Acute exacerbation in rheumatoid arthritis associated interstitial lung disease

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Title: Acute exacerbation in rheumatoid arthritis associated interstitial lung disease

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ABSTRACT

Background Acute exacerbation (AE) in idiopathic pulmonary fibrosis is characterised by acute deterioration of respiratory status and the mortality is high. Recently, AE was reported in patients with other interstitial lung diseases, especially rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Objectives To investigate the risk factors and prognosis associated with AE in patients with RA-ILD.

Design A retrospective cohort study.

Setting A single academic hospital.

Participants 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA. ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings.

Main outcome measures Overall survival and cumulative AE incidence were analysed using Kaplan–Meier method. Cox hazards analysis was used to determine significant variables associated with AE occurrence and survival status.

Results A total of 11 patients (22%) developed AE, with an overall 1-year incidence of 2.8%. Univariate analysis revealed that higher age at ILD diagnosis [hazard ratio

(HR), 1.11; 95% confidence interval (CI), 1.02–1.21; $P = 0.01$], usual interstitial pneumonia (UIP) pattern on HRCT (HR, 1.95; 95% CI, 1.07–3.63; $P = 0.03$) and treatment with methotrexate (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were risk factors for AE. Of 11 patients who developed AE during observation period, seven (64%) died of initial AE. In survival, AE was a prognostic factor for poor outcome (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$).

Conclusions In patients with RA-ILD, higher age at ILD diagnosis, UIP pattern on HRCT and treatment with methotrexate are risk factors for AE. Furthermore, AE has a serious impact on their survival. We should carefully observe the patients having any of these risk factors.

Article focus;

Acute exacerbation occurs not only in patients with idiopathic pulmonary fibrosis (IPF) but also in patients with rheumatoid arthritis associated interstitial lung disease (RA-ILD).

What is the risk factor for AE and does AE impact on prognosis in patients with RA-ILD?

Key messages;

In patients with RA-ILD, higher age at ILD diagnosis, UIP pattern on HRCT, and treatment with methotrexate are risk factors for AE occurrence.

In patients with RA-ILD, AE is associated with poor prognosis.

Strengths and limitations of this study;

AE may have a serious impact on the survival of patients with RA-ILD as well as that with IPF. Thus, the patients with any of these risk factors should be carefully observed.

Given its retrospective study design, it is subject to several possible biases. Therefore, prospective studies are necessary to confirm our results.

INTRODUCTION

Acute exacerbation (AE) is a recently established and an increasingly recognised occurrence in idiopathic pulmonary fibrosis (IPF).[1] AE is characterized by acute deterioration in respiratory status, with newly developed bilateral ground-glass opacities and/or consolidations on chest radiographs or computed tomography scans. It should be in the absence of other alternative causes such as infection, left heart failure, pulmonary embolism, and an identifiable cause of acute lung injury. AE reportedly occurs not only in patients with IPF but also in patients with other interstitial lung diseases (ILDs), including idiopathic nonspecific interstitial pneumonia (NSIP), collagen vascular disease-associated ILDs (CVD-ILDs) and other forms of ILD.[2-4] The in-hospital mortality associated with AE in patients with CVD-ILD was demonstrated to be as high as that in patients with IPF,[1-4] suggesting that AE may be associated with poor prognosis in patients with CVD-ILD.

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder of unknown etiology that primarily involves joints.[5] ILD is the most common extra-articular manifestations,[6] with a prevalence of 1%–58%.[7-12] We and Park *et al* previously reported that RA-associated ILD (RA-ILD) was the most common CVD-ILD associated with AE.[3, 4] However the risk factors and prognosis associated with AE in patients

with RA-ILD are not clarified.

In the present study, we attempted to elucidate the cumulative incidence of AE, its risk factors, and prognostic factors in patients with RA-ILD.

MATERIALS AND METHODS

Subjects

Institutional review board in Hamamatsu University School of Medicine approved this study (approval number 24-191) and waived patient approval or informed consent because the study involved a retrospective review of patient records and images. We retrospectively reviewed 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012 at Hamamatsu University Hospital in Japan. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA.[13] Patients with other coexisting CVD were excluded. In addition, because our aim was to investigate the features of AE among patients with a chronic course of RA-ILD, patients with no evidence of chronic ILD were also excluded.

ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings. HRCT findings such as bilateral areas with ground-glass attenuation, reticular opacities

and honeycomb patterns were interpreted and defined as ILD by a consensus between radiologists and pulmonologists. All cases underwent transbronchial lung biopsy and bronchoalveolar lavage, and 21 (41%) cases underwent surgical lung biopsy (SLB) to definitively diagnose ILD or rule out other diseases. The patients with environmental exposures, suspected of drug induced pneumonia (ILD developed within 1 year after initiation of new drug), or with other known causes of ILD were excluded after considering exposure history and the findings of appropriate tests and histopathological examinations.

Acute exacerbation (AE)

AE was defined using recently proposed criteria[1] that were slightly modified for adaptation to RA-ILD: previous diagnosis of RA-ILD, unexplained worsening or development of dyspnea within 30 days of onset, new bilateral ground-glass abnormalities and/or consolidation superimposed on a reticular or honeycomb pattern on HRCT, no evidence of pulmonary infection on negative respiratory culture, including endotracheal aspirate or bronchoalveolar lavage, and serological test results for respiratory pathogens, and exclusion of alternative causes such as left heart failure, pulmonary embolism, and an identifiable cause of acute lung injury. Patients with AE

were required to meet all five criteria. In our institution, cultures of sputum, blood, urine, and bronchoalveolar lavage fluid, and serological tests examined for mycobacteria, fungi, bacteria, and some viruses were routinely performed. Echocardiography and, if necessary, CT scanning with intravenous contrast were performed to rule out left heart failure or pulmonary thromboembolism. The patients who developed acute pneumonitis within 1 year after initiation of drug for RA were excluded because drug-induced pneumonitis was not completely ruled out. Patients who did or did not develop AE during the observation period were classified into the AE and non-AE groups, respectively.

Data collection

All clinical and laboratory data were collected from medical records. The observation period was calculated from the date of diagnosis of RA-ILD to the last visit. The AE-free period was defined as the time elapsed between the date of RA-ILD diagnosis and the first AE occurrence (AE group) or the last visit (non-AE group).

Review of radiographic findings

HRCT images taken at the time of RA-ILD diagnosis were reviewed. These images

comprised 1 to 2.5-mm collimation sections at 10 mm intervals. They were reconstructed by a high spatial frequency algorithm, and were displayed at window settings appropriate for viewing the lung parenchyma (window level, -600 to -800 Hounsfield units; window width, 1200 to 2000 Hounsfield units). HRCT images were randomised and reviewed independently by two expert chest radiologists (with 23 and 12 years of experience) who were unaware of the related clinical information.

RA-ILD on HRCT was classified as a usual interstitial pneumonia (UIP) pattern or a non-UIP pattern according to recent guideline.[14] Briefly, a UIP pattern on HRCT was characterised by subpleural and basal predominance, reticular abnormalities, honeycombing with or without traction bronchiectasis and the absence of features listed as inconsistent with a UIP pattern, including upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormalities, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping and consolidation in bronchopulmonary segment(s)/lobe(s). If the HRCT pattern did not meet the criteria, it was interpreted as a non-UIP pattern. Disagreements regarding HRCT interpretation were resolved by a consensus between both radiologists.

Review of histopathological findings

SLB specimens were obtained from at least two sites. A diagnosis of RA-ILD was originally made in all cases on the basis of histological features evaluated by a lung pathologist at our hospital, correlated with the clinical and radiological findings. All SLB specimens were also reviewed by a second lung pathologist with 36 years of experience. The histological classification of interstitial pneumonia was based on the consensus statement criteria for idiopathic interstitial pneumonias,[15] and histological patterns that could not be classified according to the criteria were categorised as unclassified interstitial pneumonia.

Statistical analysis

All values are expressed as median (range) or number (%). The Mann-Whitney U test was used for nonparametric comparisons involving continuous data, whereas Fisher's exact test was used for comparing categorical data. Interobserver agreement on HRCT pattern was analyzed using the κ statistic test. Interobserver agreement was classified as follows: poor (κ = 0–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80) and excellent (κ = 0.81-1.00). Survival was evaluated using the Kaplan–Meier method and the log-rank test. The cumulative AE incidence was obtained from a Kaplan–Meier survival curve by treating AE as the death variable. The 1-year

AE incidence was calculated by dividing the number of patients who developed AE by the total of AE-free period (year) of all the patients. Cox hazards analysis was used to determine significant variables associated with survival and AE occurrence. In all analyses, $P < 0.05$ was considered statistically significant. All data were analysed using commercially available software (JMP version 9.0.3a, SAS Institute Inc, Cary, NC, USA).

RESULTS

Patient characteristics (Table 1)

The median age at onset of RA and diagnosis of RA-ILD was 61 (range, 28–82) years and 62 (range, 31–83) years, respectively. The median observation period and AE-free period was 8.5 (range, 1–17) years and 7 (range, 1–17) years, respectively.

During the observation period, 11 patients (22%) developed AE. The median age at the onset of AE was 72 (range, 60–86) years. There were no statistically significant differences in age at onset of RA, age at diagnosis of RA-ILD, sex, observation period, AE-free period, smoking habits, predicted forced vital capacity (%FVC) and arterial oxygen pressure (PaO_2) between the AE and non-AE groups.

In the AE group, seven of 11 patients (64%) died of initial AE during the observation

period. In the non-AE group, 5 of 40 patients (13%) died. There was a statistically significant difference in the mortality rate between the AE and non-AE groups.

HRCT pattern (Table 1)

Of the 51 patients with RA-ILD, 14 (27%) exhibited the UIP pattern on HRCT. HRCT images of eight of 40 patients (20%) in the non-AE group and six of 11 (55%) patients in the AE group demonstrated a UIP pattern. Interobserver agreement between both radiologists was moderate (κ statistic test, $\kappa = 0.44$). The number of patients who exhibited a UIP pattern on HRCT was significantly higher in the AE group than in the non-AE group.

Correlation between histopathological findings and HRCT pattern (Table 2)

Among the 51 patients, 21 (41%) underwent SLB. Histopathological analysis revealed a UIP in 12 patients, NSIP in 7, desquamative interstitial pneumonia in 1 and an unclassified interstitial pneumonia in 1. The correlation between histopathological and HRCT pattern was evaluated in 21 histopathologically confirmed patients. When the pattern was identified as a UIP pattern on HRCT, the sensitivity, specificity, positive predictive value and negative predictive value for detecting histopathological UIP was

41.7%, 100%, 100% and 56.3%, respectively.

Treatment for RA (Table 3)

Of the 51 patients, 37 (73%) had received treatment for RA at their final visit (non-AE group) or at AE onset (AE group). Specifically, 29 patients (57%) received corticosteroids, 17 (33%) received immunosuppressants except for MTX, 10 (20%) received MTX and 17 (33%) received other drugs. The number of patients who received MTX was significantly higher in the AE group than in the non-AE group (55% vs. 10%, $P = 0.001$).

AE incidence

The cumulative AE incidence in patients with RA-ILD is shown in Figure 1. The AE incidence was significantly higher in patients with a UIP pattern on HRCT (UIP pattern group) than in patients with a non-UIP pattern on HRCT (non-UIP pattern group) (log-rank test, $P = 0.018$). The overall 1-year AE incidence was 2.8%. The 1-year AE incidence was 6.5% in the UIP pattern group and 1.7 % in the non-UIP pattern group.

Univariate analysis (Table 4) revealed that higher age at ILD diagnosis [hazard ratio (HR), 1.11; 95% confidence interval (CI), 1.02–1.21; $P = 0.01$], UIP pattern on HRCT

(HR, 1.95; 95% CI, 1.07–3.63; $P = 0.03$) and treatment with MTX (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were significant risk factors for AE occurrence.

Survival

The overall survival of patients with RA-ILD is shown in Figure 2. The 5-year survival was 90% in all patients, 70% in the UIP pattern group and 97% in the non-UIP pattern group. Survival was significantly poorer in the UIP pattern group than in the non-UIP pattern group (log-rank test, $P = 0.04$). In addition, significantly worse survival was demonstrated in the AE group compared with the non-AE group (Figure 3, log-rank test, $P = 0.001$).

Univariate analysis (Table 5) revealed that higher age at ILD diagnosis (HR, 1.08; 95% CI, 0.99–1.17; $P = 0.057$) and UIP pattern on HRCT (HR, 1.74; 95% CI, 0.97–3.12; $P = 0.06$) showed a trend toward poor outcome, while AE (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$) was significantly associated with poor survival.

DISCUSSION

To our knowledge, the present study is the first one focusing on the risk factors and prognosis associated with AE in patients with RA-ILD. The overall 1-year AE incidence

was 2.8% among the RA-ILD patients. Univariate analysis identified that a UIP pattern on HRCT, MTX treatment and higher age at ILD diagnosis were significant risk factors for AE. Furthermore, AE was a prognostic factor for poor survival.

The 1-year AE incidence among patients with IPF has been reported to be 5-19%,[16, 17] whereas that among patients with other ILDs was 4.2% for idiopathic NSIP, 3.3 % for CVD-ILD and 5.6 % for CVD-UIP.[4] In the present study, patients with RA-ILD had a relatively lower incidence of AE. However, the 1-year AE incidence among patients with a UIP pattern on HRCT was 6.5%, comparable to that in patients with IPF. Furthermore, a UIP pattern on HRCT was a risk factor for AE. In a previous report of small number of biopsy-proven cases, AE incidence among patients with RA-UIP was 11.1%, also similar to that among patients with IPF.[4] The correlation between pathological and radiological UIP patterns has been established in IPF, but not in RA-ILD.[18] In the present study, determination of a UIP pattern on HRCT exhibited high specificity and positive predictive values for the detection of pathological UIP. Therefore, a typical UIP pattern on HRCT was assumed to be highly suggestive of pathological UIP in patients with RA-ILD as well as IPF.[14, 18] Collectively, these results suggest that AE occurs less frequently in RA-ILD than in IPF, while AE incidence in a subgroup with pathological UIP or a UIP pattern on HRCT may be as

high as that in patients with IPF.

The present study also identified MTX treatment as a risk factor for AE. MTX is widely used to treat RA, while its toxicity affects the pulmonary system. Diagnostic criteria for MTX-associated pneumonitis (MTX-pneumonitis) have been proposed previously.[19] However, the specificity of the criteria has not been fully examined yet. MTX-pneumonitis typically occurs with acute/subacute onset early in the course of MTX treatment,[19-22] in particular, mostly within the first year[23] and often presents a hypersensitive pneumonitis pattern. Patients with MTX-pneumonitis generally respond to discontinuation of MTX or corticosteroid treatment and have a favorable prognosis.[19-22] In the present study, 6 of 11 patients with AE had received MTX, and 5 of the 6 patients had been treated for 3 or more years. The remaining patient had been treated for 1 year. In all 6 patients, their respiratory conditions progressively deteriorated despite discontinuation of MTX, and they poorly responded to high-dose corticosteroid. Consequently, on the basis of inconsistency in terms of MTX treatment duration and clinical features, we diagnosed these patients with AE of RA-ILD. Similar to AE in patients with IPF, the etiology of AE in RA-ILD is unknown; however, several reports have suggested that AE may be a distinct manifestation of the primary disease process, a distinct condition associated with undiagnosed infection, or a subsequent

acceleration of a fibroproliferative process caused by acute direct stress to the lung.[1] In the present study, RA joint disease activity in all patients with AE was stable at the time of AE occurrence; therefore, RA activity may not be related to AE occurrence, a finding similar to that of a previous study.[4] MTX possibly accelerates the fibroproliferative process of RA-ILD. It was reported that MTX treatment was a risk factor for RA-ILD progression.[10] For RA-ILD, MTX may be associated not only with newly developing drug-induced pneumonitis but also with deterioration of pre-existing ILD, including AE. Therefore, we think that MTX treatment should be avoided in RA patients with ILD.

The present study found that patients with a UIP pattern on HRCT had significantly poorer survival than those with a non-UIP pattern. In addition, AE was a prognostic factor for poor outcome. AE has a serious impact on the survival of patients with IPF,[17] and it may also affect the prognosis in other ILDs.[3, 4] Consistent with these reports, the present study revealed that seven (64%) of 11 patients with AE died of respiratory failure, giving rise to high in-hospital mortality, and that survival in the AE group was significantly poorer than that in the non-AE group. Therefore, AE is suggested to be a predictor of poor prognosis in patients with RA-ILD as well as patients with IPF.

Other prognostic factors in RA-ILD have been reported, including pathological UIP,[24-28] UIP pattern on HRCT,[29] and age at RA-ILD onset.[30] In the present study, pathological UIP could not be identified as prognostic factors because the number of biopsy-proven cases were small. However, we observed similar results regarding UIP pattern on HRCT and age at RA-ILD onset.

This study had several limitations. First, given its retrospective study design, it is subject to several possible biases. For instance, selection and recall bias may exist. Second, because of the relatively small sample size, it may be difficult to determine the precise incidence of AE. Therefore, larger studies are necessary to confirm our results. Third, because the presence of a UIP pattern on HRCT had low sensitivity for the detection of pathologic UIP, it was likely that some patients with a non-UIP pattern on HRCT may have had pathological UIP. Finally, RA includes a variety of manifestations. Therefore, other comorbidities may have affected the results.

In conclusion, higher age at ILD diagnosis, UIP pattern on HRCT and treatment with MTX are risk factors for AE occurrence in patients with RA-ILD. Furthermore, the mortality associated with AE is high and AE is prognostic factor for poor outcome. AE has a serious impact on the survival of patients with RA-ILD. Thus, we should carefully observe the patients having any of these risk factors.

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Y.N. had full access to all the data in present study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authorship:

H.H., Y.N., T.S., and K.C. designed research; H.H., D.H., T.F., and N.I. contributed acquisition of data; H.H., Y.N., T.J., H.S, T.C., M.K., N.E., and T.S. interpreted and analyzed data.

H.H., Y.N., T.J., and T.C. wrote the paper; and H.S., M.K., D.H., N.E., T.F., N.I., T.S., and K.C. revised the paper.

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Data sharing:

No unpublished data from the study are available.

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Table 1 Clinical characteristics

Characteristics	Total N = 51 (100)	Non-AE group[#] N = 40 (78)	AE group[¶] N = 11 (22)	P value[+]
Median age, years (range)				
at RA diagnosis	61 (28-82)	60 (28-81)	65 (42-82)	0.15
at ILD diagnosis	62 (31-83)	62 (31-83)	69 (58-83)	0.15
at AE onset			72 (60-86)	
Sex Male, n (%)	29 (57)	23 (58)	6 (55)	0.86
Observation period, years (range)	8.5 (1-17)	9 (1-17)	6.4 (2-14)	0.45
AE-free period, years (range)	7(1-17)	9 (1-17)	6 (2-14)	0.19
Smoking habit, n (%)				
Never	20 (39)	18 (45)	2 (18)	
Former	24 (47)	16 (40)	8 (73)	0.15
Current	7 (14)	6 (15)	1 (9)	
PaO_2, torr (range)	82.4 (67-109)	81 (67-102)	85.8 (74-109)	0.19
%FVC, % (range)	91.1 (50.6-130)	87.5 (51-130)	95 (60-125)	0.38
HRCT pattern, n (%)				
UIP pattern	14 (27)	8 (20)	6 (55)	0.02[§]
non-UIP pattern	37 (73)	32 (80)	5 (45)	
Death during observation period, n (%)	12 (24)	5 (13)	7 (64)	0.001[§]
caused by respiratory failure	8 (16)	2 (5)	7 (64)	0.02[§]
caused by other diseases	4 (8)	3 (8)	0 (0)	

Data are presented as n (%), median (range).

AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; HRCT, high resolution computed tomography; UIP pattern, usual interstitial pneumonia pattern.

[#]Non-AE group, patients who did not develop AE during observation period.

[¶] AE group, patients who developed AE during observation period.

[+] Non-AE group vs AE group

[§] $p < 0.05$

In the AE group, 7 patients died of respiratory failure caused by AE. In the non-AE group, 2 died of respiratory failure caused by bacterial pneumonia or pneumocystis pneumonia, 1 of gastric bleeding and 2 of unknown causes.

Table 2 Correlation between histopathological findings and HRCT pattern in 21 histopathologically confirmed patients.

	Histopathological pattern		Total
	UIP	Other pattern	
UIP pattern on HRCT	5	0	5
non-UIP pattern on HRCT	7	9	16
Total	12	9	21

Data are presented as number.

HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

Other pattern means other histopathological pattern except for UIP including nonspecific interstitial pneumonia, desquamative interstitial pneumonia and unclassifiable interstitial pneumonia.

When HRCT pattern was identified as a UIP pattern on HRCT, the sensitivity, specificity, positive predictive value and negative predictive value for detecting histopathological UIP was 41.7%, 100%, 100% and 56.3%, respectively.

Table 3 Treatment for RA at final visit[#] or AE onset[¶]

	Total N = 51	non-AE group[+] N = 40 (78%)	AE group[§] N = 11 (22%)	P value
Treatment, yes	37 (73)	27(68)	10 (91)	0.12
Corticosteroid	29 (57)	22 (55)	7 (64)	0.61
Immunosuppressant except for MTX	17 (33)	14 (35)	3 (27)	0.63
MTX	10 (20)	4 (10)	6 (55)	0.001[*]
Other drugs	17 (33)	13 (33)	4 (36)	0.81

Data are presented as n (%) and compared between non-AE group and AE group using Fisher's exact test.

Immunosuppressant except for MTX included azathioprine (n=1), cycrophosphaminde (n=1), etanercept (n=2), mizoribine (n=7), and tacrolimus (n=6).

Other drugs included actarit (n=2), bucillamine (n=5), meloxicam (n=1), and salazosulfapyridine (n=11).

AE, acute exacerbation; ILD, interstitial lung disease; MTX, methotrexate.

[#] In non-AE group.

[¶] In AE group.

[+] Non-AE group, patients who did not develop AE during the observation period.

[§] AE group, patients who developed AE during observation period.

[*] $p < 0.05$

Table 4 Risk factors for AE occurrence according to univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	1.03	0.97-1.10	0.35
Age at ILD diagnosis	1.11	1.02-1.21	0.01+
Sex, male	0.90	0.49-1.69	0.73
Smoking habit, yes	1.60	0.81-4.10	0.19
UIP pattern on HRCT, yes	1.95	1.07-3.63	0.03+
PaO_2 at ILD diagnosis	1.05	0.98-1.12	0.14
%FVC at ILD diagnosis	1.02	0.99-1.06	0.24
Treatment for RA at final visit# or AE onset¶			
Corticosteroids	0.97	0.53-1.92	0.94
Immunosuppressant except for MTX	0.76	0.35-1.41	0.39
MTX	3.04	1.62-6.02	0.001+
Other drugs	0.98	0.50-1.80	0.96

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

In non-AE group.

¶ In AE group.

+ $p < 0.05$

Table 5 Prognostic factors for survival, univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	0.98	0.93-1.04	0.48
Age at ILD diagnosis	1.08	0.99-1.17	0.057
Sex, male	1.14	0.63-2.22	0.67
Smoking habit, yes	1.70	0.87-4.35	0.13
UIP pattern on HRCT, yes	1.74	0.97-3.12	0.06
PaO_2 at ILD diagnosis	1.05	0.98-1.11	0.15
%FVC at ILD diagnosis	1.01	0.98-1.04	0.55
AE during observation period, yes	2.47	1.39-4.56	0.003[+]
Treatment for RA at final visit[#] or AE onset[¶]			
Corticosteroids	1.23	0.67-2.65	0.52
Immunosuppressant except for MTX	0.69	0.32-1.27	0.25
MTX	1.44	0.67-2.68	0.31
Other drugs	0.76	0.36-1.41	0.40

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

[#] In non-AE group.

[¶] In AE group.

[+] $p < 0.05$

Figure legends

Figure 1. Cumulative AE incidence in patients with RA-ILD.

Patients with UIP pattern on HRCT had a significantly higher incidence of AE compared with non-UIP pattern on HRCT (log-rank p=0.018).

AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 2. Overall survival and the survival according to HRCT pattern subgroup.

Patients with UIP pattern on HRCT had a significantly worse survival compared with those with non-UIP pattern on HRCT (log-rank p=0.04).

UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 3. Survival of AE group and non-AE group.

Patients who developed AE during observation periods (AE group) had a significantly worse survival compared with those who did not (non-AE group) (log-rank p=0.001).

AE, acute exacerbation.

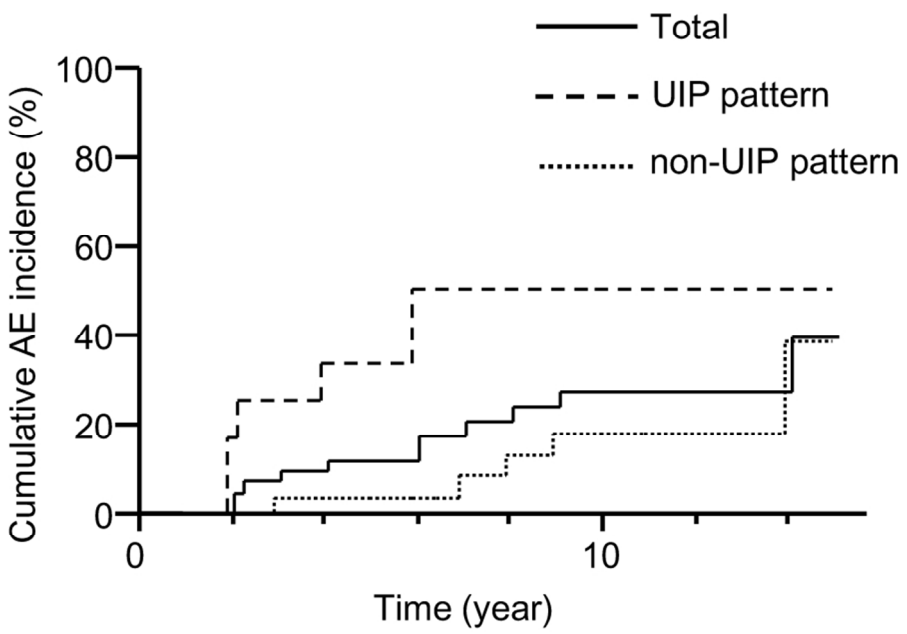

FIGURE 1.

Figure 1. Cumulative AE incidence in patients with RA-ILD.

Patients with UIP pattern on HRCT had a significantly higher incidence of AE compared with non-UIP pattern on HRCT (log-rank p=0.018).
AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.
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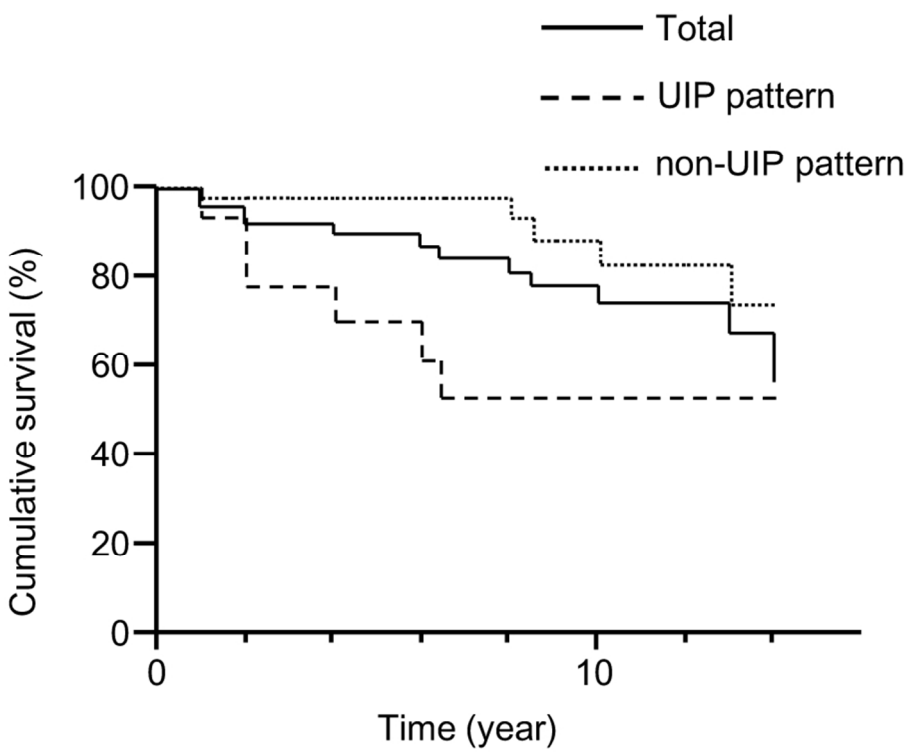

FIGURE 2.

Figure 2. Overall survival and the survival according to HRCT pattern subgroup.

Patients with UIP pattern on HRCT had a significantly worse survival compared with those with non-UIP pattern on HRCT (log-rank p=0.04).
UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.
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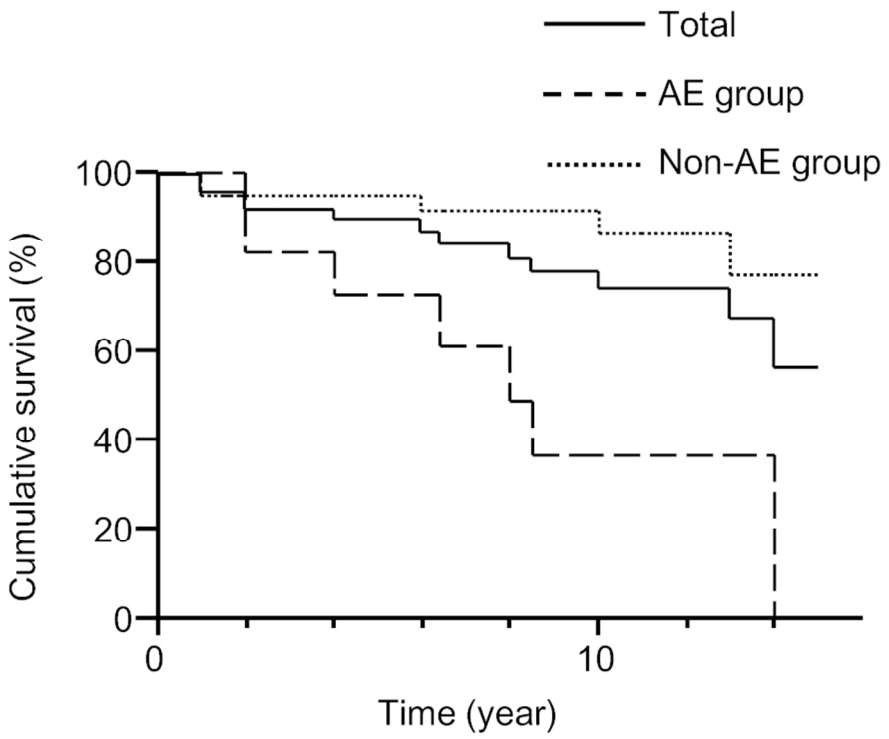

FIGURE 3.

Figure 3. Survival of AE group and non-AE group.

Patients who developed AE during observation periods (AE group) had a significantly worse survival compared with those who did not (non-AE group) (log-rank p=0.001).
AE, acute exacerbation.
85x85mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Acute exacerbation in rheumatoid arthritis associated interstitial lung disease

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ABSTRACT

Background Acute exacerbation (AE) in idiopathic pulmonary fibrosis is characterised by acute deterioration of respiratory status and the mortality is high. Recently, AE was reported in patients with other interstitial lung diseases, especially rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Objectives To investigate the risk factors and prognosis associated with AE in patients with RA-ILD.

Design A retrospective case-control study.

Setting A single academic hospital.

Participants 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA. ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings.

Main outcome measures Overall survival and cumulative AE incidence were analysed using Kaplan–Meier method. Cox hazards analysis was used to determine significant variables associated with AE occurrence and survival status.

Results A total of 11 patients (22%) developed AE, with an overall 1-year incidence of 2.8%. Univariate analysis revealed that higher age at ILD diagnosis [hazard ratio

(HR), 1.11; 95% confidence interval (CI), 1.02–1.21; $P = 0.01$], usual interstitial pneumonia (UIP) pattern on HRCT (HR, 1.95; 95% CI, 1.07–3.63; $P = 0.03$) and treatment with methotrexate (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were risk factors for AE. Of 11 patients who developed AE during observation period, seven (64%) died of initial AE. In survival, AE was a prognostic factor for poor outcome (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$).

Conclusions In patients with RA-ILD, higher age at ILD diagnosis, UIP pattern on HRCT and treatment with methotrexate are risk factors for AE. Furthermore, AE has a serious impact on their survival.

Article focus;

Acute exacerbation occurs not only in patients with idiopathic pulmonary fibrosis (IPF) but also in patients with rheumatoid arthritis associated interstitial lung disease (RA-ILD).

What is the risk factor for AE and does AE impact on prognosis in patients with RA-ILD?

Key messages;

In patients with RA-ILD, higher age at ILD diagnosis, UIP pattern on HRCT, and treatment with methotrexate are risk factors for AE occurrence.

In patients with RA-ILD, AE is associated with poor prognosis.

Strengths and limitations of this study;

AE has a serious impact on the survival of patients with RA-ILD.

Given its retrospective study design, it is subject to several possible biases. Therefore, prospective studies are necessary to confirm our results.

INTRODUCTION

Acute exacerbation (AE) is a recently established and an increasingly recognised occurrence in idiopathic pulmonary fibrosis (IPF).[1] AE is characterised by acute deterioration in respiratory status, with newly developed bilateral ground-glass opacities and/or consolidations on chest radiographs or computed tomography scans. It should be in the absence of other alternative causes such as infection, left heart failure, pulmonary embolism, and an identifiable cause of acute lung injury. AE reportedly occurs not only in patients with IPF but also in patients with other interstitial lung diseases (ILDs), including idiopathic nonspecific interstitial pneumonia (NSIP), collagen vascular disease-associated ILDs (CVD-ILDs) and other forms of ILD.[2-4] The in-hospital mortality associated with AE in patients with CVD-ILD was demonstrated to be as high as that in patients with IPF,[1-4] suggesting that AE may be associated with poor prognosis in patients with CVD-ILD.

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder of unknown etiology that primarily involves joints.[5] ILD is one of common extra-articular manifestations.[6, 7] The reported prevalence is variable (1–58%) and depends on the detection and diagnostic method, or the selected population.[8-13] We and Park *et al* previously reported that RA-associated ILD (RA-ILD) was the most common

CVD-ILD associated with AE.[3, 4] However the risk factors and prognosis associated with AE in patients with RA-ILD are not clarified.

In the present study, we attempted to elucidate the cumulative incidence of AE, its risk factors, and prognostic factors in patients with RA-ILD.

MATERIALS AND METHODS

Subjects

Institutional review board in Hamamatsu University School of Medicine approved this study (approval number 24-191) and waived patient approval or informed consent because the study involved a retrospective review of patient records and images. We retrospectively reviewed 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012 at Hamamatsu University Hospital in Japan. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA.[14] Patients with other coexisting CVD were excluded. In addition, because our aim was to investigate the features of AE among patients with a chronic course of RA-ILD, patients with no evidence of chronic ILD were also excluded.

ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings.

HRCT findings such as bilateral areas with ground-glass attenuation, reticular opacities and honeycomb patterns were interpreted and defined as ILD by a consensus between radiologists and pulmonologists. All cases underwent transbronchial lung biopsy and bronchoalveolar lavage, and 21 (41%) cases underwent surgical lung biopsy (SLB) to definitively diagnose ILD or rule out other diseases. The patients with environmental exposures, suspected of drug induced pneumonia (ILD developed within 1 year after initiation of new drug), or with other known causes of ILD were excluded after considering exposure history and the findings of appropriate tests and histopathological examinations.

Acute exacerbation (AE)

AE was defined using recently proposed criteria[1] that were slightly modified for adaptation to RA-ILD: previous diagnosis of RA-ILD, unexplained worsening or development of dyspnea within 30 days of onset, new bilateral ground-glass abnormalities and/or consolidation superimposed on a reticular or honeycomb pattern on HRCT, no evidence of pulmonary infection on negative respiratory culture, including endotracheal aspirate or bronchoalveolar lavage, and serological test results for respiratory pathogens, and exclusion of alternative causes such as left heart failure,

pulmonary embolism, and an identifiable cause of acute lung injury. Patients with AE were required to meet all five criteria. In our institution, cultures of sputum, blood, urine, and bronchoalveolar lavage fluid, and serological tests examined for mycobacteria, fungi, bacteria, and some viruses were routinely performed. Echocardiography and, if necessary, CT scanning with intravenous contrast were performed to rule out left heart failure or pulmonary thromboembolism. The patients who developed acute pneumonitis within 1 year after initiation of drug for RA were excluded because drug-induced pneumonitis was not completely ruled out. Patients who did or did not develop AE during the observation period were classified into the AE and non-AE groups, respectively.

Data collection

All clinical and laboratory data were collected from medical records. The observation period was calculated from the date of diagnosis of RA-ILD to the last visit. The AE-free period was defined as the time elapsed between the date of RA-ILD diagnosis and the first AE occurrence (AE group) or the last visit (non-AE group).

Review of radiographic findings

HRCT images taken at the time of RA-ILD diagnosis were reviewed. These images comprised 1 to 2.5-mm collimation sections at 10 mm intervals. They were reconstructed by a high spatial frequency algorithm, and were displayed at window settings appropriate for viewing the lung parenchyma (window level, -600 to -800 Hounsfield units; window width, 1200 to 2000 Hounsfield units). HRCT images were randomised and reviewed independently by two expert chest radiologists (with 23 and 12 years of experience) who were unaware of the related clinical information. Interobserver agreement was classified as follows: poor (κ = 0–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80) and excellent (κ = 0.81-1.00).

RA-ILD on HRCT was classified as a usual interstitial pneumonia (UIP) pattern or a non-UIP pattern according to recent guideline with slight modification.[15] Briefly, a UIP pattern on HRCT was characterised by subpleural and basal predominance, reticular abnormalities, honeycombing with or without traction bronchiectasis and the absence of features listed as inconsistent with a UIP pattern, including upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormalities, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping and consolidation in bronchopulmonary segment(s)/lobe(s). If

the HRCT pattern did not meet the criteria, it was interpreted as a non-UIP pattern. Disagreements regarding HRCT interpretation were resolved by a consensus between both radiologists.

Review of histopathological findings

SLB specimens were obtained from at least two sites. A diagnosis of RA-ILD was originally made in all cases on the basis of histological features evaluated by a lung pathologist at our hospital, correlated with the clinical and radiological findings. All SLB specimens were also reviewed by a second lung pathologist with 36 years of experience. The histological classification of interstitial pneumonia was based on the consensus statement criteria for idiopathic interstitial pneumonias,[16] and histological patterns that could not be classified according to the criteria were categorised as unclassified interstitial pneumonia.

Statistical analysis

All values are expressed as median (range) or number (%). The Mann-Whitney U test was used for nonparametric comparisons involving continuous data, whereas Fisher's exact test was used for comparing categorical data. Interobserver agreement on HRCT

pattern was analyzed using the κ statistic test. Survival was evaluated using the Kaplan–Meier method and the log-rank test according to observation period. The cumulative AE incidence was obtained from a Kaplan–Meier survival curve by treating AE as the death variable according to AE free period. The 1-year AE incidence was based on person year method and calculated by dividing the number of patients who developed AE by the total of AE-free period (year) of all the patients. Cox hazards analysis was used to determine significant variables associated with survival and AE occurrence. In all analyses, $P < 0.05$ was considered statistically significant. All data were analysed using commercially available software (JMP version 9.0.3a, SAS Institute Inc, Cary, NC, USA).

RESULTS

Patient characteristics (Table 1)

A total of 82 patients with RA-ILD were identified from medical records at Hamamatsu University Hospital. From these, 11 patients with other coexisting CVDs, 8 with no evidence of chronic ILD and an initial acute/subacute course of ILD, and 3 suspected of drug-induced pneumonitis were excluded. In addition, 9 patients for whom no initial HRCT images were available for review were also excluded. The remaining

51 patients with RA-ILD were included in this study.(Figure 1)

The median age at onset of RA and diagnosis of RA-ILD was 61 (range, 28–82) years and 62 (range, 31–83) years, respectively. The median observation period and AE-free period was 8.5 (range, 1–17) years and 7 (range, 1–17) years, respectively.

During the observation period, 11 patients (22%) developed AE. The median age at the onset of AE was 72 (range, 60–86) years. There were no statistically significant differences in age at onset of RA, age at diagnosis of RA-ILD, sex, observation period, AE-free period, smoking habits, predicted forced vital capacity (%FVC) at diagnosis of RA-ILD, and arterial oxygen pressure (PaO_2) at diagnosis of RA-ILD between the AE and non-AE groups. Also there were no statistically significant differences in articular disease activities (RF and DAS28-CRP) at the last visit (non-AE group) or the first AE occurrence (AE group).

In the AE group, seven of 11 patients (64%) died of initial AE during the observation period. In the non-AE group, 2 of 40 patients (5%) died of respiratory failure. There was a statistically significant difference in the mortality rate between the AE and non-AE groups.

Extra-articular manifestations except for ILD had been observed in 8 (16%) of 51 patients (pericarditis in 2 patients, pleuritis in 1, neuropathy in 2, cutaneous vasculitis in

2, glomerulonephritis in 1, rheumatoid nodule in 2). There was no significant difference in the incidence between AE group and non-AE group (27% vs. 13%, *P*=0.26).

HRCT pattern (Table 1)

Of the 51 patients with RA-ILD, 14 (27%) exhibited the UIP pattern on HRCT. HRCT images of eight of 40 patients (20%) in the non-AE group and six of 11 (55%) patients in the AE group demonstrated a UIP pattern. Interobserver agreement between both radiologists was moderate (κ statistic test, κ = 0.44). The number of patients who exhibited a UIP pattern on HRCT was significantly higher in the AE group than in the non-AE group.

When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

Diagnostic accuracy of HRCT pattern for histopathological pattern (Table 2)

Among the 51 patients, 21 (41%) underwent SLB. Histopathological analysis revealed a UIP in 12 patients, NSIP in 7, desquamative interstitial pneumonia in 1 and an unclassified interstitial pneumonia in 1. The diagnostic accuracy of HRCT pattern for histopathological pattern was evaluated in 21 histopathologically confirmed patients.

When the pattern was identified as a UIP pattern on HRCT, the sensitivity, specificity, positive predictive value and negative predictive value for detecting histopathological UIP was 41.7%, 100%, 100% and 56.3%, respectively.

Treatment for RA (Table 3)

Of the 51 patients, 37 (73%) had received treatment for RA at their final visit (non-AE group) or at AE onset (AE group). Specifically, 29 patients (57%) had received corticosteroids, 17 (33%) received immunosuppressants except for MTX, 10 (20%) received MTX and 17 (33%) received other drugs. There were 6 (55%) patients who had received MTX in AE group while 4 (10%) patients in non-AE group and statistically significant difference was observed between the groups ($P = 0.001$).

No patients had received MTX before in AE group while 2 in non-AE group. Thus, there were 6 (55%) patients who had experienced MTX treatment during observation period in AE group while 6 (15%) patients in non-AE group. Median cumulative MTX dose were 1952mg (384-3872) in 6 patients who had experienced MTX among AE group and 802mg (32-2496) in 6 patients among non-AE group. No statistically significant difference was observed between two groups in cumulative MTX dose (P=0.20).

Articular disease activities (RF and DAS28-CRP) were compared between patients who had received MTX at the last visit or at the first AE occurrence, and those who had not. Median RF (range) were 112 IU/mL (16-334) and 284 IU/mL (6-2666) (P=0.25), Median DAS28-CRP (range) were 1.94 (1.02-3.87) and 1.97 (1.02-5.13) (P=0.78), respectively. There were no statistically significant differences in articular disease activities.

AE incidence

The cumulative AE incidence in patients with RA-ILD is shown in Figure 2. The 5-year AE incidence was 11% [95% confidence interval (CI), 2–21%] in all patients, 33% (95% CI, 7–60%) in patients with a UIP pattern on HRCT (UIP pattern group) and 3% (95% CI, 0–9%) in patients with a non-UIP pattern on HRCT (non-UIP pattern group). The AE incidence was significantly higher in UIP pattern group than in non-UIP pattern group (log-rank test, P = 0.018). The overall 1-year AE incidence was 2.8%. The 1-year AE incidence was 6.5% in the UIP pattern group and 1.7 % in the non-UIP pattern group.

Univariate analysis (Table 4) revealed that higher age at ILD diagnosis [hazard ratio (HR), 1.11; 95% CI, 1.02–1.21; P = 0.01], UIP pattern on HRCT (HR, 1.95; 95% CI,

1.07–3.63; $P = 0.03$) and treatment with MTX (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were significant risk factors for AE occurrence.

Survival

The overall survival of patients with RA-ILD is shown in Figure 3. The 5-year survival was 90% (95% CI, 81–98%) in all patients, 70% (95% CI, 44–94%) in the UIP pattern group and 97% (95% CI, 92–100%) in the non-UIP pattern group. Survival was significantly poorer in the UIP pattern group than in the non-UIP pattern group (log-rank test, $P = 0.04$). In addition, significantly worse survival was demonstrated in the AE group compared with the non-AE group (Figure 4, log-rank test, $P = 0.001$).

Univariate analysis (Table 5) revealed that higher age at ILD diagnosis (HR, 1.08; 95% CI, 0.99–1.17; $P = 0.057$) and UIP pattern on HRCT (HR, 1.74; 95% CI, 0.97–3.12; $P = 0.06$) showed a trend toward poor outcome, while AE (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$) was significantly associated with poor survival.

DISCUSSION

To our knowledge, the present study is the first one focusing on the risk factors and

prognosis associated with AE in patients with RA-ILD. The overall 1-year AE incidence was 2.8% among the RA-ILD patients. Univariate analysis identified that a UIP pattern on HRCT, MTX treatment and higher age at ILD diagnosis were significant risk factors for AE. Furthermore, AE was a prognostic factor for poor survival.

The 1-year AE incidence among patients with IPF has been reported to be 5-19%,[17, 18] whereas that among patients with other ILDs was 4.2% for idiopathic NSIP, 3.3 % for CVD-ILD and 5.6 % for CVD-UIP.[4] In the present study, the 1-year AE incidence among patients with a UIP pattern on HRCT was 6.5% and cumulative incidence was significantly higher in UIP pattern group than in non-UIP pattern group. Furthermore, a UIP pattern on HRCT was a risk factor for AE. In a previous report of small number of biopsy-proven cases, AE incidence among patients with RA-UIP was reported to be 11.1%, similar to that among patients with IPF.[4] The correlation between pathological and radiological UIP patterns has been established in IPF, but not in RA-ILD.[19] In the present study, determination of a UIP pattern on HRCT exhibited high specificity and positive predictive values for the detection of pathological UIP pattern. Therefore, a typical UIP pattern on HRCT was assumed to be highly suggestive of pathological UIP pattern in patients with RA-ILD as well as IPF.[15, 19] Collectively, these results suggest that AE incidence in a subgroup with pathological UIP pattern or a UIP pattern

on HRCT may be higher than that in other patterns..

The present study also identified MTX treatment as a risk factor for AE. MTX is widely used to treat RA, while its toxicity affects the pulmonary system. Diagnostic criteria for MTX-associated pneumonitis (MTX-pneumonitis) have been proposed previously.[20] However, the specificity of the criteria has not been fully examined yet. MTX-pneumonitis typically occurs with acute/subacute onset early in the course of MTX treatment,[20-23] in particular, mostly within the first year[24] and often presents a hypersensitive pneumonitis pattern. Patients with MTX-pneumonitis generally respond to discontinuation of MTX or corticosteroid treatment and have a favorable prognosis.[20-23] In the present study, 6 of 11 patients with AE had received MTX, and 5 of the 6 patients had been treated for 3 or more years. The remaining patient had been treated for 1 year. In all 6 patients, their respiratory conditions progressively deteriorated despite discontinuation of MTX, and they poorly responded to high-dose corticosteroid. Consequently, on the basis of inconsistency in terms of MTX treatment duration and clinical features, we diagnosed these patients with AE of RA-ILD.

Similar to AE in patients with IPF, the etiology of AE in RA-ILD is unknown; however, several reports have suggested that AE may be a distinct manifestation of the primary disease process, a distinct condition associated with undiagnosed infection, or a

subsequent acceleration of a fibroproliferative process caused by acute direct stress to the lung.[1] In the present study, DAS28-CRP in all patients with AE showed low disease activity or remission at the time of AE occurrence, and no significant difference in articular disease activities was observed between AE group and non-AE group or regardless of MTX treatment; therefore, RA activity may not be related to AE occurrence, a finding similar to that of a previous study.[4] MTX possibly accelerates the fibroproliferative process of RA-ILD. It was reported that MTX treatment was a risk factor for RA-ILD progression.[12] For RA-ILD, MTX may be associated not only with newly developing drug-induced pneumonitis but also with deterioration of pre-existing ILD, including AE.

The present study found that patients with a UIP pattern on HRCT had significantly poorer survival than those with a non-UIP pattern. In addition, AE was a prognostic factor for poor outcome. AE has a serious impact on the survival of patients with IPF,[18] and it may also affect the prognosis in other ILDs.[3, 4] Consistent with these reports, the present study revealed that seven (64%) of 11 patients with AE died of respiratory failure, giving rise to high in-hospital mortality, and that survival in the AE group was significantly poorer than that in the non-AE group. Therefore, AE is suggested to be a predictor of poor prognosis in patients with RA-ILD as well as

patients with IPF.

Other prognostic factors in RA-ILD have been reported, including pathological UIP,[25-29] UIP pattern on HRCT,[30] and age at RA-ILD onset.[31] In the present study, pathological UIP could not be identified as prognostic factors because the number of biopsy-proven cases were small. However, we observed similar results regarding UIP pattern on HRCT and age at RA-ILD onset.

In our study, the average time between age at onset of RA and that of RA-ILD was relatively shorter than some previous reports.[7, 8] However, Gabbay et al [11] reported that nearly 60 % of the patients have interstitial lung disease in recent onset RA. In another point of view, since the current authors' institution is regional referral center for interstitial lung disease, referral bias might have increased the proportion of patients with early-stage ILD, leading above results.

This study had several limitations. First, given its retrospective study design, it is subject to several possible biases. For instance, selection and recall bias may exist. Second, because of the relatively small sample size, it may be difficult to determine the precise incidence of AE and the number of event (AE occurrence or death) was too small to perform multivariate analysis. Therefore, larger studies are necessary to confirm our results. Third, because the presence of a UIP pattern on HRCT had low

sensitivity and negative predictive value for the detection of pathologic UIP, it was likely that some patients with a non-UIP pattern on HRCT may have had pathological UIP. HRCT criteria used in our study do not aim to detect pathological UIP but to clinically diagnose IPF and to exclude alternative diagnosis.[15] The frequency of honeycombing on HRCT differs between RA-ILD and IPF, and some ILDs by other causes including RA-ILD have some of findings inconsistent with UIP. Therefore, HRCT pattern in RA-ILD may be more frequently interpreted as non-UIP pattern than that in IPF. In our study, 2 of 5 patients with histopathological UIP in the absence of a UIP pattern on HRCT develop AE. Thus, SLB may have to be considered for these patients to make pathological diagnosis and to predict AE. Finally, RA includes a variety of manifestations. Therefore, other comorbidities may have affected the results.

In conclusion, higher age at ILD diagnosis, UIP pattern on HRCT and treatment with MTX are risk factors for AE occurrence in patients with RA-ILD. Furthermore, the mortality associated with AE is high and AE is prognostic factor for poor outcome. Larger prospective studies investigating acute exacerbations in RA-ILD are indicated.

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Y.N. had full access to all the data in present study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authorship:

H.H., Y.N., T.S., and K.C. designed research; H.H., D.H., T.F., and N.I. contributed acquisition of data; H.H., Y.N., T.J., H.S, T.C., M.K., N.E., and T.S. interpreted and analyzed data.

H.H., Y.N., T.J., and T.C. wrote the paper; and H.S., M.K., D.H., N.E., T.F., N.I., T.S., and K.C. revised the paper.

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Table 1 Clinical characteristics

Characteristics	Total N = 51 (100)	Non-AE group[#] N = 40 (78)	AE group[¶] N = 11 (22)	P value[+]
Median age, years (range)				
at RA diagnosis	61 (28-82)	60 (28-81)	65 (42-82)	0.15
at ILD diagnosis	62 (31-83)	62 (31-83)	69 (58-83)	0.15
at AE onset			72 (60-86)	
Sex Male, n (%)	29 (57)	23 (58)	6 (55)	0.86
Observation period, years (range)	8.5 (1-17)	9 (1-17)	6.4 (2-14)	0.45
AE-free period, years (range)	7(1-17)	9 (1-17)	6 (2-14)	0.19
Smoking habit, n (%)				
Never	20 (39)	18 (45)	2 (18)	
Former	24 (47)	16 (40)	8 (73)	0.15
Current	7 (14)	6 (15)	1 (9)	
RF, IU/mL (range)[*]	197 (6-2666)	189 (6-2666)	205 (39-2530)	0.47
DAS28-CRP, score (range)[*]	1.95(1.02-5.13)	2.53(1.02-5.13)	1.82(1.47-2.3)	0.62
PaO_2, torr (range)	82.4 (67-109)	81 (67-102)	85.8 (74-109)	0.19
%FVC, % (range)	91.1 (50.6-130)	87.5 (51-130)	95 (60-125)	0.38
HRCT pattern, n (%)				
UIP pattern	14 (27)	8 (20)	6 (55)	0.02[§]
non-UIP pattern	37 (73)	32 (80)	5 (45)	
Death during observation period, n (%)				
caused by respiratory failure	8 (16)	2 (5)	7 (64)	0.02[§]
caused by other diseases	4 (8)	3 (8)	0 (0)	

Data are presented as n (%), median (range). AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; RF, rheumatoid factor; DAS28-CRP, disease activity score 28 CRP; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; HRCT, high resolution computed tomography; UIP pattern, usual interstitial pneumonia pattern.

[#]Non-AE group, patients who did not develop AE during observation period.

[¶] AE group, patients who developed AE during observation period.

[+] Non-AE group vs AE group

[§] $p < 0.05$

[*] at the first AE occurrence (AE group) or the last visit (non-AE group).

When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

In the AE group, 7 patients died of respiratory failure caused by AE. In the non-AE group, 2 died of respiratory failure caused by bacterial pneumonia or pneumocystis pneumonia, 1 of gastric bleeding and 2 of unknown causes.

Table 2 Diagnostic accuracy of HRCT pattern for histopathological pattern in 21 histopathologically confirmed patients.

	Histopathological pattern		Total
	UIP	Other pattern	
UIP pattern on HRCT	5	0	5
non-UIP pattern on HRCT	7	9	16
Total	12	9	21

Data are presented as number.

HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

Other pattern means other histopathological pattern except for UIP including nonspecific interstitial pneumonia, desquamative interstitial pneumonia and unclassifiable interstitial pneumonia.

When HRCT pattern was identified as a UIP pattern on HRCT, the sensitivity, specificity, positive predictive value and negative predictive value for detecting histopathological UIP was 41.7%, 100%, 100% and 56.3%, respectively.

Table 3 Treatment for RA at final visit[#] or AE onset[¶]

	Total N = 51	non-AE group[+] N = 40 (78%)	AE group[§] N = 11 (22%)	P value
Treatment, yes	37 (73)	27(68)	10 (91)	0.12
Corticosteroid	29 (57)	22 (55)	7 (64)	0.61
Immunosuppressant except for MTX	17 (33)	14 (35)	3 (27)	0.63
MTX	10 (20)	4 (10)	6 (55)	0.001[*]
Other drugs	17 (33)	13 (33)	4 (36)	0.81

Data are presented as n (%) and compared between non-AE group and AE group using Fisher's exact test.

Immunosuppressant except for MTX included azathioprine (n=1), cycrophosphaminde (n=1), etanercept (n=2), mizoribine (n=7), and tacrolimus (n=6).

Other drugs included actarit (n=2), bucillamine (n=5), meloxicam (n=1), and salazosulfapyridine (n=11).

AE, acute exacerbation; ILD, interstitial lung disease; MTX, methotrexate.

[#] In non-AE group.

[¶] In AE group.

[+] Non-AE group, patients who did not develop AE during the observation period.

[§] AE group, patients who developed AE during observation period.

[*] $p < 0.05$

Table 4 Risk factors for AE occurrence according to univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	1.03	0.97-1.10	0.35
Age at ILD diagnosis	1.11	1.02-1.21	0.01+
Sex, male	0.90	0.49-1.69	0.73
Smoking habit, yes	1.60	0.81-4.10	0.19
UIP pattern on HRCT, yes	1.95	1.07-3.63	0.03+
PaO_2 at ILD diagnosis	1.05	0.98-1.12	0.14
%FVC at ILD diagnosis	1.02	0.99-1.06	0.24
Treatment for RA at final visit# or AE onset¶			
Corticosteroids	0.97	0.53-1.92	0.94
Immunosuppressant except for MTX	0.76	0.35-1.41	0.39
MTX	3.04	1.62-6.02	0.001+
Other drugs	0.98	0.50-1.80	0.96

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

In non-AE group.

¶ In AE group.

+ $p < 0.05$

Table 5 Prognostic factors for survival, univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	0.98	0.93-1.04	0.48
Age at ILD diagnosis	1.08	0.99-1.17	0.057
Sex, male	1.14	0.63-2.22	0.67
Smoking habit, yes	1.70	0.87-4.35	0.13
UIP pattern on HRCT, yes	1.74	0.97-3.12	0.06
PaO_2 at ILD diagnosis	1.05	0.98-1.11	0.15
%FVC at ILD diagnosis	1.01	0.98-1.04	0.55
AE during observation period, yes	2.47	1.39-4.56	0.003[+]
Treatment for RA at final visit[#] or AE onset[¶]			
Corticosteroids	1.23	0.67-2.65	0.52
Immunosuppressant except for MTX	0.69	0.32-1.27	0.25
MTX	1.44	0.67-2.68	0.31
Other drugs	0.76	0.36-1.41	0.40

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

[#] In non-AE group.

[¶] In AE group.

[+] $p < 0.05$

Figure legends

Figure 1. Numbers of patients included in this study.

82 patients with RA-ILD were assessed for eligibility. From these, 31 patients were excluded, and 51 patients with chronic course of RA-ILD were included. During observation period, 11 patients developed AE.

RA, rheumatoid arthritis; ILD, interstitial lung disease; AE, acute exacerbation.

Figure 2. Cumulative AE incidence in patients with RA-ILD.

Patients with UIP pattern on HRCT had a significantly higher incidence of AE compared with non-UIP pattern on HRCT (log-rank p=0.018).

AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 3. Overall survival and the survival according to HRCT pattern subgroup.

Patients with UIP pattern on HRCT had a significantly worse survival compared with those with non-UIP pattern on HRCT (log-rank p=0.04).

UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 4. Survival of AE group and non-AE group.

Patients who developed AE during observation periods (AE group) had a significantly worse survival compared with those who did not (non-AE group) (log-rank p=0.001).

AE, acute exacerbation.

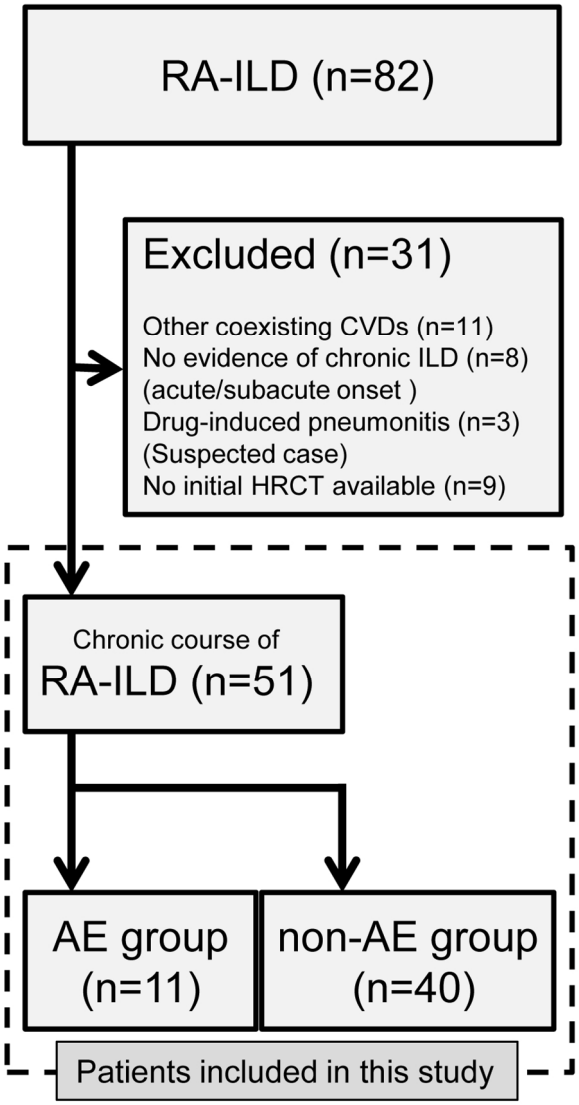

FIGURE 1.

Figure 1. Numbers of patients included in this study.

82 patients with RA-ILD were assessed for eligibility. From these, 31 patients were excluded, and 51 patients with chronic course of RA-ILD were included. During observation period, 11 patients developed AE. RA, rheumatoid arthritis; ILD, interstitial lung disease; AE, acute exacerbation.
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ABSTRACT

Background Acute exacerbation (AE) in idiopathic pulmonary fibrosis is characterised by acute deterioration of respiratory status and the mortality is high. Recently, AE was reported in patients with other interstitial lung diseases, especially rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Objectives To investigate the risk factors and prognosis associated with AE in patients with RA-ILD.

Design A retrospective ~~cohort~~case-control study.

Setting A single academic hospital.

Participants 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA. ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings.

Main outcome measures Overall survival and cumulative AE incidence were analysed using Kaplan–Meier method. Cox hazards analysis was used to determine significant variables associated with AE occurrence and survival status.

Results A total of 11 patients (22%) developed AE, with an overall 1-year incidence of 2.8%. Univariate analysis revealed that higher age at ILD diagnosis [hazard ratio

(HR), 1.11; 95% confidence interval (CI), 1.02–1.21; $P = 0.01$], usual interstitial pneumonia (UIP) pattern on HRCT (HR, 1.95; 95% CI, 1.07–3.63; $P = 0.03$) and treatment with methotrexate (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were risk factors for AE. Of 11 patients who developed AE during observation period, seven (64%) died of initial AE. In survival, AE was a prognostic factor for poor outcome (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$).

Conclusions In patients with RA-ILD, higher age at ILD diagnosis, UIP pattern on HRCT and treatment with methotrexate are risk factors for AE. Furthermore, AE has a serious impact on their survival. ~~We should carefully observe the patients having any of these risk factors.~~

Article focus;

Acute exacerbation occurs not only in patients with idiopathic pulmonary fibrosis (IPF) but also in patients with rheumatoid arthritis associated interstitial lung disease (RA-ILD).

What is the risk factor for AE and does AE impact on prognosis in patients with RA-ILD?

Key messages;

In patients with RA-ILD, higher age at ILD diagnosis, UIP pattern on HRCT, and treatment with methotrexate are risk factors for AE occurrence.

In patients with RA-ILD, AE is associated with poor prognosis.

Strengths and limitations of this study;

AE ~~may have~~has a serious impact on the survival of patients with RA-ILD~~ as well as that with IPF. Thus, the patients with any of these risk factors should be carefully observed~~.

Given its retrospective study design, it is subject to several possible biases. Therefore, prospective studies are necessary to confirm our results.

INTRODUCTION

Acute exacerbation (AE) is a recently established and an increasingly recognised occurrence in idiopathic pulmonary fibrosis (IPF).[1] AE is characterised by acute deterioration in respiratory status, with newly developed bilateral ground-glass opacities and/or consolidations on chest radiographs or computed tomography scans. It should be in the absence of other alternative causes such as infection, left heart failure, pulmonary embolism, and an identifiable cause of acute lung injury. AE reportedly occurs not only in patients with IPF but also in patients with other interstitial lung diseases (ILDs), including idiopathic nonspecific interstitial pneumonia (NSIP), collagen vascular disease-associated ILDs (CVD-ILDs) and other forms of ILD.[2-4] The in-hospital mortality associated with AE in patients with CVD-ILD was demonstrated to be as high as that in patients with IPF,[1-4] suggesting that AE may be associated with poor prognosis in patients with CVD-ILD.

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder of unknown etiology that primarily involves joints.[5] ILD is ~~the most~~one of common extra-articular manifestations~~,[~~.[6~~] with a~~, 7] The reported prevalence ~~of~~ is variable (1~~% –~~58~~%.[7-12~~%) and depends on the detection and diagnostic method, or the selected population.[8-13] We and Park *et al* previously reported that RA-associated

ILD (RA-ILD) was the most common CVD-ILD associated with AE.[3, 4] However the risk factors and prognosis associated with AE in patients with RA-ILD are not clarified.

In the present study, we attempted to elucidate the cumulative incidence of AE, its risk factors, and prognostic factors in patients with RA-ILD.

MATERIALS AND METHODS

Subjects

Institutional review board in Hamamatsu University School of Medicine approved this study (approval number 24-191) and waived patient approval or informed consent because the study involved a retrospective review of patient records and images. We retrospectively reviewed 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012 at Hamamatsu University Hospital in Japan. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA.[~~13~~14] Patients with other coexisting CVD were excluded. In addition, because our aim was to investigate the features of AE among patients with a chronic course of RA-ILD, patients with no evidence of chronic ILD were also excluded.

ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings.

HRCT findings such as bilateral areas with ground-glass attenuation, reticular opacities and honeycomb patterns were interpreted and defined as ILD by a consensus between radiologists and pulmonologists. All cases underwent transbronchial lung biopsy and bronchoalveolar lavage, and 21 (41%) cases underwent surgical lung biopsy (SLB) to definitively diagnose ILD or rule out other diseases. The patients with environmental exposures, suspected of drug induced pneumonia (ILD developed within 1 year after initiation of new drug), or with other known causes of ILD were excluded after considering exposure history and the findings of appropriate tests and histopathological examinations.

Acute exacerbation (AE)

AE was defined using recently proposed criteria[1] that were slightly modified for adaptation to RA-ILD: previous diagnosis of RA-ILD, unexplained worsening or development of dyspnea within 30 days of onset, new bilateral ground-glass abnormalities and/or consolidation superimposed on a reticular or honeycomb pattern on HRCT, no evidence of pulmonary infection on negative respiratory culture, including endotracheal aspirate or bronchoalveolar lavage, and serological test results for respiratory pathogens, and exclusion of alternative causes such as left heart failure,

pulmonary embolism, and an identifiable cause of acute lung injury. Patients with AE were required to meet all five criteria. In our institution, cultures of sputum, blood, urine, and bronchoalveolar lavage fluid, and serological tests examined for mycobacteria, fungi, bacteria, and some viruses were routinely performed. Echocardiography and, if necessary, CT scanning with intravenous contrast were performed to rule out left heart failure or pulmonary thromboembolism. The patients who developed acute pneumonitis within 1 year after initiation of drug for RA were excluded because drug-induced pneumonitis was not completely ruled out. Patients who did or did not develop AE during the observation period were classified into the AE and non-AE groups, respectively.

Data collection

All clinical and laboratory data were collected from medical records. The observation period was calculated from the date of diagnosis of RA-ILD to the last visit. The AE-free period was defined as the time elapsed between the date of RA-ILD diagnosis and the first AE occurrence (AE group) or the last visit (non-AE group).

Review of radiographic findings

HRCT images taken at the time of RA-ILD diagnosis were reviewed. These images comprised 1 to 2.5-mm collimation sections at 10 mm intervals. They were reconstructed by a high spatial frequency algorithm, and were displayed at window settings appropriate for viewing the lung parenchyma (window level, -600 to -800 Hounsfield units; window width, 1200 to 2000 Hounsfield units). HRCT images were randomised and reviewed independently by two expert chest radiologists (with 23 and 12 years of experience) who were unaware of the related clinical information. Interobserver agreement was classified as follows: poor (κ = 0–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80) and excellent (κ = 0.81-1.00).

RA-ILD on HRCT was classified as a usual interstitial pneumonia (UIP) pattern or a non-UIP pattern according to recent guideline ~~[~~14 with slight modification.[15] Briefly, a UIP pattern on HRCT was characterised by subpleural and basal predominance, reticular abnormalities, honeycombing with or without traction bronchiectasis and the absence of features listed as inconsistent with a UIP pattern, including upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormalities, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping and consolidation in bronchopulmonary segment(s)/lobe(s). If

the HRCT pattern did not meet the criteria, it was interpreted as a non-UIP pattern. Disagreements regarding HRCT interpretation were resolved by a consensus between both radiologists.

Review of histopathological findings

SLB specimens were obtained from at least two sites. A diagnosis of RA-ILD was originally made in all cases on the basis of histological features evaluated by a lung pathologist at our hospital, correlated with the clinical and radiological findings. All SLB specimens were also reviewed by a second lung pathologist with 36 years of experience. The histological classification of interstitial pneumonia was based on the consensus statement criteria for idiopathic interstitial pneumonias,[~~15~~16] and histological patterns that could not be classified according to the criteria were categorised as unclassified interstitial pneumonia.

Statistical analysis

All values are expressed as median (range) or number (%). The Mann-Whitney U test was used for nonparametric comparisons involving continuous data, whereas Fisher's exact test was used for comparing categorical data. Interobserver agreement on HRCT

pattern was analyzed using the κ statistic test. ~~Interobserver agreement was classified as follows: poor (κ = 0–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80) and excellent (κ = 0.81-1.00).~~ Survival was evaluated using the Kaplan–Meier method and the log-rank test according to observation period. The cumulative AE incidence was obtained from a Kaplan–Meier survival curve by treating AE as the death variable~~.~~ according to AE free period. The 1-year AE incidence was based on person year method and calculated by dividing the number of patients who developed AE by the total of AE-free period (year) of all the patients. Cox hazards analysis was used to determine significant variables associated with survival and AE occurrence. In all analyses, $P < 0.05$ was considered statistically significant. All data were analysed using commercially available software (JMP version 9.0.3a, SAS Institute Inc, Cary, NC, USA).

RESULTS

Patient characteristics (Table 1)

A total of 82 patients with RA-ILD were identified from medical records at Hamamatsu University Hospital. From these, 11 patients with other coexisting CVDs, 8 with no evidence of chronic ILD and an initial acute/subacute course of ILD, and 3

suspected of drug-induced pneumonitis were excluded. In addition, 9 patients for whom no initial HRCT images were available for review were also excluded. The remaining 51 patients with RA-ILD were included in this study.(Figure 1)

The median age at onset of RA and diagnosis of RA-ILD was 61 (range, 28–82) years and 62 (range, 31–83) years, respectively. The median observation period and AE-free period was 8.5 (range, 1–17) years and 7 (range, 1–17) years, respectively.

During the observation period, 11 patients (22%) developed AE. The median age at the onset of AE was 72 (range, 60–86) years. There were no statistically significant differences in age at onset of RA, age at diagnosis of RA-ILD, sex, observation period, AE-free period, smoking habits, predicted forced vital capacity (%FVC) at diagnosis of RA-ILD, and arterial oxygen pressure (PaO_2) at diagnosis of RA-ILD between the AE and non-AE groups. Also there were no statistically significant differences in articular disease activities (RF and DAS28-CRP) at the last visit (non-AE group) or the first AE occurrence (AE group).

In the AE group, seven of 11 patients (64%) died of initial AE during the observation period. In the non-AE group, ~~5~~2 of 40 patients (~~13~~5%) died of respiratory failure. There was a statistically significant difference in the mortality rate between the AE and non-AE groups.

Extra-articular manifestations except for ILD had been observed in 8 (16%) of 51 patients (pericarditis in 2 patients, pleuritis in 1, neuropathy in 2, cutaneous vasculitis in 2, glomerulonephritis in 1, rheumatoid nodule in 2). There was no significant difference in the incidence between AE group and non-AE group (27% vs. 13%, *P*=0.26).

HRCT pattern (Table 1)

Of the 51 patients with RA-ILD, 14 (27%) exhibited the UIP pattern on HRCT. HRCT images of eight of 40 patients (20%) in the non-AE group and six of 11 (55%) patients in the AE group demonstrated a UIP pattern. Interobserver agreement between both radiologists was moderate (κ statistic test, κ = 0.44). The number of patients who exhibited a UIP pattern on HRCT was significantly higher in the AE group than in the non-AE group.

~~**Correlation between**~~When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

Diagnostic accuracy of HRCT pattern for histopathological ~~**findings and HRCT**~~

pattern (Table 2)

Among the 51 patients, 21 (41%) underwent SLB. Histopathological analysis revealed a UIP in 12 patients, NSIP in 7, desquamative interstitial pneumonia in 1 and an unclassified interstitial pneumonia in 1. The ~~correlation between~~diagnostic accuracy of HRCT pattern for histopathological ~~and HRCT~~ pattern was evaluated in 21 histopathologically confirmed patients. When the pattern was identified as a UIP pattern on HRCT, the sensitivity, specificity, positive predictive value and negative predictive value for detecting histopathological UIP was 41.7%, 100%, 100% and 56.3%, respectively.

Treatment for RA (Table 3)

Of the 51 patients, 37 (73%) had received treatment for RA at their final visit (non-AE group) or at AE onset (AE group). Specifically, 29 patients (57%) had received corticosteroids, 17 (33%) received immunosuppressants except for MTX, 10 (20%) received MTX and 17 (33%) received other drugs. ~~The number of~~There were 6 (55%) patients who had received MTX ~~was significantly higher~~ in ~~the~~ AE group ~~than~~while 4 (10%) patients in ~~the~~ non-AE group ~~(55% vs. 10%,~~ and statistically significant difference was observed between the groups (P = 0.001).

No patients had received MTX before in AE group while 2 in non-AE group. Thus, there were 6 (55%) patients who had experienced MTX treatment during observation period in AE group while 6 (15%) patients in non-AE group. Median cumulative MTX dose were 1952mg (384-3872) in 6 patients who had experienced MTX among AE group and 802mg (32-2496) in 6 patients among non-AE group. No statistically significant difference was observed between two groups in cumulative MTX dose (*P*=0.20).

Articular disease activities (RF and DAS28-CRP) were compared between patients who had received MTX at the last visit or at the first AE occurrence, and those who had not. Median RF (range) were 112 IU/mL (16-334) and 284 IU/mL (6-2666) (*P*=0.25), Median DAS28-CRP (range) were 1.94 (1.02-3.87) and 1.97 (1.02-5.13) (*P*=0.78), respectively. There were no statistically significant differences in articular disease activities.

AE incidence

The cumulative AE incidence in patients with RA-ILD is shown in Figure ~~1~~2. The 5-year AE incidence was ~~significantly higher~~11% [95% confidence interval (CI), 2–21%] in all patients, 33% (95% CI, 7–60%) in patients with a UIP pattern on HRCT

(UIP pattern group) ~~than~~and 3% (95% CI, 0–9%) in patients with a non-UIP pattern on HRCT (non-UIP pattern group~~)~~). The AE incidence was significantly higher in UIP pattern group than in non-UIP pattern group (log-rank test, $P = 0.018$). The overall 1-year AE incidence was 2.8%. The 1-year AE incidence was 6.5% in the UIP pattern group and 1.7 % in the non-UIP pattern group.

Univariate analysis (Table 4) revealed that higher age at ILD diagnosis [hazard ratio (HR), 1.11; 95% ~~confidence interval (CI),~~CI, 1.02–1.21; $P = 0.01$], UIP pattern on HRCT (HR, 1.95; 95% CI, 1.07–3.63; $P = 0.03$) and treatment with MTX (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were significant risk factors for AE occurrence.

Survival

The overall survival of patients with RA-ILD is shown in Figure ~~2~~3. The 5-year survival was 90% (95% CI, 81–98%) in all patients, 70% (95% CI, 44–94%) in the UIP pattern group and 97% (95% CI, 92–100%) in the non-UIP pattern group. Survival was significantly poorer in the UIP pattern group than in the non-UIP pattern group (log-rank test, $P = 0.04$). In addition, significantly worse survival was demonstrated in the AE group compared with the non-AE group (Figure ~~3~~4, log-rank test, $P = 0.001$).

Univariate analysis (Table 5) revealed that higher age at ILD diagnosis (HR, 1.08; 95% CI, 0.99–1.17; $P = 0.057$) and UIP pattern on HRCT (HR, 1.74; 95% CI, 0.97–3.12; $P = 0.06$) showed a trend toward poor outcome, while AE (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$) was significantly associated with poor survival.

DISCUSSION

To our knowledge, the present study is the first one focusing on the risk factors and prognosis associated with AE in patients with RA-ILD. The overall 1-year AE incidence was 2.8% among the RA-ILD patients. Univariate analysis identified that a UIP pattern on HRCT, MTX treatment and higher age at ILD diagnosis were significant risk factors for AE. Furthermore, AE was a prognostic factor for poor survival.

The 1-year AE incidence among patients with IPF has been reported to be 5-19%,[~~16,~~ 17, 18] whereas that among patients with other ILDs was 4.2% for idiopathic NSIP, 3.3 % for CVD-ILD and 5.6 % for CVD-UIP.[4] In the present study, ~~patients with RA-ILD had a relatively lower incidence of AE. However,~~ the 1-year AE incidence among patients with a UIP pattern on HRCT was 6.5~~%, comparable to that~~% and cumulative incidence was significantly higher in ~~patients with IPF~~UIP pattern group than in non-UIP pattern group. Furthermore, a UIP pattern on HRCT was a risk factor

for AE. In a previous report of small number of biopsy-proven cases, AE incidence among patients with RA-UIP was reported to be 11.1%, ~~also~~ similar to that among patients with IPF.[4] The correlation between pathological and radiological UIP patterns has been established in IPF, but not in RA-ILD.[~~18~~19] In the present study, determination of a UIP pattern on HRCT exhibited high specificity and positive predictive values for the detection of pathological UIP pattern. Therefore, a typical UIP pattern on HRCT was assumed to be highly suggestive of pathological UIP pattern in patients with RA-ILD as well as IPF.[~~14, 18~~15, 19] Collectively, these results suggest that AE ~~occurs less frequently in RA-ILD than in IPF, while AE~~ incidence in a subgroup with pathological UIP pattern or a UIP pattern on HRCT may be ~~as high as~~higher than that in ~~patients with IPF.~~other patterns..

The present study also identified MTX treatment as a risk factor for AE. MTX is widely used to treat RA, while its toxicity affects the pulmonary system. Diagnostic criteria for MTX-associated pneumonitis (MTX-pneumonitis) have been proposed previously.[~~19~~20] However, the specificity of the criteria has not been fully examined yet. MTX-pneumonitis typically occurs with acute/subacute onset early in the course of MTX treatment,[~~19-22~~20-23] in particular, mostly within the first year[~~23~~24] and often presents a hypersensitive pneumonitis pattern. Patients with MTX-pneumonitis

generally respond to discontinuation of MTX or corticosteroid treatment and have a favorable prognosis.[~~19-22~~20-23] In the present study, 6 of 11 patients with AE had received MTX, and 5 of the 6 patients had been treated for 3 or more years. The remaining patient had been treated for 1 year. In all 6 patients, their respiratory conditions progressively deteriorated despite discontinuation of MTX, and they poorly responded to high-dose corticosteroid. Consequently, on the basis of inconsistency in terms of MTX treatment duration and clinical features, we diagnosed these patients with AE of RA-ILD.

Similar to AE in patients with IPF, the etiology of AE in RA-ILD is unknown; however, several reports have suggested that AE may be a distinct manifestation of the primary disease process, a distinct condition associated with undiagnosed infection, or a subsequent acceleration of a fibroproliferative process caused by acute direct stress to the lung.[1] In the present study, ~~RA joint disease activity~~ DAS28-CRP in all patients with AE ~~was stable~~showed low disease activity or remission at the time of AE occurrence, and no significant difference in articular disease activities was observed between AE group and non-AE group or regardless of MTX treatment; therefore, RA activity may not be related to AE occurrence, a finding similar to that of a previous study.[4] MTX possibly accelerates the fibroproliferative process of RA-ILD. It was

reported that MTX treatment was a risk factor for RA-ILD progression.[~~10~~12] For RA-ILD, MTX may be associated not only with newly developing drug-induced pneumonitis but also with deterioration of pre-existing ILD, including AE. ~~Therefore, we think that MTX treatment should be avoided in RA patients with ILD.~~

The present study found that patients with a UIP pattern on HRCT had significantly poorer survival than those with a non-UIP pattern. In addition, AE was a prognostic factor for poor outcome. AE has a serious impact on the survival of patients with IPF,[~~17~~18] and it may also affect the prognosis in other ILDs.[3, 4] Consistent with these reports, the present study revealed that seven (64%) of 11 patients with AE died of respiratory failure, giving rise to high in-hospital mortality, and that survival in the AE group was significantly poorer than that in the non-AE group. Therefore, AE is suggested to be a predictor of poor prognosis in patients with RA-ILD as well as patients with IPF.

Other prognostic factors in RA-ILD have been reported, including pathological UIP,[~~24-28~~25-29] UIP pattern on HRCT,[~~29~~30] and age at RA-ILD onset.[~~30~~31] In the present study, pathological UIP could not be identified as prognostic factors because the number of biopsy-proven cases were small. However, we observed similar results regarding UIP pattern on HRCT and age at RA-ILD onset.

In our study, the average time between age at onset of RA and that of RA-ILD was relatively shorter than some previous reports.[7, 8] However, Gabbay et al [11] reported that nearly 60 % of the patients have interstitial lung disease in recent onset RA. In another point of view, since the current authors' institution is regional referral center for interstitial lung disease, referral bias might have increased the proportion of patients with early-stage ILD, leading above results.

This study had several limitations. First, given its retrospective study design, it is subject to several possible biases. For instance, selection and recall bias may exist. Second, because of the relatively small sample size, it may be difficult to determine the precise incidence of AE- and the number of event (AE occurrence or death) was too small to perform multivariate analysis. Therefore, larger studies are necessary to confirm our results. Third, because the presence of a UIP pattern on HRCT had low sensitivity and negative predictive value for the detection of pathologic UIP, it was likely that some patients with a non-UIP pattern on HRCT may have had pathological UIP. HRCT criteria used in our study do not aim to detect pathological UIP but to clinically diagnose IPF and to exclude alternative diagnosis.[15] The frequency of honeycombing on HRCT differs between RA-ILD and IPF, and some ILDs by other causes including RA-ILD have some of findings inconsistent with UIP. Therefore,

HRCT pattern in RA-ILD may be more frequently interpreted as non-UIP pattern than that in IPF. In our study, 2 of 5 patients with histopathological UIP in the absence of a UIP pattern on HRCT develop AE. Thus, SLB may have to be considered for these patients to make pathological diagnosis and to predict AE. Finally, RA includes a variety of manifestations. Therefore, other comorbidities may have affected the results.

In conclusion, higher age at ILD diagnosis, UIP pattern on HRCT and treatment with MTX are risk factors for AE occurrence in patients with RA-ILD. Furthermore, the mortality associated with AE is high and AE is prognostic factor for poor outcome. ~~AE has a serious impact on the survival of patients with RA-ILD. Thus, we should carefully observe the patients having any of these risk factors.~~Larger prospective studies investigating acute exacerbations in RA-ILD are indicated.

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Y.N. had full access to all the data in present study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authorship:

H.H., Y.N., T.S., and K.C. designed research; H.H., D.H., T.F., and N.I. contributed acquisition of data; H.H., Y.N., T.J., H.S, T.C., M.K., N.E., and T.S. interpreted and analyzed data.

H.H., Y.N., T.J., and T.C. wrote the paper; and H.S., M.K., D.H., N.E., T.F., N.I., T.S., and K.C. revised the paper.

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All authors do not have any personal or financial support or involvement with organization(s) that have financial interest in the subject matter, or any competing interest.

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Institutional review board in Hamamatsu University School of Medicine approved this study (approval number 24-191) and waived patient approval or informed consent because the study involved a retrospective review of patient records and images.

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Table 1 Clinical characteristics

Characteristics	Total N = 51 (100)	Non-AE group[#] N = 40 (78)	AE group[¶] N = 11 (22)	P value[+]
Median age, years (range)				
at RA diagnosis	61 (28-82)	60 (28-81)	65 (42-82)	0.15
at ILD diagnosis	62 (31-83)	62 (31-83)	69 (58-83)	0.15
at AE onset			72 (60-86)	
Sex Male, n (%)	29 (57)	23 (58)	6 (55)	0.86
Observation period, years (range)	8.5 (1-17)	9 (1-17)	6.4 (2-14)	0.45
AE-free period, years (range)	7(1-17)	9 (1-17)	6 (2-14)	0.19
Smoking habit, n (%)				
Never	20 (39)	18 (45)	2 (18)	
Former	24 (47)	16 (40)	8 (73)	0.15
Current	7 (14)	6 (15)	1 (9)	
RF, IU/mL (range)[*]	197 (6-2666)	189 (6-2666)	205 (39-2530)	0.47
DAS28-CRP, score (range)[*]	1.95(1.02-5.13)	2.53(1.02-5.13)	1.82(1.47-2.3)	0.62
PaO_2, torr (range)	82.4 (67-109)	81 (67-102)	85.8 (74-109)	0.19
%FVC, % (range)	91.1 (50.6-130)	87.5 (51-130)	95 (60-125)	0.38
HRCT pattern, n (%)				
UIP pattern	14 (27)	8 (20)	6 (55)	0.02[§]
non-UIP pattern	37 (73)	32 (80)	5 (45)	
Death during observation period, n (%)	~~12 (24)~~	~~5 (13)~~	~~7 (64)~~	~~0.001~~[§]
caused by respiratory failure	8 (16)	2 (5)	7 (64)	0.02[§]
caused by other diseases	4 (8)	3 (8)	0 (0)	

Data are presented as n (%), median (range).

AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; RF, rheumatoid factor; DAS28-CRP, disease activity score 28 CRP; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; HRCT, high resolution computed tomography; UIP pattern, usual interstitial pneumonia pattern.

[#]Non-AE group, patients who did not develop AE during observation period.

[¶] AE group, patients who developed AE during observation period.

[+] Non-AE group vs AE group

[§] $p < 0.05$

[*] at the first AE occurrence (AE group) or the last visit (non-AE group).

When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

In the AE group, 7 patients died of respiratory failure caused by AE. In the non-AE group, 2 died of respiratory failure caused by bacterial pneumonia or pneumocystis pneumonia, 1 of gastric bleeding and 2 of unknown causes.

Table 2 ~~Correlation between~~Diagnostic accuracy of HRCT pattern for histopathological ~~findings and HRCT~~ pattern in 21 histopathologically confirmed patients.

	Histopathological pattern		Total
	UIP	Other pattern	
UIP pattern on HRCT	5	0	5
non-UIP pattern on HRCT	7	9	16
Total	12	9	21

Data are presented as number.

HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

Other pattern means other histopathological pattern except for UIP including nonspecific interstitial pneumonia, desquamative interstitial pneumonia and unclassifiable interstitial pneumonia.

When HRCT pattern was identified as a UIP pattern on HRCT, the sensitivity, specificity, positive predictive value and negative predictive value for detecting histopathological UIP was 41.7%, 100%, 100% and 56.3%, respectively.

Table 3 Treatment for RA at final visit[#] or AE onset[¶]

	Total N = 51	non-AE group[+] N = 40 (78%)	AE group[§] N = 11 (22%)	P value
Treatment, yes	37 (73)	27(68)	10 (91)	0.12
Corticosteroid	29 (57)	22 (55)	7 (64)	0.61
Immunosuppressant except for MTX	17 (33)	14 (35)	3 (27)	0.63
MTX	10 (20)	4 (10)	6 (55)	0.001[*]
Other drugs	17 (33)	13 (33)	4 (36)	0.81

Data are presented as n (%) and compared between non-AE group and AE group using Fisher's exact test.

Immunosuppressant except for MTX included azathioprine (n=1), cycrophosphaminde (n=1), etanercept (n=2), mizoribine (n=7), and tacrolimus (n=6).

Other drugs included actarit (n=2), bucillamine (n=5), meloxicam (n=1), and salazosulfapyridine (n=11).

AE, acute exacerbation; ILD, interstitial lung disease; MTX, methotrexate.

[#] In non-AE group.

[¶] In AE group.

[+] Non-AE group, patients who did not develop AE during the observation period.

[§] AE group, patients who developed AE during observation period.

[*] $p < 0.05$

Table 4 Risk factors for AE occurrence according to univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	1.03	0.97-1.10	0.35
Age at ILD diagnosis	1.11	1.02-1.21	0.01+
Sex, male	0.90	0.49-1.69	0.73
Smoking habit, yes	1.60	0.81-4.10	0.19
UIP pattern on HRCT, yes	1.95	1.07-3.63	0.03+
PaO_2 at ILD diagnosis	1.05	0.98-1.12	0.14
%FVC at ILD diagnosis	1.02	0.99-1.06	0.24
Treatment for RA at final visit# or AE onset¶			
Corticosteroids	0.97	0.53-1.92	0.94
Immunosuppressant except for MTX	0.76	0.35-1.41	0.39
MTX	3.04	1.62-6.02	0.001+
Other drugs	0.98	0.50-1.80	0.96

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

In non-AE group.

¶ In AE group.

+ $p < 0.05$

Table 5 Prognostic factors for survival, univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	0.98	0.93-1.04	0.48
Age at ILD diagnosis	1.08	0.99-1.17	0.057
Sex, male	1.14	0.63-2.22	0.67
Smoking habit, yes	1.70	0.87-4.35	0.13
UIP pattern on HRCT, yes	1.74	0.97-3.12	0.06
PaO_2 at ILD diagnosis	1.05	0.98-1.11	0.15
%FVC at ILD diagnosis	1.01	0.98-1.04	0.55
AE during observation period, yes	2.47	1.39-4.56	0.003[+]
Treatment for RA at final visit[#] or AE onset[¶]			
Corticosteroids	1.23	0.67-2.65	0.52
Immunosuppressant except for MTX	0.69	0.32-1.27	0.25
MTX	1.44	0.67-2.68	0.31
Other drugs	0.76	0.36-1.41	0.40

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

[#] In non-AE group.

[¶] In AE group.

[+] $p < 0.05$

Figure legends

Figure 1. Numbers of patients included in this study.

82 patients with RA-ILD were assessed for eligibility. From these, 31 patients were excluded, and 51 patients with chronic course of RA-ILD were included. During observation period, 11 patients developed AE.

RA, rheumatoid arthritis; ILD, interstitial lung disease; AE, acute exacerbation.

Figure 2. Cumulative AE incidence in patients with RA-ILD.

Patients with UIP pattern on HRCT had a significantly higher incidence of AE compared with non-UIP pattern on HRCT (log-rank p=0.018).

AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure ~~2~~3. Overall survival and the survival according to HRCT pattern subgroup.

Patients with UIP pattern on HRCT had a significantly worse survival compared with those with non-UIP pattern on HRCT (log-rank p=0.04).

UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure ~~3~~4. Survival of AE group and non-AE group.

Patients who developed AE during observation periods (AE group) had a significantly worse survival compared with those who did not (non-AE group) (log-rank p=0.001).

AE, acute exacerbation.

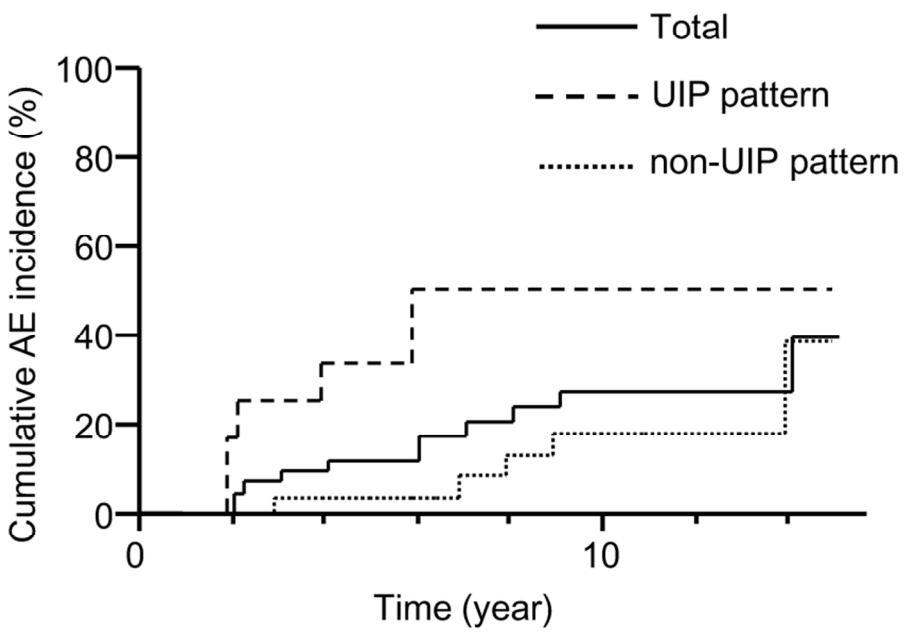

FIGURE 2.

Figure 2. Cumulative AE incidence in patients with RA-ILD.

Patients with UIP pattern on HRCT had a significantly higher incidence of AE compared with non-UIP pattern on HRCT (log-rank p=0.018).
AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.
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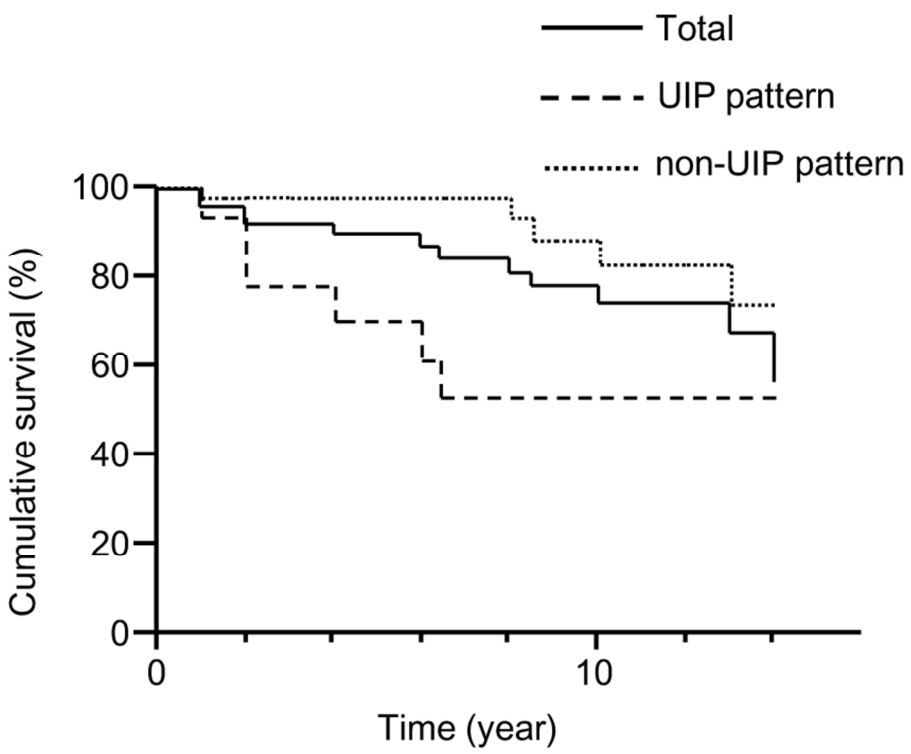

FIGURE 3.

Figure 3. Overall survival and the survival according to HRCT pattern subgroup.

Patients with UIP pattern on HRCT had a significantly worse survival compared with those with non-UIP pattern on HRCT (log-rank p=0.04).
UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.
80x80mm (300 x 300 DPI)

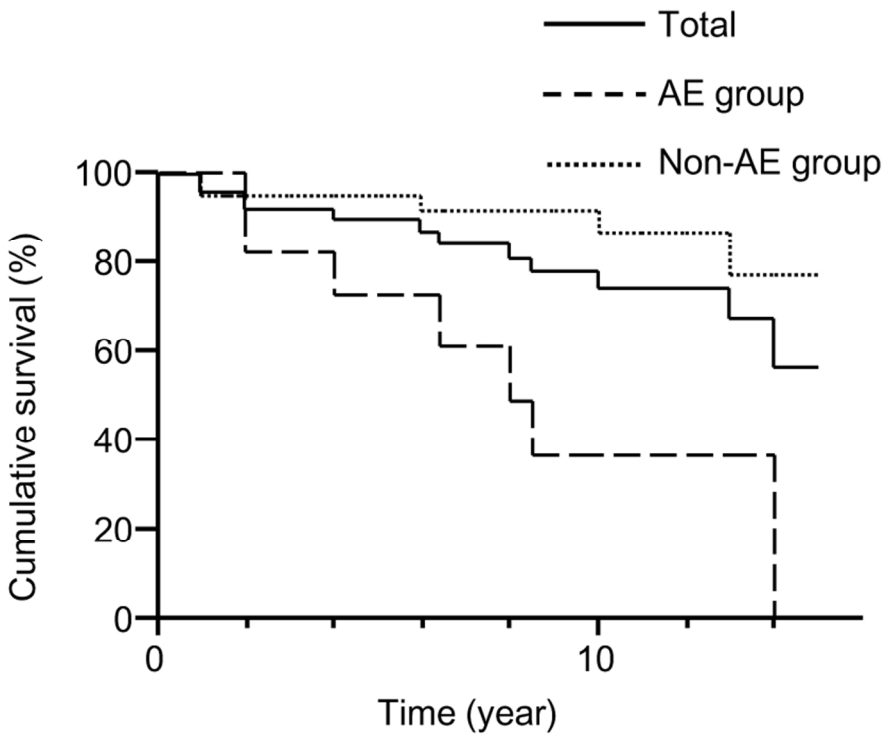

FIGURE 4.

Figure 4. Survival of AE group and non-AE group.

Patients who developed AE during observation periods (AE group) had a significantly worse survival compared with those who did not (non-AE group) (log-rank p=0.001).
AE, acute exacerbation.
80x80mm (300 x 300 DPI)

Title: Acute exacerbation in rheumatoid arthritis associated interstitial lung disease

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ABSTRACT

Background Acute exacerbation (AE) in idiopathic pulmonary fibrosis is characterised by acute deterioration of respiratory status and the mortality is high. Recently, AE was reported in patients with other interstitial lung diseases, especially rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Objectives To investigate the risk factors and prognosis associated with AE in patients with RA-ILD.

Design A retrospective case-control study.

Setting A single academic hospital.

Participants 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA. ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings.

Main outcome measures Overall survival and cumulative AE incidence were analysed using Kaplan–Meier method. Cox hazards analysis was used to determine significant variables associated with AE occurrence and survival status.

Results A total of 11 patients (22%) developed AE, with an overall 1-year incidence of 2.8%. Univariate analysis revealed that higher age at ILD diagnosis [hazard ratio

(HR), 1.11; 95% confidence interval (CI), 1.02–1.21; $P = 0.01$], usual interstitial pneumonia (UIP) pattern on HRCT (HR, 1.95; 95% CI, 1.07–3.63; $P = 0.03$) and treatment with methotrexate (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were risk factors for AE. Of 11 patients who developed AE during observation period, seven (64%) died of initial AE. In survival, AE was a prognostic factor for poor outcome (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$).

Conclusions In patients with RA-ILD, higher age at ILD diagnosis, UIP pattern on HRCT and treatment with methotrexate are risk factors for AE. Furthermore, AE has a serious impact on their survival.

Article focus;

Acute exacerbation occurs not only in patients with idiopathic pulmonary fibrosis (IPF) but also in patients with rheumatoid arthritis associated interstitial lung disease (RA-ILD).

What is the risk factor for AE and does AE impact on prognosis in patients with RA-ILD?

Key messages;

In patients with RA-ILD, higher age at ILD diagnosis, UIP pattern on HRCT, and treatment with methotrexate are risk factors for AE occurrence.

In patients with RA-ILD, AE is associated with poor prognosis.

Strengths and limitations of this study;

AE has a serious impact on the survival of patients with RA-ILD.

Given its retrospective study design, it is subject to several possible biases. Therefore, prospective studies are necessary to confirm our results.

INTRODUCTION

Acute exacerbation (AE) is a recently established and an increasingly recognised occurrence in idiopathic pulmonary fibrosis (IPF).[1] AE is characterised by acute deterioration in respiratory status, with newly developed bilateral ground-glass opacities and/or consolidations on chest radiographs or computed tomography scans. It should be in the absence of other alternative causes such as infection, left heart failure, pulmonary embolism, and an identifiable cause of acute lung injury. AE reportedly occurs not only in patients with IPF but also in patients with other interstitial lung diseases (ILDs), including idiopathic nonspecific interstitial pneumonia (NSIP), collagen vascular disease-associated ILDs (CVD-ILDs) and other forms of ILD.[2-4] The in-hospital mortality associated with AE in patients with CVD-ILD was demonstrated to be as high as that in patients with IPF,[1-4] suggesting that AE may be associated with poor prognosis in patients with CVD-ILD.

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder of unknown etiology that primarily involves joints.[5] ILD is one of common extra-articular manifestations.[6, 7] The reported prevalence is variable (1–58%) and depends on the detection and diagnostic method, or the selected population.[8-13] We and Park *et al* previously reported that RA-associated ILD (RA-ILD) was the most common

CVD-ILD associated with AE.[3, 4] However the risk factors and prognosis associated with AE in patients with RA-ILD are not clarified.

In the present study, we attempted to elucidate the cumulative incidence of AE, its risk factors, and prognostic factors in patients with RA-ILD.

MATERIALS AND METHODS

Subjects

Institutional review board in Hamamatsu University School of Medicine approved this study (approval number 24-191) and waived patient approval or informed consent because the study involved a retrospective review of patient records and images. We retrospectively reviewed 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012 at Hamamatsu University Hospital in Japan. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA.[14] Patients with other coexisting CVD were excluded. In addition, because our aim was to investigate the features of AE among patients with a chronic course of RA-ILD, patients with no evidence of chronic ILD were also excluded.

ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings.

HRCT findings such as bilateral areas with ground-glass attenuation, reticular opacities and honeycomb patterns were interpreted and defined as ILD by a consensus between radiologists and pulmonologists. All cases underwent transbronchial lung biopsy and bronchoalveolar lavage, and 21 (41%) cases underwent surgical lung biopsy (SLB) to definitively diagnose ILD or rule out other diseases. The patients with environmental exposures, suspected of drug induced pneumonia (ILD developed within 1 year after initiation of new drug), or with other known causes of ILD were excluded after considering exposure history and the findings of appropriate tests and histopathological examinations.

Acute exacerbation (AE)

AE was defined using recently proposed criteria[1] that were slightly modified for adaptation to RA-ILD: previous diagnosis of RA-ILD, unexplained worsening or development of dyspnea within 30 days of onset, new bilateral ground-glass abnormalities and/or consolidation superimposed on a reticular or honeycomb pattern on HRCT, no evidence of pulmonary infection on negative respiratory culture, including endotracheal aspirate or bronchoalveolar lavage, and serological test results for respiratory pathogens, and exclusion of alternative causes such as left heart failure,

pulmonary embolism, and an identifiable cause of acute lung injury. Patients with AE were required to meet all five criteria. In our institution, cultures of sputum, blood, urine, and bronchoalveolar lavage fluid, and serological tests examined for mycobacteria, fungi, bacteria, and some viruses were routinely performed. Echocardiography and, if necessary, CT scanning with intravenous contrast were performed to rule out left heart failure or pulmonary thromboembolism. The patients who developed acute pneumonitis within 1 year after initiation of drug for RA were excluded because drug-induced pneumonitis was not completely ruled out. Patients who did or did not develop AE during the observation period were classified into the AE and non-AE groups, respectively.

Data collection

All clinical and laboratory data were collected from medical records. The observation period was calculated from the date of diagnosis of RA-ILD to the last visit. The AE-free period was defined as the time elapsed between the date of RA-ILD diagnosis and the first AE occurrence (AE group) or the last visit (non-AE group).

Review of radiographic findings

HRCT images taken at the time of RA-ILD diagnosis were reviewed. These images comprised 1 to 2.5-mm collimation sections at 10 mm intervals. They were reconstructed by a high spatial frequency algorithm, and were displayed at window settings appropriate for viewing the lung parenchyma (window level, -600 to -800 Hounsfield units; window width, 1200 to 2000 Hounsfield units). HRCT images were randomised and reviewed independently by two expert chest radiologists (with 23 and 12 years of experience) who were unaware of the related clinical information. Interobserver agreement was classified as follows: poor (κ = 0–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80) and excellent (κ = 0.81-1.00).

RA-ILD on HRCT was classified as a usual interstitial pneumonia (UIP) pattern or a non-UIP pattern according to recent guideline with slight modification.[15] Briefly, a UIP pattern on HRCT was characterised by subpleural and basal predominance, reticular abnormalities, honeycombing with or without traction bronchiectasis and the absence of features listed as inconsistent with a UIP pattern, including upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormalities, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping and consolidation in bronchopulmonary segment(s)/lobe(s). If

the HRCT pattern did not meet the criteria, it was interpreted as a non-UIP pattern. Disagreements regarding HRCT interpretation were resolved by a consensus between both radiologists.

Review of histopathological findings

SLB specimens were obtained from at least two sites. A diagnosis of RA-ILD was originally made in all cases on the basis of histological features evaluated by a lung pathologist at our hospital, correlated with the clinical and radiological findings. All SLB specimens were also reviewed by a second lung pathologist with 36 years of experience. The histological classification of interstitial pneumonia was based on the consensus statement criteria for idiopathic interstitial pneumonias,[16] and histological patterns that could not be classified according to the criteria were categorised as unclassified interstitial pneumonia.

Statistical analysis

All values are expressed as median (range) or number (%). The Mann-Whitney U test was used for nonparametric comparisons involving continuous data, whereas Fisher's exact test was used for comparing categorical data. Interobserver agreement on HRCT

pattern was analyzed using the κ statistic test. Survival was evaluated using the Kaplan–Meier method and the log-rank test according to observation period. The cumulative AE incidence was obtained from a Kaplan–Meier survival curve by treating AE as the death variable according to AE free period. The 1-year AE incidence was based on person year method and calculated by dividing the number of patients who developed AE by the total of AE-free period (year) of all the patients. Cox hazards analysis was used to determine significant variables associated with survival and AE occurrence. In all analyses, $P < 0.05$ was considered statistically significant. All data were analysed using commercially available software (JMP version 9.0.3a, SAS Institute Inc, Cary, NC, USA).

RESULTS

Patient characteristics (Table 1)

A total of 82 patients with RA-ILD were identified from medical records at Hamamatsu University Hospital. From these, 11 patients with other coexisting CVDs, 8 with no evidence of chronic ILD and an initial acute/subacute course of ILD, and 3 suspected of drug-induced pneumonitis were excluded. In addition, 9 patients for whom no initial HRCT images were available for review were also excluded. The remaining

51 patients with RA-ILD were included in this study.(Figure 1)

The median age at onset of RA and diagnosis of RA-ILD was 61 (range, 28–82) years and 62 (range, 31–83) years, respectively. The median observation period and AE-free period was 8.5 (range, 1–17) years and 7 (range, 1–17) years, respectively.

During the observation period, 11 patients (22%) developed AE. The median age at the onset of AE was 72 (range, 60–86) years. There were no statistically significant differences in age at onset of RA, age at diagnosis of RA-ILD, sex, observation period, AE-free period, smoking habits, predicted forced vital capacity (%FVC) at diagnosis of RA-ILD, and arterial oxygen pressure (PaO_2) at diagnosis of RA-ILD between the AE and non-AE groups. Also there were no statistically significant differences in articular disease activities (RF and DAS28-CRP) at the last visit (non-AE group) or the first AE occurrence (AE group).

In the AE group, seven of 11 patients (64%) died of initial AE during the observation period. In the non-AE group, 2 of 40 patients (5%) died of respiratory failure. There was a statistically significant difference in the mortality rate between the AE and non-AE groups.

Extra-articular manifestations except for ILD had been observed in 8 (16%) of 51 patients (pericarditis in 2 patients, pleuritis in 1, neuropathy in 2, cutaneous vasculitis in

2, glomerulonephritis in 1, rheumatoid nodule in 2). There was no significant difference in the incidence between AE group and non-AE group (27% vs. 13%, *P*=0.26).

HRCT pattern (Table 1)

Of the 51 patients with RA-ILD, 14 (27%) exhibited the UIP pattern on HRCT. HRCT images of eight of 40 patients (20%) in the non-AE group and six of 11 (55%) patients in the AE group demonstrated a UIP pattern. Interobserver agreement between both radiologists was moderate (κ statistic test, κ = 0.44). The number of patients who exhibited a UIP pattern on HRCT was significantly higher in the AE group than in the non-AE group.

When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

Diagnostic accuracy of HRCT pattern for histopathological pattern (Table 2)

Among the 51 patients, 21 (41%) underwent SLB. Histopathological analysis revealed a UIP in 12 patients, NSIP in 7, desquamative interstitial pneumonia in 1 and an unclassified interstitial pneumonia in 1. The diagnostic accuracy of HRCT pattern for histopathological pattern was evaluated in 21 histopathologically confirmed patients.

When the pattern was identified as a UIP pattern on HRCT, the sensitivity, specificity, positive predictive value and negative predictive value for detecting histopathological UIP was 41.7%, 100%, 100% and 56.3%, respectively.

Treatment for RA (Table 3)

Of the 51 patients, 37 (73%) had received treatment for RA at their final visit (non-AE group) or at AE onset (AE group). Specifically, 29 patients (57%) had received corticosteroids, 17 (33%) received immunosuppressants except for MTX, 10 (20%) received MTX and 17 (33%) received other drugs. There were 6 (55%) patients who had received MTX in AE group while 4 (10%) patients in non-AE group and statistically significant difference was observed between the groups ($P = 0.001$).

No patients had received MTX before in AE group while 2 in non-AE group. Thus, there were 6 (55%) patients who had experienced MTX treatment during observation period in AE group while 6 (15%) patients in non-AE group. Median cumulative MTX dose were 1952mg (384-3872) in 6 patients who had experienced MTX among AE group and 802mg (32-2496) in 6 patients among non-AE group. No statistically significant difference was observed between two groups in cumulative MTX dose (P=0.20).

Articular disease activities (RF and DAS28-CRP) were compared between patients who had received MTX at the last visit or at the first AE occurrence, and those who had not. Median RF (range) were 112 IU/mL (16-334) and 284 IU/mL (6-2666) (P=0.25), Median DAS28-CRP (range) were 1.94 (1.02-3.87) and 1.97 (1.02-5.13) (P=0.78), respectively. There were no statistically significant differences in articular disease activities.

AE incidence

The cumulative AE incidence in patients with RA-ILD is shown in Figure 2. The 5-year AE incidence was 11% [95% confidence interval (CI), 2–21%] in all patients, 33% (95% CI, 7–60%) in patients with a UIP pattern on HRCT (UIP pattern group) and 3% (95% CI, 0–9%) in patients with a non-UIP pattern on HRCT (non-UIP pattern group). The AE incidence was significantly higher in UIP pattern group than in non-UIP pattern group (log-rank test, P = 0.018). The overall 1-year AE incidence was 2.8%. The 1-year AE incidence was 6.5% in the UIP pattern group and 1.7 % in the non-UIP pattern group.

Univariate analysis (Table 4) revealed that higher age at ILD diagnosis [hazard ratio (HR), 1.11; 95% CI, 1.02–1.21; P = 0.01], UIP pattern on HRCT (HR, 1.95; 95% CI,

1.07–3.63; $P = 0.03$) and treatment with MTX (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were significant risk factors for AE occurrence.

Survival

The overall survival of patients with RA-ILD is shown in Figure 3.

The 5-year survival was 90% (95% CI, 81–98%) in all patients, 70% (95% CI, 44–94%) in the UIP pattern group and 97% (95% CI, 92–100%) in the non-UIP pattern group. Survival was significantly poorer in the UIP pattern group than in the non-UIP pattern group (log-rank test, $P = 0.04$). In addition, significantly worse survival was demonstrated in the AE group compared with the non-AE group (Figure 4, log-rank test, $P = 0.001$).

Univariate analysis (Table 5) revealed that higher age at ILD diagnosis (HR, 1.08; 95% CI, 0.99–1.17; $P = 0.057$) and UIP pattern on HRCT (HR, 1.74; 95% CI, 0.97–3.12; $P = 0.06$) showed a trend toward poor outcome, while AE (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$) was significantly associated with poor survival.

DISCUSSION

To our knowledge, the present study is the first one focusing on the risk factors and

prognosis associated with AE in patients with RA-ILD. The overall 1-year AE incidence was 2.8% among the RA-ILD patients. Univariate analysis identified that a UIP pattern on HRCT, MTX treatment and higher age at ILD diagnosis were significant risk factors for AE. Furthermore, AE was a prognostic factor for poor survival.

The 1-year AE incidence among patients with IPF has been reported to be 5-19%,[17, 18] whereas that among patients with other ILDs was 4.2% for idiopathic NSIP, 3.3 % for CVD-ILD and 5.6 % for CVD-UIP.[4] In the present study, the 1-year AE incidence among patients with a UIP pattern on HRCT was 6.5% and cumulative incidence was significantly higher in UIP pattern group than in non-UIP pattern group. Furthermore, a UIP pattern on HRCT was a risk factor for AE. In a previous report of small number of biopsy-proven cases, AE incidence among patients with RA-UIP was reported to be 11.1%, similar to that among patients with IPF.[4] The correlation between pathological and radiological UIP patterns has been established in IPF, but not in RA-ILD.[19] In the present study, determination of a UIP pattern on HRCT exhibited high specificity and positive predictive values for the detection of pathological UIP pattern. Therefore, a typical UIP pattern on HRCT was assumed to be highly suggestive of pathological UIP pattern in patients with RA-ILD as well as IPF.[15, 19] Collectively, these results suggest that AE incidence in a subgroup with pathological UIP pattern or a UIP pattern

on HRCT may be higher than that in other patterns..

The present study also identified MTX treatment as a risk factor for AE. MTX is widely used to treat RA, while its toxicity affects the pulmonary system. Diagnostic criteria for MTX-associated pneumonitis (MTX-pneumonitis) have been proposed previously.[20] However, the specificity of the criteria has not been fully examined yet. MTX-pneumonitis typically occurs with acute/subacute onset early in the course of MTX treatment,[20-23] in particular, mostly within the first year[24] and often presents a hypersensitive pneumonitis pattern. Patients with MTX-pneumonitis generally respond to discontinuation of MTX or corticosteroid treatment and have a favorable prognosis.[20-23] In the present study, 6 of 11 patients with AE had received MTX, and 5 of the 6 patients had been treated for 3 or more years. The remaining patient had been treated for 1 year. In all 6 patients, their respiratory conditions progressively deteriorated despite discontinuation of MTX, and they poorly responded to high-dose corticosteroid. Consequently, on the basis of inconsistency in terms of MTX treatment duration and clinical features, we diagnosed these patients with AE of RA-ILD.

Similar to AE in patients with IPF, the etiology of AE in RA-ILD is unknown; however, several reports have suggested that AE may be a distinct manifestation of the primary disease process, a distinct condition associated with undiagnosed infection, or a

subsequent acceleration of a fibroproliferative process caused by acute direct stress to the lung.[1] In the present study, DAS28-CRP in all patients with AE showed low disease activity or remission at the time of AE occurrence, and no significant difference in articular disease activities was observed between AE group and non-AE group or regardless of MTX treatment; therefore, RA activity may not be related to AE occurrence, a finding similar to that of a previous study.[4] MTX possibly accelerates the fibroproliferative process of RA-ILD. It was reported that MTX treatment was a risk factor for RA-ILD progression.[12] For RA-ILD, MTX may be associated not only with newly developing drug-induced pneumonitis but also with deterioration of pre-existing ILD, including AE.

The present study found that patients with a UIP pattern on HRCT had significantly poorer survival than those with a non-UIP pattern. In addition, AE was a prognostic factor for poor outcome. AE has a serious impact on the survival of patients with IPF,[18] and it may also affect the prognosis in other ILDs.[3, 4] Consistent with these reports, the present study revealed that seven (64%) of 11 patients with AE died of respiratory failure, giving rise to high in-hospital mortality, and that survival in the AE group was significantly poorer than that in the non-AE group. Therefore, AE is suggested to be a predictor of poor prognosis in patients with RA-ILD as well as

patients with IPF.

Other prognostic factors in RA-ILD have been reported, including pathological UIP,[25-29] UIP pattern on HRCT,[30] and age at RA-ILD onset.[31] In the present study, pathological UIP could not be identified as prognostic factors because the number of biopsy-proven cases were small. However, we observed similar results regarding UIP pattern on HRCT and age at RA-ILD onset.

In our study, the average time between age at onset of RA and that of RA-ILD was relatively shorter than some previous reports.[7, 8] However, Gabbay et al [11] reported that nearly 60 % of the patients have interstitial lung disease in recent onset RA. In another point of view, since the current authors' institution is regional referral center for interstitial lung disease, referral bias might have increased the proportion of patients with early-stage ILD, leading above results.

This study had several limitations. First, given its retrospective study design, it is subject to several possible biases. For instance, selection and recall bias may exist. Second, because of the relatively small sample size, it may be difficult to determine the precise incidence of AE and the number of event (AE occurrence or death) was too small to perform multivariate analysis. Therefore, larger studies are necessary to confirm our results. Third, because the presence of a UIP pattern on HRCT had low

sensitivity and negative predictive value for the detection of pathologic UIP, it was likely that some patients with a non-UIP pattern on HRCT may have had pathological UIP. HRCT criteria used in our study do not aim to detect pathological UIP but to clinically diagnose IPF and to exclude alternative diagnosis.[15] The frequency of honeycombing on HRCT differs between RA-ILD and IPF, and some ILDs by other causes including RA-ILD have some of findings inconsistent with UIP. Therefore, HRCT pattern in RA-ILD may be more frequently interpreted as non-UIP pattern than that in IPF. In our study, 2 of 5 patients with histopathological UIP in the absence of a UIP pattern on HRCT develop AE. Thus, SLB may have to be considered for these patients to make pathological diagnosis and to predict AE. Finally, RA includes a variety of manifestations. Therefore, other comorbidities may have affected the results.

In conclusion, higher age at ILD diagnosis, UIP pattern on HRCT and treatment with MTX are risk factors for AE occurrence in patients with RA-ILD. Furthermore, the mortality associated with AE is high and AE is prognostic factor for poor outcome. Larger prospective studies investigating acute exacerbations in RA-ILD are indicated.

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Y.N. had full access to all the data in present study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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H.H., Y.N., T.S., and K.C. designed research; H.H., D.H., T.F., and N.I. contributed acquisition of data; H.H., Y.N., T.J., H.S, T.C., M.K., N.E., and T.S. interpreted and analyzed data.

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Table 1 Clinical characteristics

Characteristics	Total N = 51 (100)	Non-AE group[#] N = 40 (78)	AE group[¶] N = 11 (22)	P value[+]
Median age, years (range)				
at RA diagnosis	61 (28-82)	60 (28-81)	65 (42-82)	0.15
at ILD diagnosis	62 (31-83)	62 (31-83)	69 (58-83)	0.15
at AE onset			72 (60-86)	
Sex Male, n (%)	29 (57)	23 (58)	6 (55)	0.86
Observation period, years (range)	8.5 (1-17)	9 (1-17)	6.4 (2-14)	0.45
AE-free period, years (range)	7(1-17)	9 (1-17)	6 (2-14)	0.19
Smoking habit, n (%)				
Never	20 (39)	18 (45)	2 (18)	
Former	24 (47)	16 (40)	8 (73)	0.15
Current	7 (14)	6 (15)	1 (9)	
RF, IU/mL (range)[*]	197 (6-2666)	189 (6-2666)	205 (39-2530)	0.47
DAS28-CRP, score (range)[*]	1.95(1.02-5.13)	2.53(1.02-5.13)	1.82(1.47-2.3)	0.62
PaO_2, torr (range)	82.4 (67-109)	81 (67-102)	85.8 (74-109)	0.19
%FVC, % (range)	91.1 (50.6-130)	87.5 (51-130)	95 (60-125)	0.38
HRCT pattern, n (%)				
UIP pattern	14 (27)	8 (20)	6 (55)	0.02[§]
non-UIP pattern	37 (73)	32 (80)	5 (45)	
Death during observation period, n (%)				
caused by respiratory failure	8 (16)	2 (5)	7 (64)	0.02[§]
caused by other diseases	4 (8)	3 (8)	0 (0)	

Data are presented as n (%), median (range). AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; RF, rheumatoid factor; DAS28-CRP, disease activity score 28 CRP; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; HRCT, high resolution computed tomography; UIP pattern, usual interstitial pneumonia pattern.

[#]Non-AE group, patients who did not develop AE during observation period.

[¶] AE group, patients who developed AE during observation period.

[+] Non-AE group vs AE group

[§] $p < 0.05$

[*] at the first AE occurrence (AE group) or the last visit (non-AE group).

When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

In the AE group, 7 patients died of respiratory failure caused by AE. In the non-AE group, 2 died of respiratory failure caused by bacterial pneumonia or pneumocystis pneumonia, 1 of gastric bleeding and 2 of unknown causes.

Table 2 Diagnostic accuracy of HRCT pattern for histopathological pattern in 21 histopathologically confirmed patients.

	Histopathological pattern		Total
	UIP	Other pattern	
UIP pattern on HRCT	5	0	5
non-UIP pattern on HRCT	7	9	16
Total	12	9	21

Data are presented as number.

HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

Other pattern means other histopathological pattern except for UIP including nonspecific interstitial pneumonia, desquamative interstitial pneumonia and unclassifiable interstitial pneumonia.

When HRCT pattern was identified as a UIP pattern on HRCT, the sensitivity, specificity, positive predictive value and negative predictive value for detecting histopathological UIP was 41.7%, 100%, 100% and 56.3%, respectively.

Table 3 Treatment for RA at final visit[#] or AE onset[¶]

	Total N = 51	non-AE group[+] N = 40 (78%)	AE group[§] N = 11 (22%)	P value
Treatment, yes	37 (73)	27(68)	10 (91)	0.12
Corticosteroid	29 (57)	22 (55)	7 (64)	0.61
Immunosuppressant except for MTX	17 (33)	14 (35)	3 (27)	0.63
MTX	10 (20)	4 (10)	6 (55)	0.001[*]
Other drugs	17 (33)	13 (33)	4 (36)	0.81

Data are presented as n (%) and compared between non-AE group and AE group using Fisher's exact test.

Immunosuppressant except for MTX included azathioprine (n=1), cycrophosphaminde (n=1), etanercept (n=2), mizoribine (n=7), and tacrolimus (n=6).

Other drugs included actarit (n=2), bucillamine (n=5), meloxicam (n=1), and salazosulfapyridine (n=11).

AE, acute exacerbation; ILD, interstitial lung disease; MTX, methotrexate.

[#] In non-AE group.

[¶] In AE group.

[+] Non-AE group, patients who did not develop AE during the observation period.

[§] AE group, patients who developed AE during observation period.

[*] $p < 0.05$

Table 4 Risk factors for AE occurrence according to univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	1.03	0.97-1.10	0.35
Age at ILD diagnosis	1.11	1.02-1.21	0.01+
Sex, male	0.90	0.49-1.69	0.73
Smoking habit, yes	1.60	0.81-4.10	0.19
UIP pattern on HRCT, yes	1.95	1.07-3.63	0.03+
PaO_2 at ILD diagnosis	1.05	0.98-1.12	0.14
%FVC at ILD diagnosis	1.02	0.99-1.06	0.24
Treatment for RA at final visit# or AE onset¶			
Corticosteroids	0.97	0.53-1.92	0.94
Immunosuppressant except for MTX	0.76	0.35-1.41	0.39
MTX	3.04	1.62-6.02	0.001+
Other drugs	0.98	0.50-1.80	0.96

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

In non-AE group.

¶ In AE group.

+ $p < 0.05$

Table 5 Prognostic factors for survival, univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	0.98	0.93-1.04	0.48
Age at ILD diagnosis	1.08	0.99-1.17	0.057
Sex, male	1.14	0.63-2.22	0.67
Smoking habit, yes	1.70	0.87-4.35	0.13
UIP pattern on HRCT, yes	1.74	0.97-3.12	0.06
PaO_2 at ILD diagnosis	1.05	0.98-1.11	0.15
%FVC at ILD diagnosis	1.01	0.98-1.04	0.55
AE during observation period, yes	2.47	1.39-4.56	0.003[+]
Treatment for RA at final visit[#] or AE onset[¶]			
Corticosteroids	1.23	0.67-2.65	0.52
Immunosuppressant except for MTX	0.69	0.32-1.27	0.25
MTX	1.44	0.67-2.68	0.31
Other drugs	0.76	0.36-1.41	0.40

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

[#] In non-AE group.

[¶] In AE group.

[+] $p < 0.05$

Figure legends

Figure 1. Numbers of patients included in this study.

82 patients with RA-ILD were assessed for eligibility. From these, 31 patients were excluded, and 51 patients with chronic course of RA-ILD were included. During observation period, 11 patients developed AE.

RA, rheumatoid arthritis; ILD, interstitial lung disease; AE, acute exacerbation.

Figure 2. Cumulative AE incidence in patients with RA-ILD.

Patients with UIP pattern on HRCT had a significantly higher incidence of AE compared with non-UIP pattern on HRCT (log-rank p=0.018).

AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 3. Overall survival and the survival according to HRCT pattern subgroup.

Patients with UIP pattern on HRCT had a significantly worse survival compared with those with non-UIP pattern on HRCT (log-rank p=0.04).

UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 4. Survival of AE group and non-AE group.

Patients who developed AE during observation periods (AE group) had a significantly worse survival compared with those who did not (non-AE group) (log-rank p=0.001).

AE, acute exacerbation.

Acute exacerbation in rheumatoid arthritis associated interstitial lung disease

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ABSTRACT

Background Acute exacerbation (AE) in idiopathic pulmonary fibrosis is characterised by acute deterioration of respiratory status and the mortality is high. Recently, AE was reported in patients with other interstitial lung diseases, especially rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Objectives To investigate the risk factors and prognosis associated with AE in patients with RA-ILD.

Design A retrospective case-control study.

Setting A single academic hospital.

Participants 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA. ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings.

Main outcome measures Overall survival and cumulative AE incidence were analysed using Kaplan–Meier method. Cox hazards analysis was used to determine significant variables associated with AE occurrence and survival status.

Results A total of 11 patients (22%) developed AE, with an overall 1-year incidence of 2.8%. Univariate analysis revealed that older age at ILD diagnosis [hazard ratio (HR),

1.11; 95% confidence interval (CI), 1.02–1.21; $P = 0.01$], usual interstitial pneumonia (UIP) pattern on HRCT (HR, 1.95; 95% CI, 1.07–3.63; $P = 0.03$) and methotrexate usage (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were associated with AE. Of 11 patients who developed AE during observation period, seven (64%) died of initial AE. In survival, AE was a prognostic factor for poor outcome (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$).

Conclusions In patients with RA-ILD, older age at ILD diagnosis, UIP pattern on HRCT and methotrexate usage are associated with the development of AE. Furthermore, AE has a serious impact on their survival.

Article focus;

Acute exacerbation occurs not only in patients with idiopathic pulmonary fibrosis (IPF) but also in patients with rheumatoid arthritis associated interstitial lung disease (RA-ILD).

What is the risk factor for AE and does AE impact on prognosis in patients with RA-ILD?

Key messages;

In patients with RA-ILD, older age at ILD diagnosis, UIP pattern on HRCT and methotrexate usage are associated with AE occurrence.

In patients with RA-ILD, AE is associated with poor prognosis.

Strengths and limitations of this study;

AE has a serious impact on the survival of patients with RA-ILD.

Given its retrospective study design, it is subject to several possible biases. Therefore, prospective studies are necessary to confirm our results.

INTRODUCTION

Acute exacerbation (AE) is a recently established and an increasingly recognised occurrence in idiopathic pulmonary fibrosis (IPF).[1] AE is characterised by acute deterioration in respiratory status, with newly developed bilateral ground-glass opacities and/or consolidations on chest radiographs or computed tomography scans. It should be in the absence of other alternative causes such as infection, left heart failure, pulmonary embolism, or an identifiable cause of lung injury. AE reportedly occurs not only in patients with IPF but also in patients with other interstitial lung diseases (ILDs), including idiopathic nonspecific interstitial pneumonia (NSIP), collagen vascular disease-associated ILDs (CVD-ILDs) and other forms of ILD.[2-4] The in-hospital mortality associated with AE in patients with CVD-ILD was demonstrated to be as high as that in patients with IPF,[1-4] suggesting that AE may be associated with poor prognosis in patients with CVD-ILD.

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder of unknown etiology that primarily involves joints.[5] ILD is one of common extra-articular manifestations.[6, 7] The reported prevalence is variable (1–58%) and depends on the detection and diagnostic method, or the selected population.[8-13] We and Park *et al* previously reported that RA-associated ILD (RA-ILD) was the most common

CVD-ILD associated with AE.[3, 4] However the risk factors and prognosis associated with AE in patients with RA-ILD are not clarified.

In the present study, we attempted to elucidate the cumulative incidence of AE, its risk factors, and prognostic factors in patients with RA-ILD.

MATERIALS AND METHODS

Subjects

Institutional review board in Hamamatsu University School of Medicine approved this study (approval number 24-191) and waived patient approval or informed consent because the study involved a retrospective review of patient records and images. We retrospectively reviewed 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012 at Hamamatsu University Hospital in Japan. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA.[14] Patients with other coexisting CVD were excluded. In addition, because our aim was to investigate the features of AE among patients with a chronic course of RA-ILD, patients with no evidence of chronic ILD were also excluded. Chronic ILD was defined as the ILD which had been stable for over 3 months.

ILD was diagnosed on the basis of clinical presentation, pulmonary function tests,

high resolution computed tomography (HRCT) findings, and lung biopsy findings. HRCT findings such as bilateral areas with ground-glass attenuation, reticular opacities and honeycomb patterns were interpreted and defined as ILD by a consensus between radiologists and pulmonologists. All cases underwent transbronchial lung biopsy and bronchoalveolar lavage, and 21 (41%) cases underwent surgical lung biopsy (SLB) to definitively diagnose ILD or rule out other diseases. The patients with environmental exposures, suspected of drug induced pneumonia (ILD developed within 1 year after initiation of new drug), or with other known causes of ILD were excluded after considering exposure history and the findings of appropriate tests and histopathological examinations.

Acute exacerbation (AE)

AE was defined using recently proposed criteria[1] that were slightly modified for adaptation to RA-ILD: previous diagnosis of RA-ILD, unexplained worsening or development of dyspnea within 30 days of onset, new bilateral ground-glass abnormalities and/or consolidation superimposed on a reticular or honeycomb pattern on HRCT, no evidence of pulmonary infection on negative respiratory culture, including endotracheal aspirate or bronchoalveolar lavage, and serological test results

for respiratory pathogens, and exclusion of alternative causes such as left heart failure, pulmonary embolism, or an identifiable cause of lung injury. Patients with AE were required to meet all five criteria. In our institution, cultures of sputum, blood, urine, and bronchoalveolar lavage fluid, and serological tests examined for mycobacteria, fungi, bacteria, and some viruses were routinely performed. Echocardiography and, if necessary, CT scanning with intravenous contrast were performed to rule out left heart failure or pulmonary thromboembolism. The patients who developed acute pneumonitis within 1 year after initiation of drug for RA were excluded because drug-induced pneumonitis was not completely ruled out. Patients who did or did not develop AE during the observation period were classified into the AE and non-AE groups, respectively.

Data collection

All clinical and laboratory data were collected from medical records. The observation period was calculated from the date of diagnosis of RA-ILD to the last visit. The AE-free period was defined as the time elapsed between the date of RA-ILD diagnosis and the first AE occurrence (AE group) or the last visit (non-AE group).

Review of radiographic findings

HRCT images taken at the time of RA-ILD diagnosis were reviewed. These images comprised 1 to 2.5-mm collimation sections at 10 mm intervals. They were reconstructed by a high spatial frequency algorithm, and were displayed at window settings appropriate for viewing the lung parenchyma (window level, -600 to -800 Hounsfield units; window width, 1200 to 2000 Hounsfield units). HRCT images were randomised and reviewed independently by two expert chest radiologists (with 23 and 12 years of experience) who were unaware of the related clinical information. Interobserver agreement was classified as follows: poor (κ = 0–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80) and excellent (κ = 0.81-1.00).

RA-ILD on HRCT was classified as a usual interstitial pneumonia (UIP) pattern or a non-UIP pattern according to recent guideline with slight modification.[15] Briefly, a UIP pattern on HRCT was characterised by subpleural and basal predominance, reticular abnormalities, honeycombing with or without traction bronchiectasis and the absence of features listed as inconsistent with a UIP pattern, including upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormalities, profuse micronodules, discrete cysts, diffuse mosaic

attenuation/air-trapping and consolidation in bronchopulmonary segment(s)/lobe(s). If the HRCT pattern did not meet the criteria, it was interpreted as a non-UIP pattern. Disagreements regarding HRCT interpretation were resolved by a consensus between both radiologists.

Review of histopathological findings

SLB specimens were obtained from at least two sites. A diagnosis of RA-ILD was originally made in all cases on the basis of histological features evaluated by a lung pathologist at our hospital, correlated with the clinical and radiological findings. All SLB specimens were also reviewed by a second lung pathologist with 36 years of experience. The histological classification of interstitial pneumonia was based on the consensus statement criteria for idiopathic interstitial pneumonias,[16] and histological patterns that could not be classified according to the criteria were categorised as unclassified interstitial pneumonia.

Statistical analysis

All values are expressed as median (range) or number (%). The Mann-Whitney U test was used for nonparametric comparisons involving continuous data, whereas Fisher's

exact test was used for comparing categorical data. Interobserver agreement on HRCT pattern was analyzed using the κ statistic test. Survival was evaluated using the Kaplan–Meier method and the log-rank test according to observation period. The cumulative AE incidence was obtained from a Kaplan–Meier survival curve by treating AE as the death variable according to AE free period. The 1-year AE incidence was based on person year method and calculated by dividing the number of patients who developed AE by the total of AE-free period (year) of all the patients. Cox hazards analysis was used to determine significant variables associated with survival and AE occurrence. In all analyses, $P < 0.05$ was considered statistically significant. All data were analysed using commercially available software (JMP version 9.0.3a, SAS Institute Inc, Cary, NC, USA).

RESULTS

Patient characteristics (Table 1)

A total of 82 patients with RA-ILD were identified from medical records at Hamamatsu University Hospital. From these, 11 patients with other coexisting CVDs, 8 with no evidence of chronic ILD and an initial acute/subacute course of ILD, and 3 suspected of drug-induced pneumonitis were excluded. In addition, 9 patients for whom

no initial HRCT images were available for review were also excluded. The remaining 51 patients with RA-ILD were included in this study.(Figure 1)

The median age at onset of RA and diagnosis of RA-ILD was 61 (range, 28–82) years and 62 (range, 31–83) years, respectively. The median observation period and AE-free period was 8.5 (range, 1–17) years and 7 (range, 1–17) years, respectively.

During the observation period, 11 patients (22%) developed AE. The median age at the onset of AE was 72 (range, 60–86) years. There were no statistically significant differences in age at onset of RA, age at diagnosis of RA-ILD, sex, observation period, AE-free period, smoking habits, predicted forced vital capacity (%FVC) at diagnosis of RA-ILD, and arterial oxygen pressure (PaO_2) at diagnosis of RA-ILD between the AE and non-AE groups. Also there were no statistically significant differences in articular disease activities (RF and DAS28-CRP) at the last visit (non-AE group) or the first AE occurrence (AE group).

In the AE group, seven of 11 patients (64%) died of respiratory failure caused by initial AE during the observation period. In the non-AE group, two of 40 patients (5%) died of respiratory failure. Regarding death caused by respiratory failure, there was a statistically significant difference in the mortality rate between the AE and non-AE groups (P=0.02).

Extra-articular manifestations except for ILD had been observed in 8 (16%) of 51 patients (pericarditis in 2 patients, pleuritis in 1, neuropathy in 2, cutaneous vasculitis in 2, glomerulonephritis in 1, rheumatoid nodule in 2). There were 3 (27%) patients with extra-articular manifestations beyond ILD in AE group while 5 (13%) in non-AE group. No significant difference in the incidence was observed between AE group and non-AE group (P=0.26).

HRCT pattern (Table 1)

Of the 51 patients with RA-ILD, 14 (27%) exhibited the UIP pattern on HRCT. HRCT images of eight of 40 patients (20%) in the non-AE group and six of 11 (55%) patients in the AE group demonstrated a UIP pattern. Interobserver agreement between both radiologists was moderate (κ statistic test, κ = 0.44). The number of patients who exhibited a UIP pattern on HRCT was significantly higher in the AE group than in the non-AE group.

When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

Diagnostic accuracy of HRCT pattern for histopathological pattern (Table 2)

Among the 51 patients, 21 (41%) underwent SLB. Histopathological analysis revealed a UIP in 12 patients, NSIP in 7, desquamative interstitial pneumonia in 1 and an unclassified interstitial pneumonia in 1. The diagnostic accuracy of HRCT pattern for histopathological pattern was evaluated in 21 histopathologically confirmed patients. The sensitivity, specificity, positive predictive value, and negative predictive value of HRCT for histopathological evidence of UIP is 41.7%, 100%, 100% and 56.3%, respectively.

Treatment for RA (Table 3)

Of the 51 patients, 37 (73%) had received treatment for RA at their final visit (non-AE group) or at AE onset (AE group). Specifically, 29 patients (57%) had received corticosteroids, 17 (33%) received immunosuppressants except for MTX, 10 (20%) received MTX and 17 (33%) received other drugs. There were 6 (55%) patients who had received MTX in AE group while 4 (10%) patients in non-AE group and statistically significant difference was observed between the groups ($P = 0.001$).

No patients had received MTX before in AE group while 2 in non-AE group had received MTX during observation period but discontinued prior to final visit. Thus, there were 6 (55%) patients who had experienced MTX treatment during observation

period in AE group while 6 (15%) patients in non-AE group. Median cumulative MTX dose were 1952mg (384-3872) in 6 patients who had experienced MTX among AE group and 802mg (32-2496) in 6 patients among non-AE group. No statistically significant difference was observed between two groups in cumulative MTX dose (*P*=0.20).

Articular disease activities (RF and DAS28-CRP) were compared between patients who had received MTX at the last visit or at the first AE occurrence, and those who had not. Median RF (range) were 112 IU/mL (16-334) and 284 IU/mL (6-2666) (*P*=0.25), Median DAS28-CRP (range) were 1.94 (1.02-3.87) and 1.97 (1.02-5.13) (*P*=0.78), respectively. There were no statistically significant differences in articular disease activities.

AE incidence

The cumulative AE incidence in patients with RA-ILD is shown in Figure 2. The 5-year AE incidence was 11% [95% confidence interval (CI), 2–21%] in all patients, 33% (95% CI, 7–60%) in patients with a UIP pattern on HRCT (UIP pattern group) and 3% (95% CI, 0–9%) in patients with a non-UIP pattern on HRCT (non-UIP pattern group). The AE incidence was significantly higher in UIP pattern group than in

non-UIP pattern group (log-rank test, $P = 0.018$). The overall 1-year AE incidence was 2.8%. The 1-year AE incidence was 6.5% in the UIP pattern group and 1.7 % in the non-UIP pattern group.

Univariate analysis (Table 4) revealed that older age at ILD diagnosis [hazard ratio (HR), 1.11; 95% CI, 1.02–1.21; $P = 0.01$], UIP pattern on HRCT (HR, 1.95; 95% CI, 1.07–3.63; $P = 0.03$), and MTX usage (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were associated with the development of AE.

Survival

The overall survival of patients with RA-ILD and the survival according to HRCT pattern subgroup are shown in Figure 3. The 5-year survival was 90% (95% CI, 81–98%) in all patients, 70% (95% CI, 44–94%) in the UIP pattern group and 97% (95% CI, 92–100%) in the non-UIP pattern group. Survival was significantly poorer in the UIP pattern group than in the non-UIP pattern group (log-rank test, $P = 0.04$).

The survival of AE group and non-AE group are shown in Figure 4., Significantly worse survival was demonstrated in the AE group compared with the non-AE group (log-rank test, $P = 0.001$).

Univariate analysis (Table 5) revealed that older age at ILD diagnosis (HR, 1.08;

95% CI, 0.99–1.17; $P = 0.057$) and UIP pattern on HRCT (HR, 1.74; 95% CI, 0.97–3.12; $P = 0.06$) showed a trend toward poor outcome, while AE (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$) was significantly associated with poor survival.

DISCUSSION

To our knowledge, the present study is the first one focusing on the risk factors and prognosis associated with AE in patients with RA-ILD. The overall 1-year AE incidence was 2.8% among the RA-ILD patients. Univariate analysis identified that a UIP pattern on HRCT, MTX usage, and older age at ILD diagnosis were associated with the development of AE. Furthermore, AE was a prognostic factor for poor survival.

The 1-year AE incidence among patients with IPF has been reported to be 5-19%,[17, 18] whereas that among patients with other ILDs was 4.2% for idiopathic NSIP, 3.3 % for CVD-ILD and 5.6 % for CVD-UIP.[4] In the present study, the 1-year AE incidence among patients with a UIP pattern on HRCT was 6.5% and cumulative incidence was significantly higher in UIP pattern group than in non-UIP pattern group. Therefore, a UIP pattern on HRCT was associated with the development of AE. In a previous report of small number of biopsy-proven cases, AE incidence among patients with RA-UIP was reported to be 11.1%, similar to that among patients with IPF.[4] The correlation

between pathological and radiological UIP patterns has been established in IPF, but not in RA-ILD.[19] In the present study, determination of a UIP pattern on HRCT exhibited high specificity and positive predictive values for the detection of pathological UIP pattern. Therefore, a typical UIP pattern on HRCT was assumed to be highly suggestive of pathological UIP pattern in patients with RA-ILD as well as IPF.[15, 19] Collectively, these results suggest that AE incidence in a subgroup with pathological UIP pattern or a UIP pattern on HRCT may be higher than that in other patterns..

The present study also identified MTX usage was associated with the development of AE. MTX is widely used to treat RA, while its toxicity affects the pulmonary system. Diagnostic criteria for MTX-associated pneumonitis (MTX-pneumonitis) have been proposed previously.[20] However, the specificity of the criteria has not been fully examined yet. MTX-pneumonitis typically occurs with acute/subacute onset early in the course of MTX treatment,[20-23] in particular, mostly within the first year[24] and often presents a hypersensitive pneumonitis pattern. Patients with MTX-pneumonitis generally respond to discontinuation of MTX or corticosteroid treatment and have a favorable prognosis.[20-23] In the present study, 6 of 11 patients with AE had received MTX, and 5 of the 6 patients had been treated for 3 or more years. The remaining patient had been treated for 1 year. In all 6 patients, their respiratory conditions

progressively deteriorated despite discontinuation of MTX, and they poorly responded to high-dose corticosteroid. Consequently, on the basis of inconsistency in terms of MTX treatment duration and clinical features, we diagnosed these patients with AE of RA-ILD.

Similar to AE in patients with IPF, the etiology of AE in RA-ILD is unknown; however, several reports have suggested that AE may be a distinct manifestation of the primary disease process, a distinct condition associated with undiagnosed infection, or a subsequent acceleration of a fibroproliferative process caused by acute direct stress to the lung.[1] In the present study, DAS28-CRP in all patients with AE showed low disease activity or remission at the time of AE occurrence, and no significant difference in articular disease activities was observed between AE group and non-AE group or regardless of MTX treatment; therefore, RA activity may not be related to AE occurrence, a finding similar to that of a previous study.[4] MTX possibly accelerates the fibroproliferative process of RA-ILD. It was reported that MTX treatment was a risk factor for RA-ILD progression.[12] For RA-ILD, MTX may be associated not only with newly developing drug-induced pneumonitis but also with deterioration of pre-existing ILD, including AE.

The present study found that patients with a UIP pattern on HRCT had significantly

poorer survival than those with a non-UIP pattern. In addition, AE was a prognostic factor for poor outcome. AE has a serious impact on the survival of patients with IPF,[18] and it may also affect the prognosis in other ILDs.[3, 4] Consistent with these reports, the present study revealed that seven (64%) of 11 patients with AE died of respiratory failure, giving rise to high in-hospital mortality, and that survival in the AE group was significantly poorer than that in the non-AE group. Therefore, AE is suggested to be a predictor of poor prognosis in patients with RA-ILD as well as patients with IPF.

Other prognostic factors in RA-ILD have been reported, including pathological UIP,[25-29] UIP pattern on HRCT,[30] and age at RA-ILD onset.[31] In the present study, pathological UIP could not be identified as prognostic factors because the number of biopsy-proven cases were small. However, we observed similar results regarding UIP pattern on HRCT and age at RA-ILD onset.

In our study, the average time between age at onset of RA and that of RA-ILD was relatively shorter than some previous reports.[7, 8] However, Gabbay et al [11] reported that nearly 60 % of the patients have interstitial lung disease in recent onset RA. In another point of view, since the current authors' institution is regional referral center for interstitial lung disease, referral bias might have increased the proportion of patients

with early-stage ILD, leading above results.

This study had several limitations. First, given its retrospective study design, it is subject to several possible biases. For instance, selection and recall bias may exist. Second, because of the relatively small sample size, it may be difficult to determine the precise incidence of AE and the number of event (AE occurrence or death) was too small to perform multivariate analysis. In this analysis, the incidence of extra-articular manifestations beyond ILD and the proportion of current/former smokers in AE group were higher than those in non-AE group (27% vs. 13% and 82% vs. 55%, respectively), with no statistically significant differences. Such differences might be statistically significant in a larger study. Therefore, larger studies are necessary to confirm our results. Third, because the presence of a UIP pattern on HRCT had low sensitivity and negative predictive value for the detection of pathologic UIP, it was likely that some patients with a non-UIP pattern on HRCT may have had pathological UIP. HRCT criteria used in our study do not aim to detect pathological UIP but to clinically diagnose IPF and to exclude alternative diagnosis.[15] The frequency of honeycombing on HRCT differs between RA-ILD and IPF, and some ILDs by other causes including RA-ILD have some of findings inconsistent with UIP. Therefore, HRCT pattern in RA-ILD may be more frequently interpreted as non-UIP pattern than that in IPF. In our

study, 2 of 5 patients with histopathological UIP in the absence of a UIP pattern on HRCT develop AE. Thus, SLB may have to be considered for these patients to make pathological diagnosis and to predict AE. Finally, RA includes a variety of manifestations. Therefore, other comorbidities may have affected the results.

In conclusion, older age at ILD diagnosis, UIP pattern on HRCT and MTX usage are associated with the development of AE in patients with RA-ILD. Furthermore, the mortality associated with AE is high and AE is prognostic factor for poor outcome. Larger prospective studies investigating acute exacerbations in RA-ILD are indicated.

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Guarantor statement:

Y.N. had full access to all the data in present study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authorship:

H.H., Y.N., T.S., and K.C. designed research; H.H., D.H., T.F., and N.I. contributed acquisition of data; H.H., Y.N., T.J., H.S, T.C., M.K., N.E., and T.S. interpreted and analyzed data.

H.H., Y.N., T.J., and T.C. wrote the paper; and H.S., M.K., D.H., N.E., T.F., N.I., T.S., and K.C. revised the paper.

All authors approved the paper.

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All authors do not have any personal or financial support or involvement with organization(s) that have financial interest in the subject matter, or any competing interest.

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Institutional review board in Hamamatsu University School of Medicine approved this study (approval number 24-191) and waived patient approval or informed consent because the study involved a retrospective review of patient records and images.

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Data sharing

No unpublished data from the study are available.

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Table 1 Clinical characteristics

Characteristics	Total N = 51 (100)	Non-AE group[#] N = 40 (78)	AE group[¶] N = 11 (22)	P value[+]
Median age, years (range)				
at RA diagnosis	61 (28-82)	60 (28-81)	65 (42-82)	0.15
at ILD diagnosis	62 (31-83)	62 (31-83)	69 (58-83)	0.15
at AE onset			72 (60-86)	
Sex Male, n (%)	29 (57)	23 (58)	6 (55)	0.86
Observation period, years (range)	8.5 (1-17)	9 (1-17)	6.4 (2-14)	0.45
AE-free period, years (range)	7(1-17)	9 (1-17)	6 (2-14)	0.19
Smoking habit, n (%)				
Never	20 (39)	18 (45)	2 (18)	
Former	24 (47)	16 (40)	8 (73)	0.15
Current	7 (14)	6 (15)	1 (9)	
RF, IU/mL (range)[*]	197 (6-2666)	189 (6-2666)	205 (39-2530)	0.47
DAS28-CRP, score (range)[*]	1.95(1.02-5.13)	2.53(1.02-5.13)	1.82(1.47-2.3)	0.62
PaO_2, torr (range)	82.4 (67-109)	81 (67-102)	85.8 (74-109)	0.19
%FVC, % (range)	91.1 (50.6-130)	87.5 (51-130)	95 (60-125)	0.38
HRCT pattern, n (%)				
UIP pattern	14 (27)	8 (20)	6 (55)	0.02[§]
non-UIP pattern	37 (73)	32 (80)	5 (45)	
Death during observation period, n (%)				
caused by respiratory failure	9 (18)	2 (5)	7 (64)	0.02[§]
caused by other diseases	3 (6)	3 (8)	0 (0)	

Data are presented as n (%), median (range). AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; RF, rheumatoid factor; DAS28-CRP, disease activity score 28 CRP; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; HRCT, high resolution computed tomography; UIP pattern, usual interstitial pneumonia pattern.

[#]Non-AE group, patients who did not develop AE during observation period.

[¶] AE group, patients who developed AE during observation period.

[+] Non-AE group vs AE group

[§] $p < 0.05$

[*] at the first AE occurrence (AE group) or the last visit (non-AE group).

When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

In the AE group, 7 patients died of respiratory failure caused by AE. In the non-AE group, 2 died of respiratory failure caused by bacterial pneumonia or pneumocystis pneumonia, 1 of gastric bleeding and 2 of unknown causes.

Table 2 Diagnostic accuracy of HRCT pattern for histopathological pattern in 21 histopathologically confirmed patients.

	Histopathological pattern		Total
	UIP	Other pattern	
UIP pattern on HRCT	5	0	5
non-UIP pattern on HRCT	7	9	16
Total	12	9	21

Data are presented as number.

HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

Other pattern means other histopathological pattern except for UIP including nonspecific interstitial pneumonia, desquamative interstitial pneumonia and unclassifiable interstitial pneumonia.

The sensitivity, specificity, positive predictive value, and negative predictive value of HRCT for histopathological evidence of UIP is 41.7%, 100%, 100% and 56.3%, respectively.

Table 3 Treatment for RA at final visit[#] or AE onset[¶]

	Total N = 51	non-AE group[+] N = 40 (78%)	AE group[§] N = 11 (22%)	P value
Treatment, yes	37 (73)	27(68)	10 (91)	0.12
Corticosteroid	29 (57)	22 (55)	7 (64)	0.61
Immunosuppressant except for MTX	17 (33)	14 (35)	3 (27)	0.63
MTX	10 (20)	4 (10)	6 (55)	0.001[*]
Other drugs	17 (33)	13 (33)	4 (36)	0.81

Data are presented as n (%) and compared between non-AE group and AE group using Fisher's exact test.

Immunosuppressant except for MTX included azathioprine (n=1), cycrophosphaminde (n=1), etanercept (n=2), mizoribine (n=7), and tacrolimus (n=6).

Other drugs included actarit (n=2), bucillamine (n=5), meloxicam (n=1), and salazosulfapyridine (n=11).

AE, acute exacerbation; ILD, interstitial lung disease; MTX, methotrexate.

[#] In non-AE group.

[¶] In AE group.

[+] Non-AE group, patients who did not develop AE during the observation period.

[§] AE group, patients who developed AE during observation period.

[*] $p < 0.05$

Table 4 Risk factors for AE occurrence according to univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	1.03	0.97-1.10	0.35
Age at ILD diagnosis	1.11	1.02-1.21	0.01+
Sex, male	0.90	0.49-1.69	0.73
Smoking habit, yes	1.60	0.81-4.10	0.19
UIP pattern on HRCT, yes	1.95	1.07-3.63	0.03+
PaO_2 at ILD diagnosis	1.05	0.98-1.12	0.14
%FVC at ILD diagnosis	1.02	0.99-1.06	0.24
Treatment for RA at final visit# or AE onset¶			
Corticosteroids	0.97	0.53-1.92	0.94
Immunosuppressant except for MTX	0.76	0.35-1.41	0.39
MTX	3.04	1.62-6.02	0.001+
Other drugs	0.98	0.50-1.80	0.96

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

In non-AE group.

¶ In AE group.

+ $p < 0.05$

Table 5 Prognostic factors for survival, univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	0.98	0.93-1.04	0.48
Age at ILD diagnosis	1.08	0.99-1.17	0.057
Sex, male	1.14	0.63-2.22	0.67
Smoking habit, yes	1.70	0.87-4.35	0.13
UIP pattern on HRCT, yes	1.74	0.97-3.12	0.06
PaO_2 at ILD diagnosis	1.05	0.98-1.11	0.15
%FVC at ILD diagnosis	1.01	0.98-1.04	0.55
AE during observation period, yes	2.47	1.39-4.56	0.003[+]
Treatment for RA at final visit[#] or AE onset[¶]			
Corticosteroids	1.23	0.67-2.65	0.52
Immunosuppressant except for MTX	0.69	0.32-1.27	0.25
MTX	1.44	0.67-2.68	0.31
Other drugs	0.76	0.36-1.41	0.40

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

[#] In non-AE group.

[¶] In AE group.

[+] $p < 0.05$

Figure legends

Figure 1. Numbers of patients included in this study.

82 patients with RA-ILD were assessed for eligibility. From these, 31 patients were excluded, and 51 patients with chronic course of RA-ILD were included. During observation period, 11 patients developed AE.

RA, rheumatoid arthritis; ILD, interstitial lung disease; AE, acute exacerbation.

Figure 2. Cumulative AE incidence in patients with RA-ILD.

Patients with UIP pattern on HRCT had a significantly higher incidence of AE compared with non-UIP pattern on HRCT (log-rank p=0.018).

AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 3. Overall survival and the survival according to HRCT pattern subgroup.

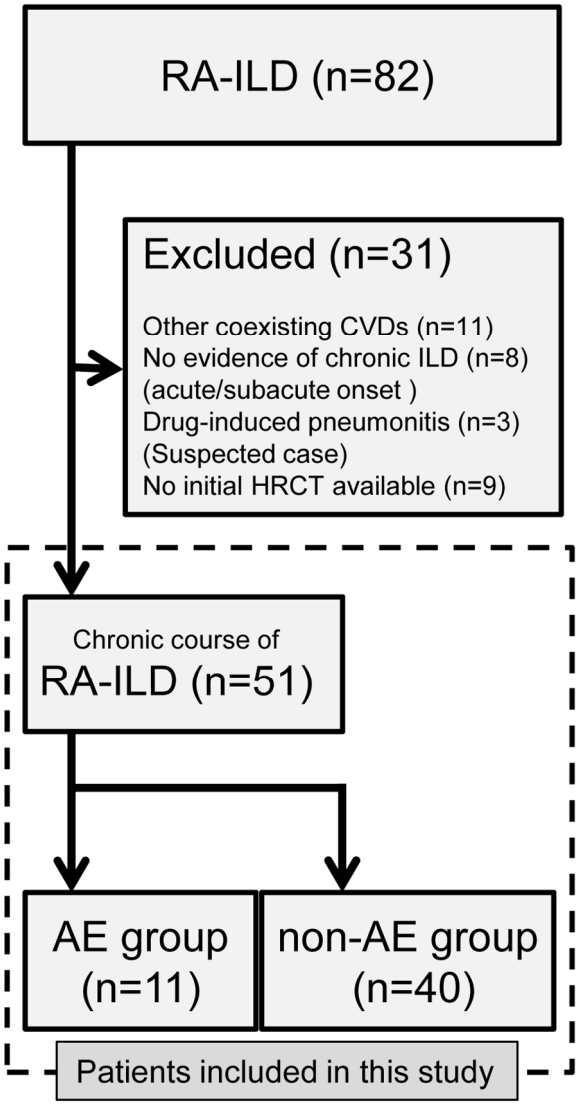
Patients with UIP pattern on HRCT had a significantly worse survival compared with those with non-UIP pattern on HRCT (log-rank p=0.04).

UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 4. Survival of AE group and non-AE group.

Patients who developed AE during observation periods (AE group) had a significantly worse survival compared with those who did not (non-AE group) (log-rank p=0.001).

AE, acute exacerbation.



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82 patients with RA-ILD were assessed for eligibility. From these, 31 patients were excluded, and 51 patients with chronic course of RA-ILD were included. During observation period, 11 patients developed AE. RA, rheumatoid arthritis; ILD, interstitial lung disease; AE, acute exacerbation.
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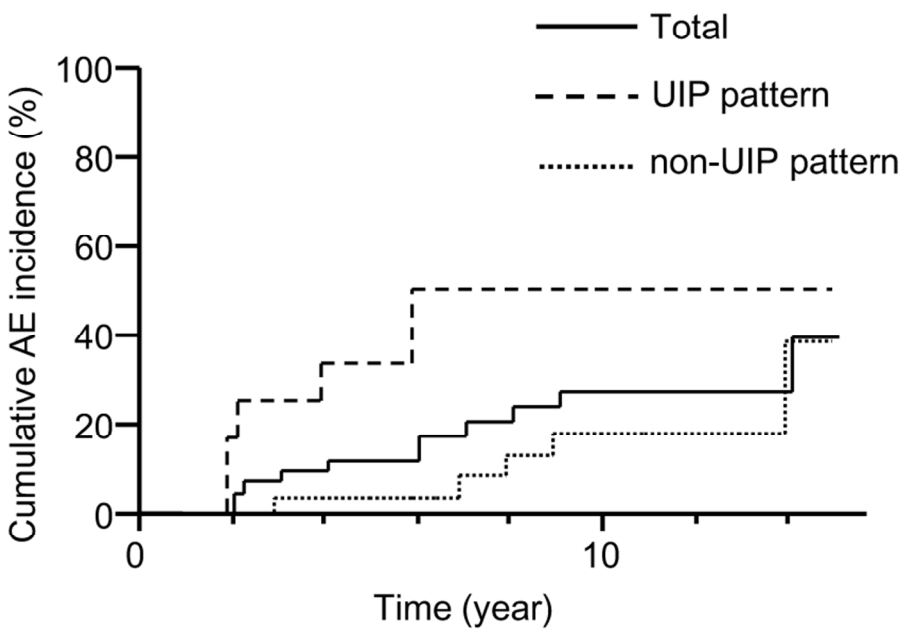

FIGURE 2.

Figure 2. Cumulative AE incidence in patients with RA-ILD.

Patients with UIP pattern on HRCT had a significantly higher incidence of AE compared with non-UIP pattern on HRCT (log-rank p=0.018).
AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.
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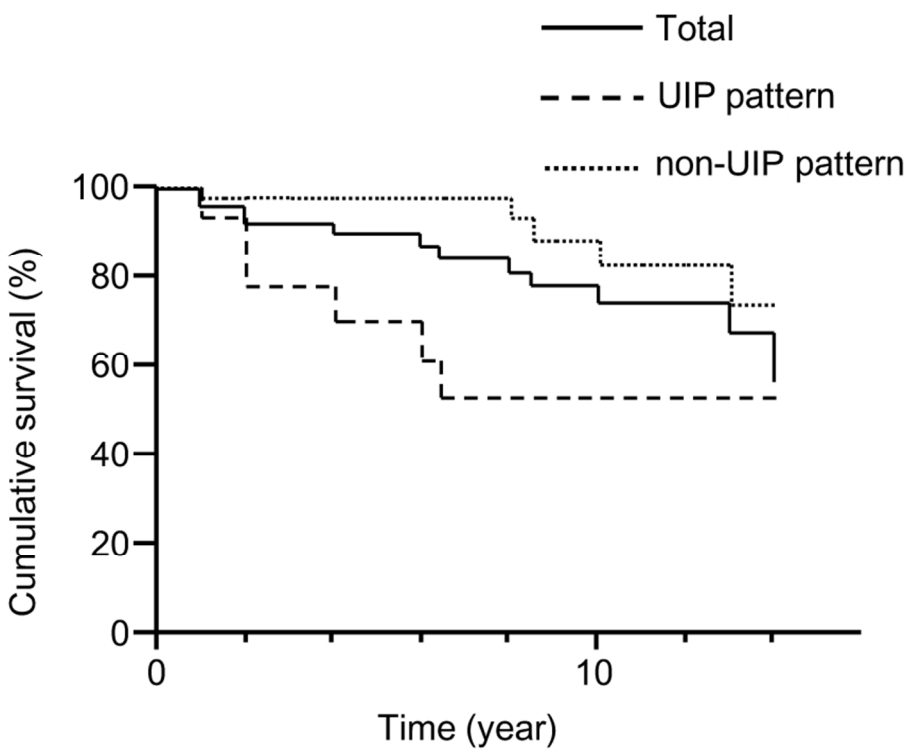

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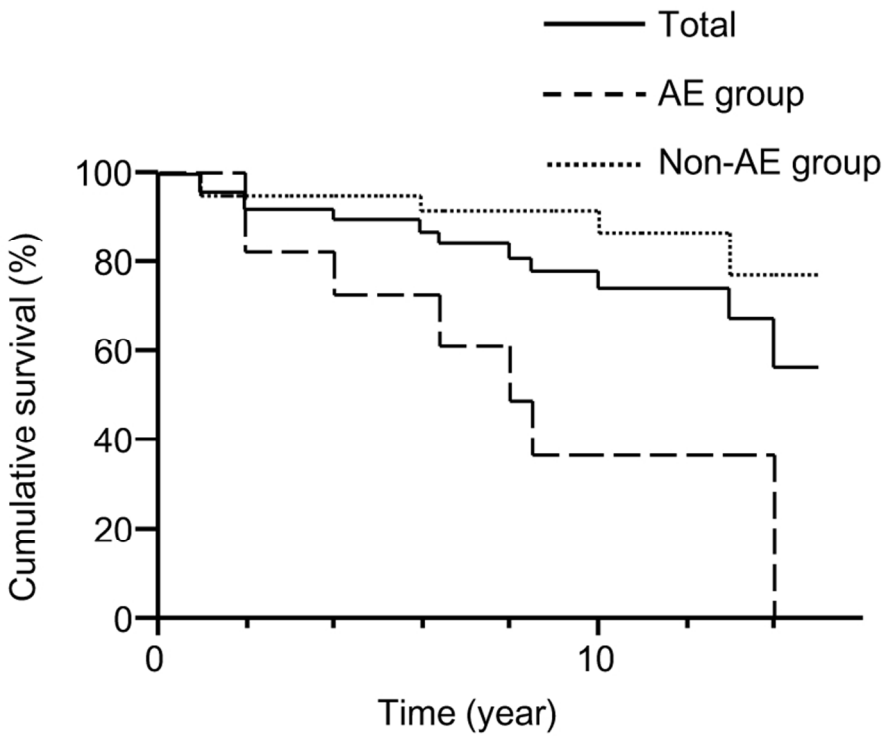

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AE, acute exacerbation.
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Title: Acute exacerbation in rheumatoid arthritis associated interstitial lung disease

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ABSTRACT

Background Acute exacerbation (AE) in idiopathic pulmonary fibrosis is characterised by acute deterioration of respiratory status and the mortality is high. Recently, AE was reported in patients with other interstitial lung diseases, especially rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Objectives To investigate the risk factors and prognosis associated with AE in patients with RA-ILD.

Design A retrospective case-control study.

Setting A single academic hospital.

Participants 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA. ILD was diagnosed on the basis of clinical presentation, pulmonary function tests, high resolution computed tomography (HRCT) findings, and lung biopsy findings.

Main outcome measures Overall survival and cumulative AE incidence were analysed using Kaplan–Meier method. Cox hazards analysis was used to determine significant variables associated with AE occurrence and survival status.

Results A total of 11 patients (22%) developed AE, with an overall 1-year incidence of 2.8%. Univariate analysis revealed that ~~higher~~ older age at ILD diagnosis [hazard

ratio (HR), 1.11; 95% confidence interval (CI), 1.02–1.21; *P* = 0.01], usual interstitial pneumonia (UIP) pattern on HRCT (HR, 1.95; 95% CI, 1.07–3.63; *P* = 0.03) and ~~treatment with~~ methotrexate usage (HR, 3.04; 95% CI, 1.62–6.02; *P* = 0.001) were ~~risk factors for~~associated with AE. Of 11 patients who developed AE during observation period, seven (64%) died of initial AE. In survival, AE was a prognostic factor for poor outcome (HR, 2.47; 95% CI, 1.39–4.56; *P* = 0.003).

Conclusions In patients with RA-ILD, old~~high~~er age at ILD diagnosis, UIP pattern on HRCT and ~~treatment with~~ methotrexate usage are ~~risk factors~~associated with ~~for~~ the development of AE. Furthermore, AE has a serious impact on their survival.

Article focus;

Acute exacerbation occurs not only in patients with idiopathic pulmonary fibrosis (IPF) but also in patients with rheumatoid arthritis associated interstitial lung disease (RA-ILD).

What is the risk factor for AE and does AE impact on prognosis in patients with RA-ILD?

Key messages;

In patients with RA-ILD, ~~higher~~ older age at ILD diagnosis, UIP pattern on HRCT~~,~~ and ~~treatment with~~ methotrexate usage are ~~risk factors for~~associated with AE occurrence.

In patients with RA-ILD, AE is associated with poor prognosis.

Strengths and limitations of this study;

AE has a serious impact on the survival of patients with RA-ILD.

Given its retrospective study design, it is subject to several possible biases. Therefore, prospective studies are necessary to confirm our results.

INTRODUCTION

Acute exacerbation (AE) is a recently established and an increasingly recognised occurrence in idiopathic pulmonary fibrosis (IPF).[1] AE is characterised by acute deterioration in respiratory status, with newly developed bilateral ground-glass opacities and/or consolidations on chest radiographs or computed tomography scans. It should be in the absence of other alternative causes such as infection, left heart failure, pulmonary embolism, or~~and~~ an identifiable cause of ~~acute~~ lung injury. AE reportedly occurs not only in patients with IPF but also in patients with other interstitial lung diseases (ILDs), including idiopathic nonspecific interstitial pneumonia (NSIP), collagen vascular disease-associated ILDs (CVD-ILDs) and other forms of ILD.[2-4] The in-hospital mortality associated with AE in patients with CVD-ILD was demonstrated to be as high as that in patients with IPF,[1-4] suggesting that AE may be associated with poor prognosis in patients with CVD-ILD.

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder of unknown etiology that primarily involves joints.[5] ILD is one of common extra-articular manifestations.[6, 7] The reported prevalence is variable (1–58%) and depends on the detection and diagnostic method, or the selected population.[8-13] We and Park *et al* previously reported that RA-associated ILD (RA-ILD) was the most common

CVD-ILD associated with AE.[3, 4] However the risk factors and prognosis associated with AE in patients with RA-ILD are not clarified.

In the present study, we attempted to elucidate the cumulative incidence of AE, its risk factors, and prognostic factors in patients with RA-ILD.

MATERIALS AND METHODS

Subjects

Institutional review board in Hamamatsu University School of Medicine approved this study (approval number 24-191) and waived patient approval or informed consent because the study involved a retrospective review of patient records and images. We retrospectively reviewed 51 consecutive patients diagnosed with RA-ILD between 1995 and 2012 at Hamamatsu University Hospital in Japan. All patients fulfilled the diagnostic criteria of the American College of Rheumatology for RA.[14] Patients with other coexisting CVD were excluded. In addition, because our aim was to investigate the features of AE among patients with a chronic course of RA-ILD, patients with no evidence of chronic ILD were also excluded. Chronic ILD was defined as the ILD which had been stable for over 3 months.

ILD was diagnosed on the basis of clinical presentation, pulmonary function tests,

high resolution computed tomography (HRCT) findings, and lung biopsy findings. HRCT findings such as bilateral areas with ground-glass attenuation, reticular opacities and honeycomb patterns were interpreted and defined as ILD by a consensus between radiologists and pulmonologists. All cases underwent transbronchial lung biopsy and bronchoalveolar lavage, and 21 (41%) cases underwent surgical lung biopsy (SLB) to definitively diagnose ILD or rule out other diseases. The patients with environmental exposures, suspected of drug induced pneumonia (ILD developed within 1 year after initiation of new drug), or with other known causes of ILD were excluded after considering exposure history and the findings of appropriate tests and histopathological examinations.

Acute exacerbation (AE)

AE was defined using recently proposed criteria[1] that were slightly modified for adaptation to RA-ILD: previous diagnosis of RA-ILD, unexplained worsening or development of dyspnea within 30 days of onset, new bilateral ground-glass abnormalities and/or consolidation superimposed on a reticular or honeycomb pattern on HRCT, no evidence of pulmonary infection on negative respiratory culture, including endotracheal aspirate or bronchoalveolar lavage, and serological test results

for respiratory pathogens, and exclusion of alternative causes such as left heart failure, pulmonary embolism, ~~and~~ or an identifiable cause of ~~acute~~ lung injury. Patients with AE were required to meet all five criteria. In our institution, cultures of sputum, blood, urine, and bronchoalveolar lavage fluid, and serological tests examined for mycobacteria, fungi, bacteria, and some viruses were routinely performed. Echocardiography and, if necessary, CT scanning with intravenous contrast were performed to rule out left heart failure or pulmonary thromboembolism. The patients who developed acute pneumonitis within 1 year after initiation of drug for RA were excluded because drug-induced pneumonitis was not completely ruled out. Patients who did or did not develop AE during the observation period were classified into the AE and non-AE groups, respectively.

Data collection

All clinical and laboratory data were collected from medical records. The observation period was calculated from the date of diagnosis of RA-ILD to the last visit. The AE-free period was defined as the time elapsed between the date of RA-ILD diagnosis and the first AE occurrence (AE group) or the last visit (non-AE group).

Review of radiographic findings

HRCT images taken at the time of RA-ILD diagnosis were reviewed. These images comprised 1 to 2.5-mm collimation sections at 10 mm intervals. They were reconstructed by a high spatial frequency algorithm, and were displayed at window settings appropriate for viewing the lung parenchyma (window level, -600 to -800 Hounsfield units; window width, 1200 to 2000 Hounsfield units). HRCT images were randomised and reviewed independently by two expert chest radiologists (with 23 and 12 years of experience) who were unaware of the related clinical information. Interobserver agreement was classified as follows: poor (κ = 0–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), good (κ = 0.61–0.80) and excellent (κ = 0.81-1.00).

RA-ILD on HRCT was classified as a usual interstitial pneumonia (UIP) pattern or a non-UIP pattern according to recent guideline with slight modification.[15] Briefly, a UIP pattern on HRCT was characterised by subpleural and basal predominance, reticular abnormalities, honeycombing with or without traction bronchiectasis and the absence of features listed as inconsistent with a UIP pattern, including upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormalities, profuse micronodules, discrete cysts, diffuse mosaic

attenuation/air-trapping and consolidation in bronchopulmonary segment(s)/lobe(s). If the HRCT pattern did not meet the criteria, it was interpreted as a non-UIP pattern. Disagreements regarding HRCT interpretation were resolved by a consensus between both radiologists.

Review of histopathological findings

SLB specimens were obtained from at least two sites. A diagnosis of RA-ILD was originally made in all cases on the basis of histological features evaluated by a lung pathologist at our hospital, correlated with the clinical and radiological findings. All SLB specimens were also reviewed by a second lung pathologist with 36 years of experience. The histological classification of interstitial pneumonia was based on the consensus statement criteria for idiopathic interstitial pneumonias,[16] and histological patterns that could not be classified according to the criteria were categorised as unclassified interstitial pneumonia.

Statistical analysis

All values are expressed as median (range) or number (%). The Mann-Whitney U test was used for nonparametric comparisons involving continuous data, whereas Fisher's

exact test was used for comparing categorical data. Interobserver agreement on HRCT pattern was analyzed using the κ statistic test. Survival was evaluated using the Kaplan–Meier method and the log-rank test according to observation period. The cumulative AE incidence was obtained from a Kaplan–Meier survival curve by treating AE as the death variable according to AE free period. The 1-year AE incidence was based on person year method and calculated by dividing the number of patients who developed AE by the total of AE-free period (year) of all the patients. Cox hazards analysis was used to determine significant variables associated with survival and AE occurrence. In all analyses, $P < 0.05$ was considered statistically significant. All data were analysed using commercially available software (JMP version 9.0.3a, SAS Institute Inc, Cary, NC, USA).

RESULTS

Patient characteristics (Table 1)

A total of 82 patients with RA-ILD were identified from medical records at Hamamatsu University Hospital. From these, 11 patients with other coexisting CVDs, 8 with no evidence of chronic ILD and an initial acute/subacute course of ILD, and 3 suspected of drug-induced pneumonitis were excluded. In addition, 9 patients for whom

no initial HRCT images were available for review were also excluded. The remaining 51 patients with RA-ILD were included in this study.(Figure 1)

The median age at onset of RA and diagnosis of RA-ILD was 61 (range, 28–82) years and 62 (range, 31–83) years, respectively. The median observation period and AE-free period was 8.5 (range, 1–17) years and 7 (range, 1–17) years, respectively.

During the observation period, 11 patients (22%) developed AE. The median age at the onset of AE was 72 (range, 60–86) years. There were no statistically significant differences in age at onset of RA, age at diagnosis of RA-ILD, sex, observation period, AE-free period, smoking habits, predicted forced vital capacity (%FVC) at diagnosis of RA-ILD, and arterial oxygen pressure (PaO_2) at diagnosis of RA-ILD between the AE and non-AE groups. Also there were no statistically significant differences in articular disease activities (RF and DAS28-CRP) at the last visit (non-AE group) or the first AE occurrence (AE group).

In the AE group, seven of 11 patients (64%) died of respiratory failure caused by initial AE during the observation period. In the non-AE group, ~~2~~ two of 40 patients (5%) died of respiratory failure. Regarding death caused by respiratory failure, t~~T~~here was a statistically significant difference in the mortality rate between the AE and non-AE groups (P=0.02).

Extra-articular manifestations except for ILD had been observed in 8 (16%) of 51 patients (pericarditis in 2 patients, pleuritis in 1, neuropathy in 2, cutaneous vasculitis in 2, glomerulonephritis in 1, rheumatoid nodule in 2). There ~~was~~ were 3 (27%) patients with extra-articular manifestations beyond ILD in AE group while 5 (13%) in non-AE group. N~~n~~o significant difference in the incidence was observed between AE group and non-AE group (~~27% vs. 13%,~~ *P*=0.26).

HRCT pattern (Table 1)

Of the 51 patients with RA-ILD, 14 (27%) exhibited the UIP pattern on HRCT. HRCT images of eight of 40 patients (20%) in the non-AE group and six of 11 (55%) patients in the AE group demonstrated a UIP pattern. Interobserver agreement between both radiologists was moderate (κ statistic test, κ = 0.44). The number of patients who exhibited a UIP pattern on HRCT was significantly higher in the AE group than in the non-AE group.

When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

Diagnostic accuracy of HRCT pattern for histopathological pattern (Table 2)

Among the 51 patients, 21 (41%) underwent SLB. Histopathological analysis revealed a UIP in 12 patients, NSIP in 7, desquamative interstitial pneumonia in 1 and an unclassified interstitial pneumonia in 1. The diagnostic accuracy of HRCT pattern for histopathological pattern was evaluated in 21 histopathologically confirmed patients. ~~When the pattern was identified as a UIP pattern on HRCT, t~~The sensitivity, specificity, positive predictive value, and negative predictive value of HRCT for ~~detecting~~ histopathological evidence of UIP ~~was~~ is 41.7%, 100%, 100% and 56.3%, respectively.

Treatment for RA (Table 3)

Of the 51 patients, 37 (73%) had received treatment for RA at their final visit (non-AE group) or at AE onset (AE group). Specifically, 29 patients (57%) had received corticosteroids, 17 (33%) received immunosuppressants except for MTX, 10 (20%) received MTX and 17 (33%) received other drugs. There were 6 (55%) patients who had received MTX in AE group while 4 (10%) patients in non-AE group and statistically significant difference was observed between the groups ($P = 0.001$).

No patients had received MTX before in AE group while 2 in non-AE group had received MTX during observation period but discontinued prior to final visit. Thus, there were 6 (55%) patients who had experienced MTX treatment during observation

period in AE group while 6 (15%) patients in non-AE group. Median cumulative MTX dose were 1952mg (384-3872) in 6 patients who had experienced MTX among AE group and 802mg (32-2496) in 6 patients among non-AE group. No statistically significant difference was observed between two groups in cumulative MTX dose (*P*=0.20).

Articular disease activities (RF and DAS28-CRP) were compared between patients who had received MTX at the last visit or at the first AE occurrence, and those who had not. Median RF (range) were 112 IU/mL (16-334) and 284 IU/mL (6-2666) (*P*=0.25), Median DAS28-CRP (range) were 1.94 (1.02-3.87) and 1.97 (1.02-5.13) (*P*=0.78), respectively. There were no statistically significant differences in articular disease activities.

AE incidence

The cumulative AE incidence in patients with RA-ILD is shown in Figure 2. The 5-year AE incidence was 11% [95% confidence interval (CI), 2–21%] in all patients, 33% (95% CI, 7–60%) in patients with a UIP pattern on HRCT (UIP pattern group) and 3% (95% CI, 0–9%) in patients with a non-UIP pattern on HRCT (non-UIP pattern group). The AE incidence was significantly higher in UIP pattern group than in

non-UIP pattern group (log-rank test, $P = 0.018$). The overall 1-year AE incidence was 2.8%. The 1-year AE incidence was 6.5% in the UIP pattern group and 1.7 % in the non-UIP pattern group.

Univariate analysis (Table 4) revealed that ~~higher~~ older age at ILD diagnosis [hazard ratio (HR), 1.11; 95% CI, 1.02–1.21; $P = 0.01$], UIP pattern on HRCT (HR, 1.95; 95% CI, 1.07–3.63; $P = 0.03$), and ~~treatment with~~ MTX usage (HR, 3.04; 95% CI, 1.62–6.02; $P = 0.001$) were associated with the development of AE.~~significant risk factors for AE occurrence.~~

Survival

The overall survival of patients with RA-ILD and the survival according to HRCT pattern subgroup are~~is~~ shown in Figure 3.

The 5-year survival was 90% (95% CI, 81–98%) in all patients, 70% (95% CI, 44–94%) in the UIP pattern group and 97% (95% CI, 92–100%) in the non-UIP pattern group. Survival was significantly poorer in the UIP pattern group than in the non-UIP pattern group (log-rank test, $P = 0.04$).

The survival of AE group and non-AE group are shown in Figure 4.~~In addition~~, S~~s~~ignificantly worse survival was demonstrated in the AE group compared with the

non-AE group (~~Figure 4,~~ log-rank test, $P = 0.001$).

Univariate analysis (Table 5) revealed that ~~higher~~ older age at ILD diagnosis (HR, 1.08; 95% CI, 0.99–1.17; $P = 0.057$) and UIP pattern on HRCT (HR, 1.74; 95% CI, 0.97–3.12; $P = 0.06$) showed a trend toward poor outcome, while AE (HR, 2.47; 95% CI, 1.39–4.56; $P = 0.003$) was significantly associated with poor survival.

DISCUSSION

To our knowledge, the present study is the first one focusing on the risk factors and prognosis associated with AE in patients with RA-ILD. The overall 1-year AE incidence was 2.8% among the RA-ILD patients. Univariate analysis identified that a UIP pattern on HRCT, MTX ~~treatment~~ usage, and ~~higher~~ older age at ILD diagnosis were associated with the development of ~~significant risk factors for~~ AE. Furthermore, AE was a prognostic factor for poor survival.

The 1-year AE incidence among patients with IPF has been reported to be 5-19%,[17, 18] whereas that among patients with other ILDs was 4.2% for idiopathic NSIP, 3.3 % for CVD-ILD and 5.6 % for CVD-UIP.[4] In the present study, the 1-year AE incidence among patients with a UIP pattern on HRCT was 6.5% and cumulative incidence was significantly higher in UIP pattern group than in non-UIP pattern group.

~~Furthermore~~Therefore, a UIP pattern on HRCT was associated with the development of ~~a risk factor for~~ AE. In a previous report of small number of biopsy-proven cases, AE incidence among patients with RA-UIP was reported to be 11.1%, similar to that among patients with IPF.[4] The correlation between pathological and radiological UIP patterns has been established in IPF, but not in RA-ILD.[19] In the present study, determination of a UIP pattern on HRCT exhibited high specificity and positive predictive values for the detection of pathological UIP pattern. Therefore, a typical UIP pattern on HRCT was assumed to be highly suggestive of pathological UIP pattern in patients with RA-ILD as well as IPF.[15, 19] Collectively, these results suggest that AE incidence in a subgroup with pathological UIP pattern or a UIP pattern on HRCT may be higher than that in other patterns..

The present study also identified MTX ~~treatment~~ usage was associated with the development of ~~as a risk factor for~~ AE. MTX is widely used to treat RA, while its toxicity affects the pulmonary system. Diagnostic criteria for MTX-associated pneumonitis (MTX-pneumonitis) have been proposed previously.[20] However, the specificity of the criteria has not been fully examined yet. MTX-pneumonitis typically occurs with acute/subacute onset early in the course of MTX treatment,[20-23] in particular, mostly within the first year[24] and often presents a hypersensitive

pneumonitis pattern. Patients with MTX-pneumonitis generally respond to discontinuation of MTX or corticosteroid treatment and have a favorable prognosis.[20-23] In the present study, 6 of 11 patients with AE had received MTX, and 5 of the 6 patients had been treated for 3 or more years. The remaining patient had been treated for 1 year. In all 6 patients, their respiratory conditions progressively deteriorated despite discontinuation of MTX, and they poorly responded to high-dose corticosteroid. Consequently, on the basis of inconsistency in terms of MTX treatment duration and clinical features, we diagnosed these patients with AE of RA-ILD.

Similar to AE in patients with IPF, the etiology of AE in RA-ILD is unknown; however, several reports have suggested that AE may be a distinct manifestation of the primary disease process, a distinct condition associated with undiagnosed infection, or a subsequent acceleration of a fibroproliferative process caused by acute direct stress to the lung.[1] In the present study, DAS28-CRP in all patients with AE showed low disease activity or remission at the time of AE occurrence, and no significant difference in articular disease activities was observed between AE group and non-AE group or regardless of MTX treatment; therefore, RA activity may not be related to AE occurrence, a finding similar to that of a previous study.[4] MTX possibly accelerates the fibroproliferative process of RA-ILD. It was reported that MTX treatment was a risk

factor for RA-ILD progression.[12] For RA-ILD, MTX may be associated not only with newly developing drug-induced pneumonitis but also with deterioration of pre-existing ILD, including AE.

The present study found that patients with a UIP pattern on HRCT had significantly poorer survival than those with a non-UIP pattern. In addition, AE was a prognostic factor for poor outcome. AE has a serious impact on the survival of patients with IPF,[18] and it may also affect the prognosis in other ILDs.[3, 4] Consistent with these reports, the present study revealed that seven (64%) of 11 patients with AE died of respiratory failure, giving rise to high in-hospital mortality, and that survival in the AE group was significantly poorer than that in the non-AE group. Therefore, AE is suggested to be a predictor of poor prognosis in patients with RA-ILD as well as patients with IPF.

Other prognostic factors in RA-ILD have been reported, including pathological UIP,[25-29] UIP pattern on HRCT,[30] and age at RA-ILD onset.[31] In the present study, pathological UIP could not be identified as prognostic factors because the number of biopsy-proven cases were small. However, we observed similar results regarding UIP pattern on HRCT and age at RA-ILD onset.

In our study, the average time between age at onset of RA and that of RA-ILD was

relatively shorter than some previous reports.[7, 8] However, Gabbay et al [11] reported that nearly 60 % of the patients have interstitial lung disease in recent onset RA. In another point of view, since the current authors' institution is regional referral center for interstitial lung disease, referral bias might have increased the proportion of patients with early-stage ILD, leading above results.

This study had several limitations. First, given its retrospective study design, it is subject to several possible biases. For instance, selection and recall bias may exist. Second, because of the relatively small sample size, it may be difficult to determine the precise incidence of AE and the number of event (AE occurrence or death) was too small to perform multivariate analysis. In this analysis, the incidence of extra-articular manifestations beyond ILD and the proportion of current/former smokers in AE group were higher than those in non-AE group (27% vs. 13% and 82% vs. 55%, respectively), with no statistically significant differences. Such differences might be statistically significant in a larger study. Therefore, larger studies are necessary to confirm our results. Third, because the presence of a UIP pattern on HRCT had low sensitivity and negative predictive value for the detection of pathologic UIP, it was likely that some patients with a non-UIP pattern on HRCT may have had pathological UIP. HRCT criteria used in our study do not aim to detect pathological UIP but to clinically

diagnose IPF and to exclude alternative diagnosis.[15] The frequency of honeycombing on HRCT differs between RA-ILD and IPF, and some ILDs by other causes including RA-ILD have some of findings inconsistent with UIP. Therefore, HRCT pattern in RA-ILD may be more frequently interpreted as non-UIP pattern than that in IPF. In our study, 2 of 5 patients with histopathological UIP in the absence of a UIP pattern on HRCT develop AE. Thus, SLB may have to be considered for these patients to make pathological diagnosis and to predict AE. Finally, RA includes a variety of manifestations. Therefore, other comorbidities may have affected the results.

In conclusion, ~~higher~~ older age at ILD diagnosis, UIP pattern on HRCT and ~~treatment with~~ MTX usage are associated with the development of~~risk factors for~~ AE ~~occurrence~~ in patients with RA-ILD. Furthermore, the mortality associated with AE is high and AE is prognostic factor for poor outcome. Larger prospective studies investigating acute exacerbations in RA-ILD are indicated.

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Guarantor statement:

Y.N. had full access to all the data in present study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Authorship:

H.H., Y.N., T.S., and K.C. designed research; H.H., D.H., T.F., and N.I. contributed acquisition of data; H.H., Y.N., T.J., H.S, T.C., M.K., N.E., and T.S. interpreted and analyzed data.

H.H., Y.N., T.J., and T.C. wrote the paper; and H.S., M.K., D.H., N.E., T.F., N.I., T.S., and K.C. revised the paper.

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Table 1 Clinical characteristics

Characteristics	Total N = 51 (100)	Non-AE group[#] N = 40 (78)	AE group[¶] N = 11 (22)	P value[+]
Median age, years (range)				
at RA diagnosis	61 (28-82)	60 (28-81)	65 (42-82)	0.15
at ILD diagnosis	62 (31-83)	62 (31-83)	69 (58-83)	0.15
at AE onset			72 (60-86)	
Sex Male, n (%)	29 (57)	23 (58)	6 (55)	0.86
Observation period, years (range)	8.5 (1-17)	9 (1-17)	6.4 (2-14)	0.45
AE-free period, years (range)	7(1-17)	9 (1-17)	6 (2-14)	0.19
Smoking habit, n (%)				
Never	20 (39)	18 (45)	2 (18)	
Former	24 (47)	16 (40)	8 (73)	0.15
Current	7 (14)	6 (15)	1 (9)	
RF, IU/mL (range)[*]	197 (6-2666)	189 (6-2666)	205 (39-2530)	0.47
DAS28-CRP, score (range)[*]	1.95(1.02-5.13)	2.53(1.02-5.13)	1.82(1.47-2.3)	0.62
PaO_2, torr (range)	82.4 (67-109)	81 (67-102)	85.8 (74-109)	0.19
%FVC, % (range)	91.1 (50.6-130)	87.5 (51-130)	95 (60-125)	0.38
HRCT pattern, n (%)				
UIP pattern	14 (27)	8 (20)	6 (55)	0.02[§]
non-UIP pattern	37 (73)	32 (80)	5 (45)	
Death during observation period, n (%)				
caused by respiratory failure	98 (1816)	2 (5)	7 (64)	0.02[§]
caused by other diseases	34 (68)	3 (8)	0 (0)	

Data are presented as n (%), median (range). AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; RF, rheumatoid factor; DAS28-CRP, disease activity score 28 CRP; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; HRCT, high resolution computed tomography; UIP pattern, usual interstitial pneumonia pattern.

[#]Non-AE group, patients who did not develop AE during observation period.

[¶] AE group, patients who developed AE during observation period.

[+] Non-AE group vs AE group

[§] $p < 0.05$

[*] at the first AE occurrence (AE group) or the last visit (non-AE group).

When HRCT pattern was identified as a UIP pattern, the positive predictive value and negative predictive value for AE occurrence was 42.9% and 86.5%, respectively.

In the AE group, 7 patients died of respiratory failure caused by AE. In the non-AE group, 2 died of respiratory failure caused by bacterial pneumonia or pneumocystis pneumonia, 1 of gastric bleeding and 2 of unknown causes.

Table 2 Diagnostic accuracy of HRCT pattern for histopathological pattern in 21 histopathologically confirmed patients.

	Histopathological pattern		Total
	UIP	Other pattern	
UIP pattern on HRCT	5	0	5
non-UIP pattern on HRCT	7	9	16
Total	12	9	21

Data are presented as number.

HRCT, high resolution computed tomography; UIP, usual interstitial pneumonia.

Other pattern means other histopathological pattern except for UIP including nonspecific interstitial pneumonia, desquamative interstitial pneumonia and unclassifiable interstitial pneumonia.

~~When HRCT pattern was identified as a UIP pattern on HRCT, t~~The sensitivity, specificity, positive predictive value, and negative predictive value of HRCT for ~~detecting~~ histopathological evidence of UIP is~~was~~ 41.7%, 100%, 100% and 56.3%, respectively.

Table 3 Treatment for RA at final visit[#] or AE onset[¶]

	Total N = 51	non-AE group[+] N = 40 (78%)	AE group[§] N = 11 (22%)	P value
Treatment, yes	37 (73)	27(68)	10 (91)	0.12
Corticosteroid	29 (57)	22 (55)	7 (64)	0.61
Immunosuppressant except for MTX	17 (33)	14 (35)	3 (27)	0.63
MTX	10 (20)	4 (10)	6 (55)	0.001[*]
Other drugs	17 (33)	13 (33)	4 (36)	0.81

Data are presented as n (%) and compared between non-AE group and AE group using Fisher's exact test.

Immunosuppressant except for MTX included azathioprine (n=1), cycrophosphaminde (n=1), etanercept (n=2), mizoribine (n=7), and tacrolimus (n=6).

Other drugs included actarit (n=2), bucillamine (n=5), meloxicam (n=1), and salazosulfapyridine (n=11).

AE, acute exacerbation; ILD, interstitial lung disease; MTX, methotrexate.

[#] In non-AE group.

[¶] In AE group.

[+] Non-AE group, patients who did not develop AE during the observation period.

[§] AE group, patients who developed AE during observation period.

[*] $p < 0.05$

Table 4 Risk factors for AE occurrence according to univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	1.03	0.97-1.10	0.35
Age at ILD diagnosis	1.11	1.02-1.21	0.01+
Sex, male	0.90	0.49-1.69	0.73
Smoking habit, yes	1.60	0.81-4.10	0.19
UIP pattern on HRCT, yes	1.95	1.07-3.63	0.03+
PaO_2 at ILD diagnosis	1.05	0.98-1.12	0.14
%FVC at ILD diagnosis	1.02	0.99-1.06	0.24
Treatment for RA at final visit# or AE onset¶			
Corticosteroids	0.97	0.53-1.92	0.94
Immunosuppressant except for MTX	0.76	0.35-1.41	0.39
MTX	3.04	1.62-6.02	0.001+
Other drugs	0.98	0.50-1.80	0.96

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

In non-AE group.

¶ In AE group.

+ $p < 0.05$

Table 5 Prognostic factors for survival, univariate cox hazard analysis.

	HR	95%CI	P value
Age at RA diagnosis	0.98	0.93-1.04	0.48
Age at ILD diagnosis	1.08	0.99-1.17	0.057
Sex, male	1.14	0.63-2.22	0.67
Smoking habit, yes	1.70	0.87-4.35	0.13
UIP pattern on HRCT, yes	1.74	0.97-3.12	0.06
PaO_2 at ILD diagnosis	1.05	0.98-1.11	0.15
%FVC at ILD diagnosis	1.01	0.98-1.04	0.55
AE during observation period, yes	2.47	1.39-4.56	0.003[+]
Treatment for RA at final visit[#] or AE onset[¶]			
Corticosteroids	1.23	0.67-2.65	0.52
Immunosuppressant except for MTX	0.69	0.32-1.27	0.25
MTX	1.44	0.67-2.68	0.31
Other drugs	0.76	0.36-1.41	0.40

RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography; PaO_2, arterial oxygen pressure; %FVC, predicted forced vital capacity; AE, acute exacerbation; MTX, methotrexate; HR, hazard ratio; 95%CI, 95% confidence interval.

[#] In non-AE group.

[¶] In AE group.

[+] $p < 0.05$

Figure legends

Figure 1. Numbers of patients included in this study.

82 patients with RA-ILD were assessed for eligibility. From these, 31 patients were excluded, and 51 patients with chronic course of RA-ILD were included. During observation period, 11 patients developed AE.

RA, rheumatoid arthritis; ILD, interstitial lung disease; AE, acute exacerbation.

Figure 2. Cumulative AE incidence in patients with RA-ILD.

Patients with UIP pattern on HRCT had a significantly higher incidence of AE compared with non-UIP pattern on HRCT (log-rank p=0.018).

AE, acute exacerbation; RA, rheumatoid arthritis; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 3. Overall survival and the survival according to HRCT pattern subgroup.

Patients with UIP pattern on HRCT had a significantly worse survival compared with those with non-UIP pattern on HRCT (log-rank p=0.04).

UIP, usual interstitial pneumonia; HRCT, high resolution computed tomography.

Figure 4. Survival of AE group and non-AE group.

Patients who developed AE during observation periods (AE group) had a significantly worse survival compared with those who did not (non-AE group) (log-rank p=0.001).

AE, acute exacerbation.