward. If the patient was managed on an outpatient setting, the disease onset was defined as subacute/chronic. In all cases with a possibility of an acute respiratory infection, appropriate microbiological samples were collected according to the clinician's consideration. Bronchoalveolar lavage was performed in 63.4% of the patients with an acute onset disease to exclude infections.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). According to Finnish legislation, no consents for inclusion are needed in retrospective register-based study. The study protocol was approved by the Ethics Committee, Hospital District of Northern Savo [statement No. 151/2015 (17/2013)]. In addition, organizational permission of KUH was obtained, which enabled data collection from the hospital registries.

Statistical analysis

The continuous data is expressed as medians (range) and categorical variables as absolute numbers (valid percentages). Different variables were compared using Mann-Whitney U-test, Kruskal-Wallis test or chi-squared test, as appropriate. Missing data was excluded from these comparisons. Logistic regression of features associated with IIM-ILD was used for multivariate analysis. Results are presented as odds ratio (OR) ± 95% confidence interval (CI). A receiver operating curve (ROC) was constructed to evaluate the diagnostic performance of the final multivariate model. Of the variables utilized in the multivariate analyses, there were no missing data. A sensitivity analysis omitting

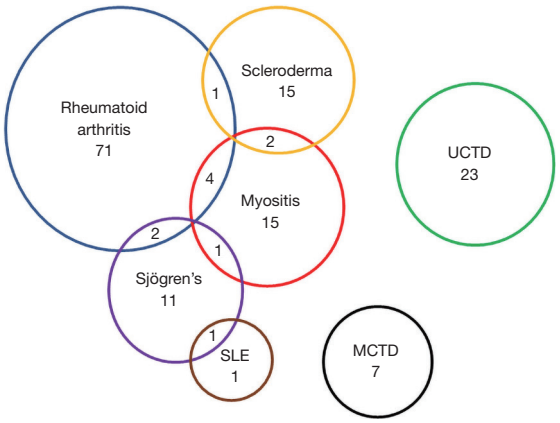

Figure 1 Diagram showing the CTD diagnoses in the cohort of 154 patients. Eleven patients fulfilled the diagnostic criteria of two different CTDs. CTD, connective tissue disease; UCTD, undifferentiated CTD; SLE, systemic lupus erythematosus; MCTD, mixed CTD.

the patients with RA was also performed. Survival time was calculated from the baseline to the date of death or December 10, 2021, when the vital status was ascertained. The Kaplan-Meier method and log-rank test were used to calculate and compare the survival curves. P values <0.05 were considered statistically significant. All data was analyzed using IBM Statistics SPSS software, version 26.0.

Results

Altogether 154 patients with confirmed CTD-ILD were identified. The most common CTDs were RA (78/50.6%), UCTD (23/14.9%), IIM (22/14.3%) and SSc (18/11.7%). Some patients fulfilled the diagnostic criteria of two different CTDs (*Figure 1*). The IIM-ILD subgroup consisted of 14 patients with ASyS, 5 with CADM, 2 with DM and 5 with PM of whom four fulfilled also criteria for ASyS.

The demographics, lung functions and radiologic findings of different CTD-ILD subgroups are presented in *Table 1*. The IIM overlap patients are displayed in a separate column and thus the statistical comparisons in *Table 1* involve only a subset of patients with IIM-ILD. The patients were mostly female and almost half of them had never smoked (*Table 1*). All but seven (95.5%) patients suffered from either cough or dyspnea. The median survival was 8.4 years. Comparing all the different CTD subgroups, patients with IIM-ILD had worse baseline FVC than patients with RA-ILD or MCTD-ILD (P values 0.004, 0.036, respectively, *Table 1*). Fever was more frequent in patients with IIM-ILD compared to RA-ILD (91.7% *vs.* 22.6%, P<0.001) or SSc-ILD (91.7% *vs.* 40.0%, P=0.022). In IIM-ILD patients the radiological NSIP/OP overlap pattern (*Figure 2*) was observed more commonly than in other subgroups.

Dichotomous comparison between IIM-ILD patients, including the overlap ones, and other CTD-ILDs is shown in *Table 2*. The patients with IIM-ILD were younger and more often non-smokers with fever (*Table 2*). They displayed radiological NSIP/OP pattern more frequently whereas UIP pattern was less common. NSIP/OP overlap pattern showed a 27.3 sensitivity and 98.5 specificity for discriminating IIM-ILD from other CTD-ILDs (*Table 2*).

Over 90% of the IIM-ILD patients had ILD onset before or simultaneously with CTD presentation, whereas this was the situation in under half of the other CTD-ILDs (*Table 3*). Every fifth IIM-ILD patient was admitted to intensive care unit (ICU) at the disease onset, which was rare in other CTD-ILDs (22.7% *vs.* 2.3%, P<0.001). Of the five IIM-ILD patients admitted to ICU, two had CADM with MDA5 antibodies, two had PM + ASyS with positive Jo-1, and one had ASyS with positive PL-12. The median survival between IIM-ILD and other CTD-ILD patients did not differ statistically significantly (101.0 *vs.* 143.0 months, P=0.663) (*Table 3*).

In multivariate analysis, NSIP/OP overlap pattern, acute onset disease treated in ICU and ILD preceding or presenting simultaneously with CTD were significantly associated with IIM-ILD (*Table 4*). This model, supplemented with age, had excellent diagnostic performance identifying IIM-ILD [area under curve (AUC) 0.845] (*Figure 3*). The analyses were repeated utilizing the Solomon criteria for ASyS, which did not change the main results (data not shown).

In sensitivity analysis omitting the patients with RA, the IIM-ILD patients were still statistically significantly more likely to develop an acute onset of the ILD simultaneously or prior to CTD with more overlap NSIP/OP radiological appearance (*Table 5*). Among all subjects with acute onset ILD the most common radiological patterns were OP (41.5%), UIP/probable UIP (19.5%), NSIP (12.2%), and NSIP/OP overlap (12.2%).

Detailed data of each IIM-ILD patients diagnostics, treatment, outcome and given medications is described in supplementary Tables S2-S4.

Discussion

To our knowledge, this is the first study to directly compare

Table 1 Baseline characteristics and radiological findings of the patients with different CTDs

Variables	All CTD-ILD (n=154)	RA-ILD (n=71, 46.1%)	SjS-ILD (n=11, 7.1%)	SSc-ILD (n=15, 9.7%)	IIM-ILD (n=15, 9.7%)	MCTD-ILD (n=7, 4.5%)	UCTD-ILD (n=23, 14.9%)	Two CTDs (n=11, 7.1%)	P value
Age (y)	66.8 (26.3–87.0)	67.6 (31.8–87.0)	70.9 (47.4–83.1)	60.7 (43.3–82.2)	58.8 (48.2–72.9)	61.0 (37.4–81.7)	67.1 (26.3–84.0)	70.0 (35.8–78.3)	0.178
Male sex	66 (42.9)	39 (54.9)	3 (27.3)	3 (20.0)	6 (40.0)	3 (42.9)	10 (43.5)	2 (18.2)	0.080
Number of deaths	93 (60.4)	49 (69.0)	5 (45.5)	9 (60.0)	6 (40.0)	4 (57.1)	12 (52.2)	8 (72.7)	0.300
Non-smokers*	74/150 (49.3)	28/70 (40.0)	7 (63.6)	8/14 (57.1)	10/14 (66.7)	4/7 (57.1)	10/23 (43.5)	7/10 (70.0)	0.197
Lung functions									
FVC % pred*	78.0 (31–123)	82.0 (40–122)	70.0 (52–93)	79.0 (31–103)	69.5 (40–102)[#,ǂ]	89.0 (63–117)	72.0 (51–106)	83.0 (74–116)	0.001
DLco % pred*	60.5 (16–109)	70.0 (28–109)	53.0 (42–77)	56.0 (33–80)	60.5 (25–77)	61.5 (55–82)	52.0 (16–106)	68.7 (42–87)	0.039
Symptoms*									
Cough	86/122 (70.5)	39/59 (66.1)	6/7 (85.7)	7/10 (70.0)	13/14 (92.9)	2/4 (50.0)	13/18 (72.2)	6/10 (60.0)	0.417
Dyspnoea	106/141 (75.2)	41/64 (64.1)	9 (81.8)	13 (86.7)	9/13 (69.2)	6/7 (85.7)	20/21 (95.2)	7/9 (77.8)	0.097
Inspiratory crackles	122/152 (80.3)	50 (70.4)	10 (90.9)	10/14 (71.4)	15 (100.0)[#,¤,ǂ]	5 (71.4)	21 (91.3)	10/10 (100.0)	0.046
Fever	48/100 (48.0)	12/53 (22.6)	4/6 (66.7)	2/5 (40.0)	11/12 (91.7)[#,¤]	2/2 (100.0)	10/13 (76.9)	6/8 (75.0)	<0.001
Radiological pattern									
UIP	54 (35.1)	37 (52.1)	1 (9.1)	3 (20.0)	1 (6.7)[#]	1 (14.3)	6 (26.1)	5 (45.5)	0.001
UIP or probable UIP	68 (44.2)	42 (59.2)	2 (18.2)	4 (26.7)	2 (13.3)[#]	2 (28.6)	10 (43.5)	6 (54.5)	0.006
NSIP	19 (12.3)	7 (9.9)	2 (18.2)	2 (13.3)	2 (13.3)	1 (14.3)	2 (8.7)	3 (27.3)	0.766
OP	22 (14.3)	9 (12.7)	3 (27.3)	1 (6.7)	5 (33.3)	0 (0.0)	4 (17.4)	0 (0.0)	0.127
NSIP/OP overlap	8 (5.2)	2 (2.8)	0 (0.0)	0 (0.0)	5 (33.3)[#,¥,¤,§]	0 (0.0)	0 (0.0)	1 (9.1)	<0.001
Indeterminate for UIP	11 (7.1)	0 (0.0)	1 (9.1)	3 (20.0)	1 (6.7)[#]	1 (14.3)	4 (17.4)	1 (9.1)	0.037
Other**	26 (16.9)	11 (15.5)	3 (27.3)	5 (33.3)	0 (0.0)[¥,¤,§]	3 (42.9)	3 (13.0)	0 (0.0)	0.043

Data are presented as median (range) or n (%). The patients who fulfilled the diagnostic criteria of two different CTDs are presented as a distinct subgroup. Seven patients with IIM-ILD fulfilled diagnostic criteria of two different CTDs. Thus, the number of IIM-ILD patients in this table is 15. One patient with systemic lupus was excluded from the comparative analysis between the subgroups. *, missing data: smoking from 4 subjects, baseline FVC from 14 subjects, baseline DLco from 22 subjects, cough data from 32, dyspnea from 13, inspiratory crackles from 2, fever from 54. **, unspecific changes (n=23), DIP (n=1), or DAD (n=2). [#], a statistically significant difference (P<0.05) between IIM-ILD and RA-ILD; [¥], P<0.05 between IIM-ILD and Sjs-ILD; [¤], P<0.05 between IIM-ILD and Ssc-ILD; [ǂ], P<0.05 between IIM-ILD and MCTD-ILD; [§], P<0.05 between IIM-ILD and UCTD-ILD. CTD, connective tissue disease; ILD, interstitial lung disease; RA, rheumatoid arthritis; SjS, Sjögrens' syndrome; SSc, systemic sclerosis; IIM, idiopathic inflammatory myositis; MCTD, mixed CTD; UCTD, undifferentiated CTD; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.

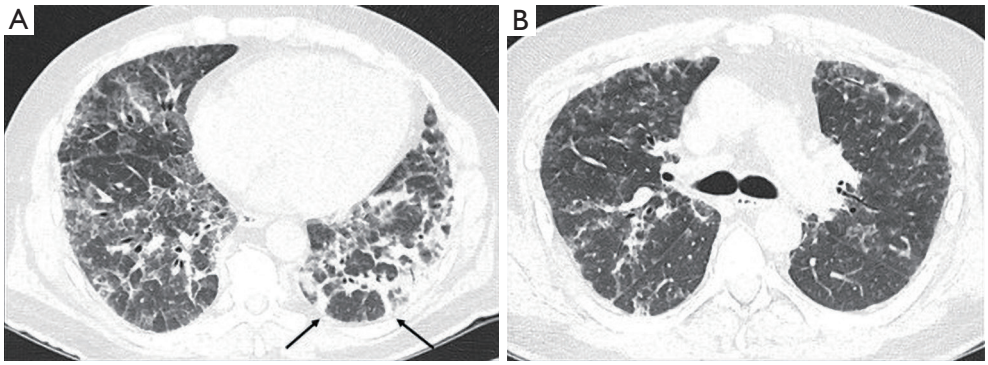

Figure 2 Representative HRCT images of a patient with clinically amyopathic dermatomyositis. HRCT images display NSIP/OP overlap pattern with lower lobe predominance. There is GGO and reticulation without honeycombing or traction bronchiectasis on the right lower lobe (A). Milder GGO and reticulation are symmetrically distributed in the upper lobes (B). These changes are consistent with NSIP. On the left lower lobe (A) the main pattern is peribronchial consolidations with perilobular pattern (arrows), a finding consistent with typical OP pattern. HRCT, high-resolution computed tomography; NSIP/OP, nonspecific interstitial pneumonia/organizing pneumonia; GGO, ground glass opacity.

Table 2 Baseline characteristics and radiological findings of the patients with inflammatory myositis-ILD compared to other CTD-ILDs. All patients (n=154) included

Variables	IIM-ILD (n=22)	Other CTD-ILDs (n=132)	P value
Age (y)	59.7 (35.8–74.8)	68.0 (26.3–87.0)	0.023
Male sex	7 (31.8)	59 (44.7)	0.258
Number of deaths	10 (45.5)	83 (62.9)	0.122
Non-smokers*	15/21 (71.4)	59/129 (45.7)	0.029
Fever*	14/17 (82.4)	34/83 (41.0)	0.002
Lung function			
FVC % predicted*	74.0 (40–116)	78.5 (31–123)	0.175
DLco % predicted*	61.5 (25–87)	58.5 (16–106)	0.668
Radiological pattern			
UIP	3 (13.6)[#]	51 (38.6)	0.023
UIP or probable UIP	5 (22.7)	63 (47.7)	0.029
NSIP	4 (18.2)	15 (11.4)	0.368
OP	5 (22.7)	17 (12.9)	0.222
NSIP/OP overlap	6 (27.3)	2 (1.5)	<0.001
Indeterminate for UIP, possible NSIP	2 (9.1)	9 (6.8)	0.702
Other**	0 (0.0)	26 (19.7)	0.022

Data were presented as median (range) or n (%). Those IIM-ILD patients that had two CTDs (one of them being IIM), are included in the IIM-ILD-group. *, missing data: smoking data from 1 IIM-ILD subjects and 3 others, baseline FVC from 2 IIM-ILD subjects and 12 others, baseline DLco data from 2 IIM-ILD subjects and 20 others, fever data from 5 IIM-ILD subjects and 49 others. **, unspecific changes (n=23), DIP (n=1), or DAD (n=2). [#], concomitant RA in two subjects. ILD, interstitial lung disease; CTD, connective tissue disease; IIM, idiopathic inflammatory myositis; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RA, rheumatoid arthritis.

Table 3 Disease onset and mortality in IIM-ILD versus other CTD-ILDs

Variables	All CTD-ILD (n=154)	IIM-ILD (n=22)	Other CTD-ILDs (n=132)	P value
Order of presentation				
ILD before CTD	29 (18.8)	7 (31.8)	22 (16.7)	0.092
ILD and CTD simultaneously	54 (35.1)	13 (59.1)	41 (31.1)	0.011
ILD before CTD or simultaneously	83 (53.9)	20 (90.9)	63 (47.7)	<0.001
CTD before ILD	71 (46.1)	2 (9.1)	69 (52.3)	<0.001
Onset				
Acute, ICU	8 (5.2)	5 (22.7)	3 (2.3)	<0.001
Acute, pulmonology ward	33 (21.4)	7 (31.8)	26 (19.7)	0.200
Acute, either ICU or pulmonology ward	41 (26.6)	12 (54.5)	29 (22.0)	0.001
Chronic/subacute, outpatient clinic	113 (73.4)	10 (45.5)	103 (78.0)	0.001
Mortality				
30 days	2 (1.3)	1 (4.5)	1 (0.8)	0.146
90 days	5 (3.2)	1 (4.5)	4 (3.0)	0.710
1 year	11 (7.1)	2 (9.1)	9 (6.8)	0.702
Survival (months)	101.0 (0.0–436.0)	143.0 (0.0–191.0)	100.0 (0.0–436.0)	0.663

Results were expressed as median (range) and n (%). IIM, idiopathic inflammatory myositis; ILD, interstitial lung disease; CTD, connective tissue disease; ICU, intensive care unit.

Table 4 Multivariate analysis of the features associated with IIM-ILD (All 154 patients are included in the analysis)

Variables	OR	95% CI	P value
Age	0.964	0.923–1.006	0.095
NSIP/OP overlap pattern in HRCT	22.2	2.348–210.291	0.007
Acute onset, ICU	19.350	1.838–203.735	0.014
ILD before CTD or simultaneously	14.317	2.447–83.766	0.003

IIM, idiopathic inflammatory myositis; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; HRCT, high-resolution computed tomography; ICU, intensive care unit; OR, odds ratio; CI, confidence interval.

IIM-ILD with other CTD-ILDs confirming that an acute disease onset was particularly associated with IIM-ILD. Further, NSIP/OP overlap pattern in HRCT, the simultaneous onset of both ILD and CTD symptoms, and younger age were associated with IIM-ILD. These findings are in line with the previous, but mostly uncontrolled studies.

An acute presentation of ILD have been observed in many uncontrolled IIM cohorts. For example, Obert *et al.* reported acute presentation of ILD in over half of the 48 IIM-ILD patients, defined as the presence of symptoms for less than 2 months (32). Fujisawa *et al.* examined 114 IIM-ILD patients and reported acute/subacute clinical presentation in 52% of the patients. The definition used for acute presentation was determined as rapidly progressive ILD with deterioration within 3 months (33). A high proportion (>50%) of acute disease onset has been described in many other IIM-ILD cohorts and case reports also (7,8,10), while others have reported smaller percentages of 9–30% (6,34). These controversies probably rise from the different patient selection, as some studies include also asymptomatic patients with an incidental finding of interstitial lung abnormalities (34). In our study, 96% of the patients suffered from either dyspnea or cough. Moreover, the definition of an acute onset varies in different studies as

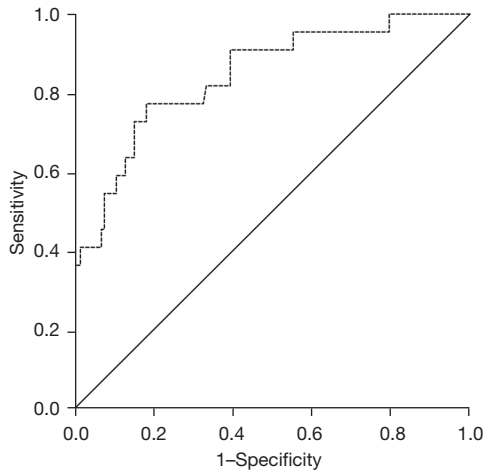

Figure 3 A ROC curve for the multivariable model: (I) age, (II) NSIP/OP overlap pattern in HRCT, (III) acute onset treated in intensive care unit, (IV) ILD before CTD onset or simultaneously (*Table 4*). The model shows excellent diagnostic performance for identifying myositis-associated ILD from all CTD-ILDs with AUC value of 0.845. ROC, receiver operating characteristic; AUC, area under the curve; NSIP/OP, nonspecific interstitial pneumonia/organizing pneumonia; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; CTD, connective tissue disease.

no official definition exists. In the present study, acute onset was based on the need for hospitalization.

We observed a high percentage (91%) of IIM-ILD patients in whom ILD had either preceded or developed simultaneously with IIM symptoms/signs. Almost as high percentages (75–78%) have been reported in many uncontrolled IIM-ILD studies (32,33). Another cohort of 33 IIM-ILD patients reported a simultaneous onset in 67% and ILD being first in 18% (6). In a Danish population-based CTD cohort however, ILD was diagnosed before CTD in only 39% of the IIM-ILD patients similarly as in other CTDs. A simultaneous onset was not reported (35). In that study, the order of presentations was derived from a national registry data without access to individual patient data, which may have affected this result (35).

Based on the previous literature and our results, it seems very common, that in IIM-ILD the respiratory and myositis-related symptoms and signs develop rather simultaneously. Therefore, it is crucial that pulmonologists are familiar with typical IIM features so that the necessary investigations are performed. The pulmonologists should look for the presence of symmetrical muscle weakness, myalgia, Gottron papules/sign, distal digital ulceration, nail fold bleeding, dysphagia, skin rashes, or Raynaud's symptom (36,37).

Table 5 Comparisons between IIM-ILD and other CTD-ILDs when the patients with RA were excluded

Variables	All CTD-ILD (n=76)	IIM-ILD (n=18)	Other CTD-ILDs (n=58)	P value
Age	64.5 (26.3–84.0)	61.2 (48.2–74.8)	65.5 (26.3–84.0)	0.169
Fever*	33/42 (78.6)	13/14 (92.9)	20/28 (71.4)	0.111
ILD before CTD or simultaneously	63 (82.9)	18 (100.0)	45 (77.9)	0.021
Onset				
Acute, ICU	5 (6.6)	5 (27.8)	0 (0.0)	<0.001
Acute, ICU or pulmonology ward	26 (34.2)	12 (66.7)	14 (24.1)	0.001
Radiological pattern				
UIP or probable UIP	22 (28.9)	3 (16.7)	19 (32.8)	0.188
NSIP	10 (13.2)	3 (16.7)	7 (12.1)	0.614
OP	13 (17.1)	5 (27.8)	8 (13.8)	0.169
NSIP/OP overlap	6 (7.9)	6 (33.3)	0 (0.0)	<0.001

*, data missing form 4 IIM-ILD patients and 30 others. IIM, idiopathic inflammatory myositis; ILD, interstitial lung disease; CTD, connective tissue disease; RA, rheumatoid arthritis; ICU, intensive care unit; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.

Currently, autoimmune serology testing is recommended for all ILD patients (29) although it is unclear what autoantibodies should be investigated (38,39). Universal screening for myositis-specific or myositis-associated antibodies in newly diagnosed ILD is controversial and currently suggested on a case-by-case consideration (29). However, especially those patients who present an acute/subacute respiratory failure with lung infiltrates, should be thoroughly examined keeping the possible IIM-ILD in mind, as stated by others also (4,38,40). Though myositis-specific and myositis-associated antibodies are useful in the diagnostics of these disorders (14), the delay of their laboratory analysis often necessitates the diagnosis on clinical grounds. Unfortunately it seems that critically ill patients are not commonly evaluated for IIM-ILD, since only 5% were tested for autoantibodies in the multinational Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) cohort with acute respiratory distress syndrome without an identified etiology (41).

According to previous literature, the most common HRCT patterns in IIM-ILD are NSIP or NSIP with OP (42), in line with our findings. In a study of 33 patients with ASyS, NSIP or mixed NSIP/OP patterns were seen in approximately 70% of subjects (43). In two recent studies of 52 PM/DM and 84 ASyS patients NSIP pattern was observed in 32–44%, OP pattern in 19–25% and NSIP/OP overlap pattern in 9-19% of the subjects (44,45). In a study of Enomoto *et al.*, the HRCT patterns of 444 biopsy-proven patients with IIPs were re-assessed. They reported that the cumulative incidence of newly-developed CTD was similar in 21 (4.7%) patients with NSIP/OP overlap pattern and 44 (9.9%) with NSIP pattern, but the developing CTD was diagnosed as IIM in 100% of the patients with NSIP/OP overlap pattern and in 56% in those with NSIP pattern (46). One previous study has compared the radiological patterns of 12 IIM-ILD and 235 non-IIM-ILD subjects, the control group consisting of CTD-ILDs (n=52), IIPs (n=115) and other ILDs (n=68). They reported a statistically significant difference in the presence of NSIP/OP pattern between the groups (14). In our study, the NSIP/OP pattern was not sensitive, but highly specific to identify IIM-ILD patients. Combining this HRCT pattern to age, order of ILD and CTD presentations and an acute onset disease treated in ICU, we observed an excellent diagnostic performance (47) separating IIM-ILD from other CTD-ILDs. The best model of Jee *et al.* (14) with the highest AUC (0.96) consisted of myositis autoantibodies line immunoblot assay combined with age, gender, CTD-features, and radiological NSIP/OP pattern supporting our findings despite of the different control group.

Most of the limitations of the study rise from its retrospective nature. In the past, all autoantibodies including myositis-panel were neither yet available in clinical practice nor routinely investigated from all ILD patients, which probably has been the situation all over the world (41). Thus, there is some missing laboratory data. In addition, different symptoms and signs were not available from all patients, which may lead to some inaccuracies. However, gathering equally large CTD-ILD cohort prospectively would take several years given the rarity of the diseases. Another limitation is the fact that the IIM-ILD subgroup is fairly small and somewhat skewed towards ASyS and CADM, which might affect the results. A high proportion of RA-ILD patients could have caused a bias, but the sensitivity analysis omitting them did not change the main results. The classification criteria for ASyS are variable (3) and it is not clear which should be used in studies. We chose to use the Connors criteria, but the main results remained statistically significant using the stricter Solomon criteria.

The strengths of this rather large CTD-ILD cohort is that the data is collected comprehensively and that both pulmonologist, rheumatologist and two radiologists have re-analyzed the data.

Conclusions

In conclusion, IIM-ILD can be distinguished from other CTD-ILDs by clinical and radiological presentation. Compared to other CTD-ILDs, the patients with IIM-ILD are younger, they more often develop an acute onset dyspnoea and fever with simultaneous onset of the systemic disease, and display radiological NSIP, OP or NSIP/OP overlap pattern. When encountering this kind of patients, the clinician should suspect IIM-ILD and promptly test muscle enzymes and comprehensive autoantibody tests including myositis-panel.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). According to the Finnish legislation, consents to participate are not required in retrospective register-based studies. The study protocol was approved by the Ethics Committee, Hospital District of Northern Savo (statement No. 151/2015 (17/2013)). In addition, organizational permission of KUH was obtained, which enabled data collection from the hospital registries.

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Supplementary

Table S1 Detailed list of demographic and other data that was gathered from the patients records of Kuopio University Hospital

Gathered data	Timepoint	Other details
Date of birth		
Date of death		
Sex		
Smoking	Lifelong	Duration, amount, pack-years, passive exposure
Exposure to asbestos	Lifelong	
Radiation therapy of the thorax region	Lifelong	
Date of CTD diagnosis		
Date of the first visit due to ILD		Regarded as baseline
Comorbidities	At any timepoint	
Respiratory symptoms	Baseline	Cough, dyspnea, hemoptysis
CTD symptoms and signs	At any timepoint	Comprehensively, considering all different CTDs
Medication	Any medication at baseline, lifelong CTD medication	
Use of long-term oxygen	AT any timepoint	
Pulmonary function tests	BASELINE ± 3 months	
Spirometry		
DLco		
Laboratory test results	AT any timepoint	ENA consists of: ANA, SSA, SSB, Sm, Sent, RNP, Scl70, Jo-1, ANA-IB)
Muscle enzymes		Myositis-panel: Mi-2 alpha, Mi-2 beta, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro52, TIF1 gamma, MDA5, NXP2, SAE1
RF		
ANA		
ACPAs		
ENA*		
Myositis-panel for 16 antigens**		

*, available from all IIM-ILD patients; **, available from 12 IIM-ILD patients. ILD, interstitial lung disease; CTD, connective tissue disease; DLco, diffusion capacity to carbon monoxide; RF, rheumatoid factor; ANA, antinuclear antibody; ACPAs, antibodies against cyclic citrullinated peptide; ENA, extractable nuclear antigen panel.

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Table S2 Autoantibodies, symptoms, and clinical findings of patients with IIM-ILD

Characteristics	IIM-ILD (N=22)
SSA/RO52	12/22 (54.5)
ANA	9/21 (42.9)
JO-1	9/22 (40.9)
PL-7	4/12 (33.3)
PL-12	1/12 (8.3)
MDA-5	3/12 (25.0)
Pm-Scl-75	1/12 (8.3)
No MSA/MAA	4 (18.2)
Synovitis	13/21 (61.9)
Mechanics hands	3/3 (100.0)
Raynaud	10/14 (71.4)
Muscle weakness	14/17 (82.4)
Myalgia	15/16 (93.8)
Elevated muscle enzymes	13/18 (72.2)
Abnormal nailfold capillaroscopy	10/17 (58.8)
Finger ulcers	8/13 (61.5)
Gottron papules/(heliotropic) rash	11/13 (84.6)
Myositis in ENMG	5/9 (55.6)

Data were presented as positive findings (n) per those for whom the data was available (%). IIM-ILD, idiopathic inflammatory myositis-associated interstitial lung disease; ANA, antinuclear antibody; JO-1, histidyl; PL-7, threonyl; PL-12, alanyl; MDA5, melanoma differentiation-associated gene 5; MSA, myositis-specific antibodies; MAA, myositis-associated antibodies; ENMG, electroneuromyography.

Table S3 Medication used in patients with IIM-ILD

Medications	IIM-ILD (N=22)
I.v. high-dose steroid	7 (31.8)
Oral corticosteroids	22 (100.0)
Cyclophosphamide	10 (45.5)
Azathioprine	13 (59.1)
Cyclosporine	8 (36.4)
Mycophenolate	8 (36.4)
Rituximab	9 (40.9)
Podophyllotoxine	4 (18.2)
Methotrexate	3 (13.6)
Tacrolimus	1 (4.5)

IIM-ILD, idiopathic inflammatory myositis-associated interstitial lung disease; i.v., intra venous.

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Table S4 Diagnostics, treatment and vital status of patients with IIM-ILD

Patient	Diagnosis	Symptoms & signs	Evidence of myositis	Antibodies	Place of treatment at onset	First-line treatment	Further treatment	Vital status
1	CADM[1]	Cough, fever, muscle weakness, myalgia, Gottron's papules, abnormal capillaroscopy,	Elevated CK, myositis in MRI, muscle biopsy did not confirm myositis	MDA5, P-ANCA, RF, CCP-Ab	ICU	cyclophosphamide i.v., pulse steroid x3 i.v.	Prednisolone, azathioprine, rituximab	Died after 3 months
2	ASyS[2] + polymyalgia rheumatica	Cough, dyspnea, sicca, muscle weaknes, myalgia, arthralgia, abnormal capillaroscopy, fever	–	PL-7	Pulm. ward.	–	Prednisolone, azathioprine, cyclophosphamide, cyclosporine	Died after 2,8 years
3	DM[1]	Cough, fever, livedo reticularis, synovitis, Raynaud, muscle weakness, myalgia, finger ulcers, abnormal capillaroscopy	Elevated CK and aldolase, abnormal ENMG, myositis in muscle biopsy	ANA	Outpatient clinic	Prednisolone, azathioprine	i.v. cyclophosphamide x3, pulse steroid x3 i.v., cyclosporine, rituximab	Alive for 15.9 years
4	CADM[1]	Cough, fever, Raynaud, muscle weakness, myalgia, synovitis, Gottron's papules, finger ulcers, abnormal capillaroscopy	Marginally elevated aldolase	–	Pulm. ward.	Prednisolone, cyclophosphamide p.o.	Cyclosporine, rituximab, mycophenolate	Died after 8.7 years
5	PM + ASyS[1,2,3]	Cough, dyspnea, fever, Raynaud, muscle weakness, myalgia, sicca, synovitis	Elevated CK, myopathy in muscle biopsy	Jo-1, SSA, RNP	Pulm. ward	Prednisolone	Prednisolone, shortly (1-2months) tried several immunosuppressants but experienced side-effects	Alive for 11.1 years
6	PM + ASyS[1,2,3]	Cough, hemoptysis, fever, muscle weakness, myalgia, synovitis, sicca, abnormal capillaroscopy, telangiectasia	Elevated CK and myoglobin, abnormal ENMG	Jo-1, SSA, SSB, RF, ANA	ICU	Pulse steroid x2 i.v., prednisolone, cyclophosphamide i.v.	Cyclophosphamide, rituximab, azathioprine, mycophenolate, cyclosporine	Died after 2.1 years
7	ASyS[2]	Dyspnea, cough, synovitis, muscle weakness, myalgia, fever	Elevated myoglobin	PL-12, SSA, SSB, RF, ANA	ICU	Pulse steroid x3 i.v., cyclophosphamide i.v	Rituximab, prednisolone	Died after 3.4 years
8	PM + ASyS[1,2]	Cough, dyspnea, fever, synovitis, difficulty to open mouth, muscle weakness	Elevated aldolase	JO-1, SSA, ANA	ICU	Prednisolone, cyclophosphamide i.v.	–	Died after 17 days
9	PM + ASyS[1,2,3]	Cough, dyspnea, fever, synovitis, mechanic's hands, finger and oral ulcers, Raynaud, muscle weakness, myalgia, abnormal capillaroscopy	Elevated CK, abnormal ENMG, myositis in muscle biopsy	Jo-1, SSA	Pulm. ward.	Prednisolone	Azathioprine	Alive for 9.1 years
10	CADM[1]	Cough, dyspnea, dysphagia, synovitis, muscle weakness, Raynaud, Gottron's papules, heliotrope rash, abnormal capillaroscopy	–	–	Pulm.ward	Pulse steroid x3 i.v., cyclosporine	Prednisolone, cyclosporine	Alive for 6.2 years
11	DM[1] + RA	Dyspnea, synovitis, sicca, muscle weakness, myalgia, rash	Elevated CK and myoglobin, abnormal ENMG and MRI, myositis in muscle biopsy	SSA	Outpatient clinic	Prednisolone, oxiklorin, azathioprine, podophyllotoxine	Pulse steroid x3 i.v., cyclophosphamide, rituximab	Died after 11.9 years of the RA diagnosis and 11 months after the DM diagnosis
12	CADM[1] + CREST	Dyspnea, fever, synovitis, muscle weakness, abnormal capillaroscopy, Raynaud, finger ulcers, dysphagia, sensitivity to sun	Elevated CK	MDA5, ACAs, SSA	Pulm. ward	Prednisolone, cyclophosphamide i.v.,	Rituximab, ciclosporine	Alive for 5.1 years
13	RA + ASyS[2,3]	Synovitis, mechanic's hands, myalgia, finger ulcers, sensitivity to sun	–	Jo1, RF, CCP-Ab	Outpatient clinic	Prednisolone, azathioprine	Rituximab, azathioprine, oxiklorin, prednisolone	Alive for 8.0 years
14	ASyS[2,3]	Myalgia, fever, sicca, Gottron's papules, mechanic's hands, Raynaud, arthralgia	–	PL-7, SSA, RF, ANA	Pulm. ward.	Prednisolone	Azathioprine, ciclosporine	Alive for 5.9 years
15	CADM[1]	Myalgia, arthralgia, fever, Gottron's papules, finger ulcers, dysphagia, dry mouth	Elevated CK	MDA-5, SSA	ICU	Prednisolone, rituximab, cyclophosphamide p.o., plasmaferesis	Tacrolimus, prednisolone	Alive for 1.9 years
16	ASyS[2]	Myalgia, arthralgia, fever, rash	–	Jo-1, SSA, Sm	Outpatient clinic	Prednisolone	Prednisolone, oxiklorin	Alive for 2.2 years
17	RA + ASyS[2]	Synovitis	–	Jo-1, ACAs, ANA, RF, CCP-Ab,	Outpatient clinic	Prednisolone, azathioprine	Prednisolone, azathioprine, podophyllotoxin	Died after 12.3 years
18	PM[1]	Muscle weakness, myalgia, arthralgia, Raynaud, thickened skin, rash, swelling of lower limb	Elevated CK and myoglobin	Pm-Scl75	Outpatient clinic	Prednisolone	Prednisolone, mycophenolate	Alive for 2.7 years
19	ASyS[2]	Muscle weakness, sicca, abnormal capillaroscopy	–	PL-7, SSA, ANA	Outpatient clinic	Prednisolone, azathioprine	Prednisolone, azathioprine, mycophenolate, ciclosporine	Alive for 4.1 years
20	RA + ASyS[2]	Synovitis	–	Jo-1	Outpatient clinic	Prednisolone, oxiklorin, azathioprine	Prednisolone, azathioprine, mycophenolate, podophyllotoxin, auranofin, cyclophosphamide	Died after 14.9 years
21	SjS + ASyS[2]	Arthralgia, sicca, dry mouth, myalgia, fever, finger ulcers	–	PL-7, SSA, RF, ANA	Outpatient clinic	–	Oxiklorin, prednisolone, mycophenolate	Alive for 2.3 years
22	Ssc + ASyS[2]	Arthralgia, abnormal capillaroscopy, Raynaud, rash, finger ulcers, kiinteä iho, dysphagia, skin vasculitis	Elevated CK and aldolase	Jo-1	Outpatient clinic	Prednisolone, cyclosporine	Prednisolone, azathioprine, cyclophosphamide	Died after 5.5 years

All available antibodies are listed in the table. [1], European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) criteria; [2], Connors' criteria; [3], Solomon criteria. IIM-ILD, idiopathic inflammatory myositis-associated interstitial lung disease; PM, polymyositis; RA, rheumatoid arthritis; ASyS, antisynthetase syndrome; DM, dermatomyositis; CADM, clinically amyopathic dermatomyositis; SjS, Sjögren's syndrome; SSc= systemic sclerosis; CK, creatine kinase; ENMG, electroneuromyography; MDA5, anti-melanoma differentiation-associated gene 5; RF, rheumatoid factor; PL7, threonyl; ANA, antinuclear antibody; Jo-1, histidyl; ACAs, anti-centromere antibodies; CCP-Ab, anticyclic citrullinated peptide antibodies; PL-12-Ab, alanyl; SSA, Sjögren's-syndrome-related antigen A; SSB, Sjögren's syndrome-related antigen B; i.v., intra venously; p.o., per oral.

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