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Lung diseases directly associated with rheumatoid arthritis and their relationship to outcome

Y. Tsuchiya*, N. Takayanagi*, H. Sugiura#, Y. Miyahara*, D. Tokunaga*, Y. Kawabata¶ and Y. Sugita*

ABSTRACT: The outcome and cause of death of each lung disease directly associated with rheumatoid arthritis (RA-LD) have been poorly investigated.

A retrospective study was conducted of 144 patients with RA-LD, in whom the median follow-up period after the initial visit for a respiratory examination was 4.5 yrs.

A total of 57 patients were identified with usual interstitial pneumonia (UIP), 31 with bronchiectasis, 16 with nonspecific interstitial pneumonia (NSIP), 11 with bronchiolitis, five with organising pneumonia (OP), five with diffuse alveolar damage (DAD) and 19 with combined disease. The 5-yr survival rates were 36.6% in the UIP group, 87.1% in the bronchiectasis group, 93.8% in the NSIP group, 88.9% in the bronchiolitis group, 60.0% in the OP group and 20.0% in the DAD group. Survival of patients with DAD was worse than that of patients with UIP. Overall, survival of patients with UIP was worse than that of patients with bronchiectasis, NSIP or bronchiolitis. Of the 144 patients, 71 (49.3%) died, of whom 58 (81.7%) died due to respiratory lesions.

Of patients with RA-LD, patients with DAD experienced the highest mortality, and the survival of patients with UIP was worse than that of patients with NSIP.

KEYWORDS: Bronchiectasis, bronchiolitis, diffuse alveolar damage, nonspecific interstitial pneumonia, rheumatoid arthritis, usual interstitial pneumonia

Rheumatoid arthritis (RA) is a destructive systemic inflammatory disorder. In addition to the impact RA has on the joints, pulmonary involvement occurs regularly, and is responsible for a significant portion of the morbidity and mortality associated with RA [1]. Although pulmonary infection, drug toxicity or both are frequent complications, lung disease directly associated with RA (RA-LD) is the most common [1]. RA-LD includes: interstitial lung diseases such as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organising pneumonia (OP) and diffuse alveolar damage (DAD); airway diseases such as bronchiectasis and bronchiolitis; pleuritis; pulmonary vascular disease; and rheumatoid nodules [1, 2]. The prevalence of the different disease patterns of RA-LD has been reported previously [2–6]; patterns specific to UIP, NSIP, OP, bronchiectasis and bronchiolitis were commonly seen on surgical lung biopsy and/or high-resolution computed tomography (HRCT), but DAD was quite uncommon. However, the difference in clinical features of patients with each type of disease has been poorly investigated.

Overall, the standardised mortality ratios of RA patients are reported as 1.27–2.26 [7, 8]. Excess mortality was seen in RA patients with infection, lymphoma, gastroenterological disorder, cardiovascular disease and pulmonary fibrosis [7, 8]. Causes of death in RA patients were cardiovascular disease in 31%, respiratory disease in 22%, solid tumours in 20%, cerebrovascular disease in 10% and other reasons in 17% [8].

In the idiopathic interstitial pneumonias (IIPs), the histological pattern seen on surgical lung biopsy is the most important predictor of early mortality [9]. In RA-LD, the prognosis of UIP [2, 5, 10–12], NSIP [11, 12], OP [2], DAD [2], bronchiectasis [13], bronchiolitis [5, 14] and interstitial lung fibrosis [15] has been reported, but the relationship between the individual disease types and outcome has not been fully investigated. Furthermore, whether the causes of death in patients with RA-LD are similar to those in all RA cohorts must be clarified. Thus the aims of the present study were to retrospectively review RA patients with RA-LD, document any differences in clinical features between the various disease types, assess impact on prognosis and analyse causes of death.

AFFILIATIONS
Depts of *Respiratory Medicine, #Radiology, and ¶Pathology, Saitama Cardiovascular and Respiratory Center, Kumagaya, Japan.

CORRESPONDENCE
Y. Tsuchiya
Dept of Respiratory Medicine
Saitama Cardiovascular and Respiratory Center
1696 Itai
Kumagaya
Saitama 360-0105
Japan
E-mail: caeser-salad.2corn-soups@nifty.com

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METHODS

Study subjects

During the 10 yrs from April 1996 to March 2006, 277 patients with pleuropulmonary complications of RA were treated at the Saitama Cardiovascular and Respiratory Center (Kumagaya, Japan) (fig. 1). Of these patients, 119 were not included because their lung disease, such as pulmonary infection, drug-induced pneumonia or lung cancer, was not directly associated with RA. Seven patients with UIP were excluded because they had simultaneous lung cancer, two because the pathological diagnosis obtained from surgical lung biopsy was unclassifiable interstitial pneumonia and five because there were less than five patients with the same disease type. The remaining 144 patients comprised the cohort of the present study. Patients were followed-up until March 2009 or until death before March 2009. All patients fulfilled the revised criteria for RA of the American Rheumatism Association [16]. The present study was approved by the institutional review board of Saitama Cardiovascular and Respiratory Center.

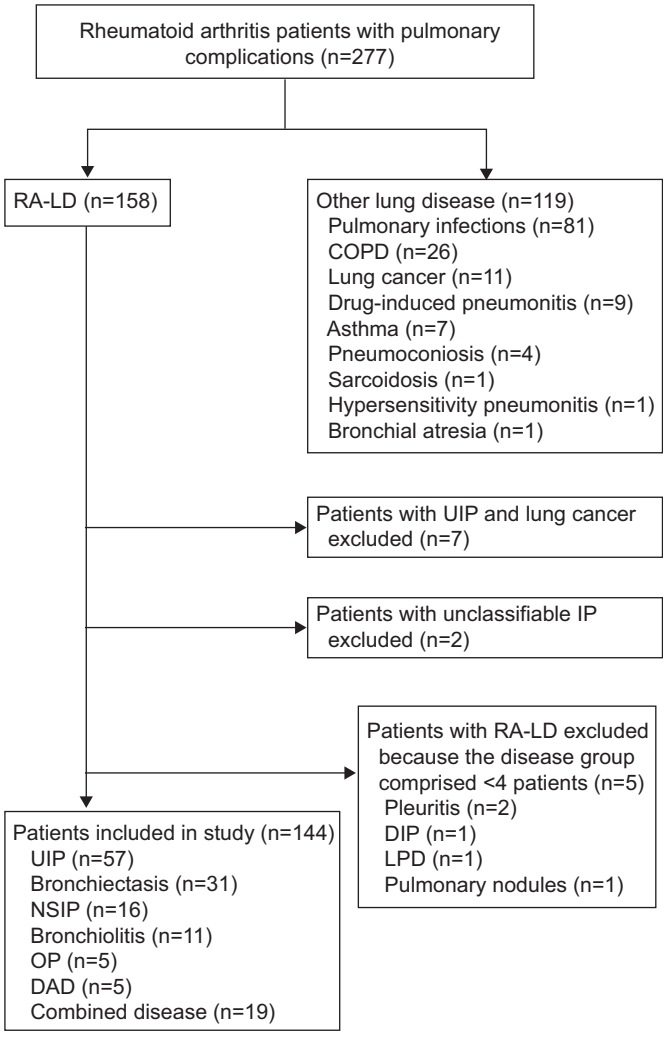

FIGURE 1. Flow diagram showing patients with lung disease directly associated with rheumatoid arthritis (RA-LD). COPD: chronic obstructive pulmonary disease; UIP: usual interstitial pneumonia; IP: interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; DAD: diffuse alveolar damage; DIP: desquamative interstitial pneumonia; LPD: lymphoproliferative disorder.

Diagnostic criteria for RA-LD

Diagnosis of RA-LD was based on the following criteria. A total of 24 patients were diagnosed on the basis of histology (two with bronchiectasis were diagnosed by lobectomy, 14 by surgical lung biopsy, three by autopsy and the remaining five by transbronchial biopsy), and 120 were diagnosed on the basis of clinico-radiological features. Pathological diagnosis of interstitial pneumonia obtained from surgical lung biopsy or autopsy was made using the consensus classification for IIPs [17]. In some patients with classic clinical and radiological features of OP or DAD, diagnosis of these diseases was confirmed by the histological pattern seen in a bronchoscopic biopsy specimen [17]. Follicular bronchiolitis (FB) was diagnosed when prominent peribronchiolar lymphoid follicles with a germinal centre were present [18]. Bronchiolitis obliterans (BO) or constrictive bronchiolitis was diagnosed if there was pathological evidence of bronchiolar luminal narrowing or occlusion by scarring [18]. The pathological diagnoses in the 24 patients included: UIP (n=3); NSIP (n=4); OP (n=2); DAD (n=3); FB (n=1); BO (n=1); FB and BO (n=3); bronchiectasis (n=2); OP and FB (n=2); UIP and FB (n=1); UIP, NSIP and FB (n=1); and UIP, OP and pleuritis (n=1).

Standard HRCT protocols were used to obtain images for evaluation. Collimation was <2.0 mm in all images, and all were reconstructed using high-resolution algorithms. Computed tomography (CT) scans were obtained at suspended end-inspiratory effort with the patients in the supine position. The scans were reviewed independently in a blinded fashion by two observers (N. Takayanagi and H. Sugiura), and were interpreted on the basis of previously published data [4, 6]. Scans consistent with UIP contained predominant basilar reticulation, traction bronchiectasis and honeycombing. Scans consistent with NSIP contained predominant bibasilar ground-glass attenuation with limited reticulation and honeycombing was absent. Scans consistent with OP contained patchy airspace consolidation associated with ground-glass attenuation. Scans consistent with DAD contained patchy or diffuse ground-glass attenuation associated with airspace consolidation, and may have shown intralobular reticulation or traction bronchiectasis. Scans consistent with bronchiolitis contained centrilobular and/or peribronchial nodules, branching linear structures and mosaic perfusion with bronchial dilatation. Each observer noted the most appropriate diagnosis for each patient. In cases of disagreement, consensus was obtained following further review.

DAD was distinguished from acute exacerbation of UIP, which was included in UIP [19]. Since FB and BO can coexist in the airways [14], they were regarded together as bronchiolitis. Some patients with combined disease were included in the combined group. Patients who had UIP and bronchiectasis together were not considered to have traction bronchiectasis caused by UIP but rather bronchiectasis limited to one or multiple lobes.

Study design

The case records of 144 patients with RA-LD were reviewed retrospectively. The following data were recorded: age at onset of RA; age at onset of RA-LD; smoking history; RA drug before the onset of RA-LD; laboratory findings; blood gas analysis

results; pulmonary function test results; treatment of RA-LD for each patient group; and number and cause of deaths. Both the existence of any differences in clinical features and prognosis between the various disease groups and causes of death were analysed.

Statistical analysis

Weighted κ coefficients of agreement (κ_W) were calculated for diagnostic data in order to quantify observer variation. The weights reflect a partial match for multiple disease diagnoses. Categorical baseline characteristics are summarised as frequency and percentage, and continuous characteristics are reported as mean±SD. In order to investigate the risk factors for each disease, baseline characteristics were compared using Fisher's exact test or the Kruskal–Wallis test in accordance with nominal and continuous variables, respectively. The survival probability of each patient group was estimated using the Kaplan–Meier method and compared by global log-rank test. Cox's regression analysis was used to examine the hazard ratio (HR) between UIP (the reference disease) and other disease groups. In all analyses, a p-value of <0.05 was considered to be significant.

RESULTS

Baseline patient clinical characteristics and demographics

The baseline clinical characteristics and demographics are shown in table 1. Of the 19 (13.2%) patients who developed RA-LD before RA onset, 11 had UIP, four NSIP, three bronchiolitis, two bronchiectasis and one OP. Corticosteroids were used in 82 patients. The median follow-up period after the initial visit for a respiratory examination was 4.5 yrs (range 0–24 yrs).

TABLE 1 Characteristics of patients with lung disease directly associated with rheumatoid arthritis (RA-LD)

Age yrs	65.2±9.8 (34–88)
Males/females	60/84
Smoking status	
Current/former	54
Never	90
Smoking history pack-yrs	16.6±28.1 (0–120)
Age at rheumatoid arthritis onset yrs	55.4±14.5 (18–82)
Age at RA-LD onset yrs	65.2±9.8 (34–88)
Duration of rheumatoid arthritis yrs	9.7±12.0 (-15–57)
Combined disease	
Two diseases	
UIP/bronchiectasis	3
UIP/bronchiolitis	2
Bronchiectasis/bronchiolitis	8
Bronchiolitis/OP	2
Three diseases	
UIP/NSIP/bronchiolitis	1
UIP/OP/pleuritis	1
Bronchiectasis/bronchiolitis/OP	1
Bronchiolitis/OP/pleuritis	1

Data are presented as mean±SD (range) or n. UIP: usual interstitial pneumonia; OP: organising pneumonia; NSIP: nonspecific interstitial pneumonia.

Patient characteristics and test findings by disease type

Patient characteristics, laboratory findings, and blood gas analysis and pulmonary function test results by disease type are shown in table 2. There was good agreement between the observers regarding radiological diagnosis (κ_W 0.718; 95% CI 0.685–0.751). UIP, OP and DAD were more likely in males and smokers. Bronchiectasis was commoner in patients with younger onset of RA, longer period from RA onset to RA-LD diagnosis and not using corticosteroids. In UIP and DAD patients, lactate dehydrogenase and C-reactive protein levels and alveolar–arterial oxygen tension difference were higher. Elevation of Krebs von den Lungen-6 (KL-6) concentration was more likely in UIP, DAD, NSIP and bronchiolitis. Elevation of arterial carbon dioxide tension was more likely in bronchiolitis.

Histopathology and HRCT pattern

All patients with the histopathology of UIP, NSIP, DAD and bronchiectasis exhibited the same HRCT pattern (fig. 2). Of the two patients with OP histopathology, one had an OP pattern and the other an OP and bronchiectasis pattern on HRCT. Of the five patients with bronchiolitis histopathology, four had a bronchiolitis pattern and one an NSIP pattern on HRCT. Five patients with combined disease showed one or two HRCT patterns of the combined disease.

Treatment of RA-LD in each patient group

Of the 57 UIP patients, 44 underwent no treatment, nine received 10–30 mg·day^{-1} prednisolone and four underwent steroid pulse therapy with subsequent administration of oral prednisolone. Two of these four patients exhibited simultaneous methotrexate pneumonitis and two had acute exacerbations of UIP. In addition, 15 of the untreated patients subsequently experienced acute exacerbations and took steroid pulse therapy at that time. Patients with bronchiectasis were provided with supportive care.

Of the 16 NSIP subjects, three were treated with steroid pulse therapy and subsequent oral prednisolone therapy, three with 30–50 mg·day^{-1} oral prednisolone and one with 30 mg·day^{-1} prednisolone plus cyclosporin. The others were merely observed and received no medications. Three of the five OP patients were administered 10–30 mg·day^{-1} oral prednisolone and the others were only observed. Six of the 11 patients with bronchiolitis underwent macrolide therapy and one patient received 30 mg·day^{-1} oral prednisolone. The remaining four patients underwent observation alone. All five DAD patients were treated with corticosteroid pulse therapy and cyclophosphamide. Of the 19 patients with combined disease, five took 20–50 mg·day^{-1} oral corticosteroids, five were given macrolide therapy, one underwent steroid pulse therapy and eight were observed but given no medication.

Survival rates and causes of death

Survival rates are presented in table 3. Of the 144 patients, 71 (49.3%) died, 58 (81.7%) of whom died due to respiratory lesions. The median survival time of all RA-LD patients was 8.1 yrs, the 5-yr survival rate was 60.1% and the 10-yr survival rate was 46.0%. The median survival rates by RA-LD were 3.9 yrs for UIP, 9.3 yrs for bronchiolitis, 17 yrs for NSIP and 0.2 yrs for DAD. The 5-yr survival rates were 36.6% for UIP, 87.1% for bronchiectasis, 93.8% for NSIP, 60.0% for OP, 88.9% for bronchiolitis and 20% for DAD; the 10-yr survival rates were 24.6% for UIP, 81.7% for bronchiectasis, 93.8% for NSIP, 60.0% for OP, 47.4% for bronchiolitis and 0% for DAD.

TABLE 2 Background, laboratory findings, and blood gas analysis and pulmonary function test results in each patient group with lung disease directly associated with rheumatoid arthritis (RA-LD)

	UIP	Bronchiectasis	NSIP	Bronchiolitis	OP	DAD	Combined	p-value
Males/females	33/24	4/27	6/10	2/9	4/1	4/1	7/12	<0.001
Age at rheumatoid arthritis onset yrs	60.2±12.8	46.2±14.3	52.3±12.5	50.8±11.6	63.8±8.2	59.4±12.9	58.1±16.8	<0.001
Age at RA-LD onset yrs	67.7±9.4	61.7±10.5	61.3±6.9	62.4±8.7	64.8±9.5	65.2±7.8	68.3±11.1	0.016
Duration of rheumatoid arthritis yrs	7.5±11.6	15.5±12.9	9.1±13.2	11.5±14.9	1.0±2.0	5.8±8.3	10.2±11.0	0.029
Smokers/nonsmokers	29/28	5/26	7/9	1/10	3/2	3/2	6/13	0.005
Smoking history pack-yrs	25.8±35.4	4.7±12.1	13.3±20.9	1.2±4.1	24.8±22.7	32.0±30.3	14.8±26.2	0.003
Steroid use/nonuse before RA-LD	41/16	10/21	8/8	7/4	2/3	3/2	11/8	0.021
DMARDs use/nonuse before RA-LD	38/19	20/11	12/4	9/2	4/1	2/3	12/7	0.749
WBCs cells·μL^{-1}	10130±5243	9142±4428	8638±3458	8564±3558	6500±1012	13080±3813	8531±2415	0.097
LDH U·L^{-1}	439±598	225±80	274±108	256±90	176±26	743±42	245±108	<0.001
CRP mg·dL^{-1}	8.4±8.4	5.6±7.5	5.2±8.4	2.3±3.3	7.2±1.7	17.2±15.0	4.5±6.7	0.008
ESR mm·h^{-1}	77.7±37.4	62.0±35.3	63.2±31.2	63.1±44.0	77.3±29.5	81.0±17.5	69.0±38.0	0.416
RF IU·mL^{-1}	509±1068	224±354	242±563	317±369	439±434	946±984	8221±2402	0.672
KL-6 U·L^{-1}	797±588	299±104	783±1095	770±700	367±191	1158±350	411±187	<0.001
***P*$_{a,O_2}$ mmHg**	65.2±14.1	73.1±14.2	83.0±13.4	70.0±15.3	77.8±7.5	45.7±10.4	70.0±13.0	0.003
***P*$_{a,CO_2}$ mmHg**	36.9±4.5	37.2±4.6	40.3±2.9	45.5±5.6	40.0±6.1	30.7±5.3	40.0±8.4	0.004
***P*$_{A-a,O_2}$ mmHg**	39±17	30±13	17±14	23±13	29±24	66±16	30±17	0.001
VC % pred	70.4±18.0	79.9±18.9	76.2±14.2	75.9±20.6	71.0±21.8	65.4±3.3$^{\#}$	75.0±18.0	0.519
FEV$_1$/FVC %	80.1±10.0	86.2±14.6	80.7±10.0	69.6±12.3	82.0±15.4	78.8±2.6$^{\#}$	78.0±15.0	0.059
***D*$_{L,CO}$ % pred**	78.9±13.9	86.8±14.6	79.1±11.1	92.4±15.8	85.8±21.1	77.2±4.0$^{\#}$	85.0±12.0	0.172

Data are presented as mean±SD or n. UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; DAD: diffuse alveolar damage; DMARD: disease-modifying anti-rheumatic drug; WBC: white blood cell; LDH: lactate dehydrogenase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; KL: Krebs von den Lungen; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension; P_{A-a,O_2}: alveolar–arterial oxygen tension difference; VC: vital capacity; % pred: % predicted; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide. $^{\#}$: pulmonary function test results were unavailable for three of the DAD patients (thus n=2).

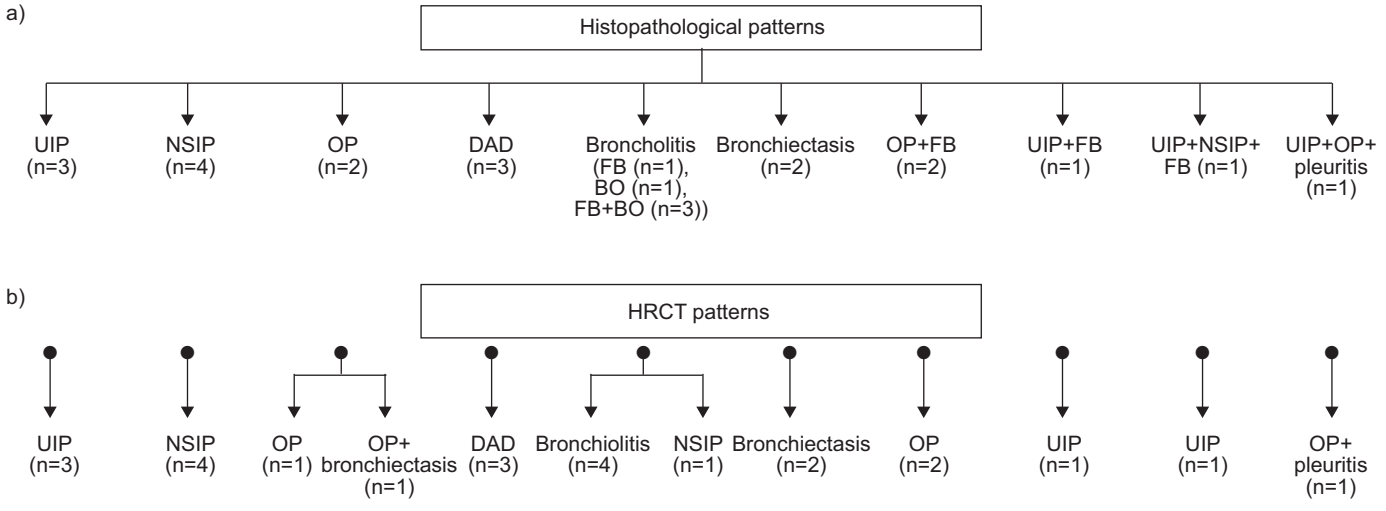

FIGURE 2. Flow chart showing a) histopathological and b) high-resolution computed tomography (HRCT) patterns in patients with lung disease directly associated with rheumatoid arthritis. UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; DAD: diffuse alveolar damage; FB: follicular bronchiolitis; BO: bronchiolitis obliterans.

TABLE 3 Survival and causes of death in patients with lung disease directly associated with rheumatoid arthritis

	UIP	Bronchiectasis	NSIP	Bronchiolitis	OP	DAD	Combined	Total
Patients	57	31	16	11	5	5	19	144
Median survival yrs	3.9		17	9.3		0.2	8.0	8.1
5-yr survival %	36.6	87.1	93.8	88.9	60.0	20.0	59.2	60.1
10-yr survival %	24.6	81.7	93.8	47.4	60.0	0.0	38.9	46.0
Total deaths	45 (78.9)	5 (16.1)	2 (12.5)	3 (27.3)	2 (40.0)	5 (100)	9 (47.4)	71 (49.3)
Cause of death								
Acute exacerbation of UIP	15	0	0	0	0	0	4	19
Acute exacerbation of bronchiectasis	0	2	0	0	0	0	1	3
Disease progression	9	0	0	1	0	3	0	13
Pneumonia	5	1	0	1	1	0	1	9
Other pulmonary infections	3	1	0	0	0	0	0	4
Lung cancer	5	1	0	0	0	0	0	6
Pneumothorax	1	0	0	1	0	0	0	2
Drug-induced pneumonitis	1	0	0	0	0	0	0	1
Radiation pneumonitis[#]	1	0	0	0	0	0	0	1
Nonrespiratory disease	5	0	2	0	1	2	3	13

Data are presented as n or n (%), unless otherwise indicated. UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; DAD: diffuse alveolar damage. [#]: due to irradiation for oesophageal cancer. $p<0.001$ (global log-rank test).

Estimated survival times differed significantly between the seven RA-LD groups ($p<0.001$) (fig. 3). The survival time of patients with DAD was significantly worse than that of those with UIP (HR 2.892). The survival times of patients with bronchiectasis (HR 0.158), NSIP (HR 0.116) and bronchiolitis (HR 0.247) were significantly better than those of patients with UIP (table 4).

Causes of death in UIP patients were acute exacerbation (n=15), chronic disease progression (n=9), lung cancer (n=5), pneumonia (n=5) or other reasons (n=11). Causes of death are summarised in table 3.

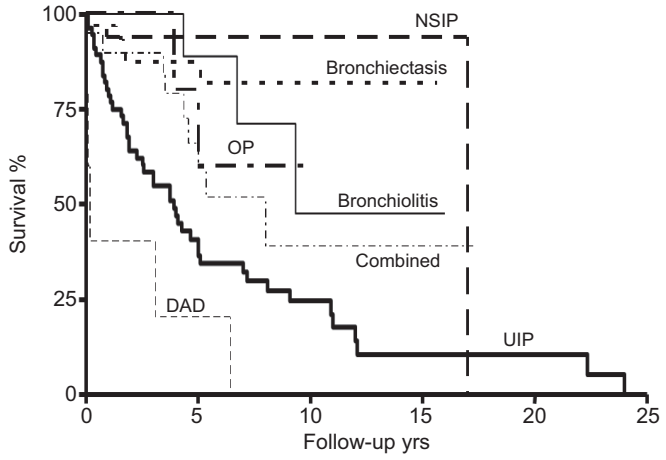

FIGURE 3. Comparison of Kaplan–Meier survival curves between patient groups. NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; DAD: diffuse alveolar damage; UIP: usual interstitial pneumonia.

DISCUSSION

RA-LD, including UIP, NSIP, OP, DAD, bronchiectasis, bronchiolitis and combined disease, was clinicopathologically investigated in order to determine differences in clinical features, especially in relation to prognosis and causes of death in RA patients with these diseases. Of the seven disease entities, the survival rate of patients with DAD was the shortest and that of patients with NSIP the longest, in comparison with patients with UIP. Of the patients with RA-LD, >80% died from pulmonary diseases.

LEE *et al.* [11] reported that males and smokers more frequently have RA-associated UIP. In the present study, UIP was more likely to be seen in males and smokers. Some reports indicate that bronchiectasis complicated by RA is frequent in non-smokers [20]; however, other reports show no significant difference [21]. In addition, one report showed that bronchiectasis

TABLE 4 Comparison of survival between patient groups using Cox's proportional hazards regression analysis model[#]

	Hazard ratio	95% CI	p-value
DAD	2.892	1.134–0.376	0.026
Bronchiectasis	0.158	0.063–0.400	<0.001
NSIP	0.116	0.028–0.477	0.003
OP	0.353	0.085–1.462	0.151
Bronchiolitis	0.247	0.077–0.799	0.020
Combined	0.501	0.244–1.030	0.060

DAD: diffuse alveolar damage; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia. [#]: with usual interstitial pneumonia as reference disease.

was the precedent in 30 (94%) of 32 patients before RA onset [21], whereas another report suggested that bronchiectasis was the precedent in five out of 23 RA patients [22]. Bronchiectasis was confirmed before RA onset in only two of the present 31 patients with bronchiectasis.

Elevation of KL-6 level is known to occur in patients with interstitial pneumonia, hypersensitivity pneumonitis and pulmonary alveolar proteinosis. KINOSHITA *et al.* [23] reported that the KL-6 level in patients with advanced RA/UIP can increase to >1,000 $U \cdot mL^{-1}$ but does not increase in patients with airway disease or OP. In the present study, KL-6 elevation was observed in patients with UIP, DAD, NSIP and bronchiolitis.

The median survival time of the present patients with UIP was 3.9 yrs. In general, the median survival time of patients with idiopathic pulmonary fibrosis (IPF) is 2–4 yrs [9, 17]. FLAHERTY *et al.* [24] compared 99 IPF and nine UIP patients (including four with RA/UIP) with complications of collagen vascular disease (CVD). The prognosis of CVD/UIP is better than that of IPF because less fibrotic foci are present histopathologically in CVD/UIP [25]. In contrast, the median survival time of patients with RA/pulmonary fibrosis reported by HAKALA [15] was 3.5 yrs, which is similar to the present findings. PARK *et al.* [10] and KIM *et al.* [12] found no difference in prognosis between IPF and RA/UIP. Moreover, SONG *et al.* [26] reported that, in UIP associated with CVD, patients with RA/UIP have the gravest prognosis. Further accumulation of data is required in order to adequately compare prognosis between IPF and RA/UIP.

It was reported that the 5- and 10-yr survival rates of patients with idiopathic NSIP were 82.3% and 73.2%, respectively [27]. No fatal cases of RA/NSIP were reported by LEE *et al.* [11]. In the present study, the 5- and 10-yr survival rates for RA/NSIP were both 93.8%, and there were no fatal cases owing to respiratory disease.

DAD is not frequent in RA-LD, occurring in only one (1.5%) out of 67 cases in the CT review of TANAKA *et al.* [4], and two (5%) out of 40 cases of open lung biopsy of YOUSEM *et al.* [2]. Of the present 144 patients, five (3.4%) had DAD. The mortality rate of idiopathic DAD is high (⩾50%), with most deaths occurring 1–2 months after onset of illness [16]. Few reports address the prognosis of RA/DAD. YOUSEM *et al.* [2] reported that one out of two patients died from DAD, and the other improved. PARAMBIL *et al.* [28] reported five patients with RA/DAD. Four had pre-existing RA-associated interstitial lung disease, and one had pure DAD; only this patient survived. In the present five patients, three died of disease progression due to DAD early after hospital admission.

The 5-yr mortality rate of cryptogenic OP is generally 5% [9]. In one report, two out of six RA/OP patients died, one from primary disease and the other from other disease [2]. Although two out of the present five OP patients died, the individual causes of death were pneumonia and malignant lymphoma and not OP itself. The prognosis of OP might be as good as that of cryptogenic OP.

The 10-yr survival rate of the present RA/bronchiectasis patients was 81.7%. SWINSON *et al.* [13] reported that the 5-yr survival rate of their RA/bronchiectasis patients was 68.8%. The mortality was higher than that of the general population, or for RA or bronchiectasis alone. SHADICK *et al.* [22] reported a mortality rate of 17.4% in 23 RA/bronchiectasis patients. In the five fatal cases of RA/bronchiectasis in the present study, acute exacerbations or pulmonary infections accounted for 80% of the causes of death. Infection control would be beneficial for improvement of the prognosis.

The 5-yr survival rate of the present RA/bronchiolitis patients was 88.9%, but the 10-yr survival rate decreased to 47.4%. BO often presents with severe respiratory failure, and is resistant to treatment. Therefore, the prognosis is particularly poor [29]. DEVOUASSOUX *et al.* [30] define patients with BO in RA as those with a forced expiratory volume in 1 s/forced vital capacity of <50% and/or residual volume/total lung capacity of >140%. They followed up 25 patients for an average of 48.2 months, during which time four (16%) patients died and 40% lapsed into chronic respiratory failure. HAYAKAWA *et al.* [14] suggested that erythromycin may be useful for the management of RA/bronchiolitis. Six out of the present 11 RA/bronchiolitis patients received erythromycin or clarithromycin, and cough and sputum production decreased in five of these patients. A prospective study is required in order to further prove the efficacy of these drugs.

HAKALA *et al.* [15] reported that 80% of RA/lung fibrosis patients died of progression of primary lung disease, and only a few patients died of lung cancer, pulmonary tuberculosis or cardiovascular disease. LEE *et al.* [11] reported that five out of 10 patients with RA/UIP died. Causes of death consisted of exacerbation in one patient, pulmonary infection in another and steady progression of lung disease in the remaining three. In the present study, 58 (81.7%) out of 71 patients died of respiratory complications. In comparison with a report indicating that 22% of RA patients died from respiratory complications [8], the present results would indicate that the death rate from pulmonary complications is higher in patients with RA-LD than in patients with RA alone.

One limitation of the present study is that the diagnosis was not proven pathologically in a large number of the patients. However, if only patients diagnosed pathologically were included in a study, those patients with a distinctive radiographic pattern of UIP would probably not undergo surgical lung biopsy and might be excluded from the study. The pattern of radiographic abnormalities seen on HRCT in RA has proven to be an excellent predictor of the underlying pathological pattern [1]. In addition, the present κ_W results were good with regard to radiological diagnosis, and, among the patients for whom histopathology results were available, all patients with HRCT patterns of UIP, NSIP, DAD or bronchiectasis showed the same histology. The present study includes many patients who were diagnosed with the aid of imaging tools; however, we believe that there are few inaccuracies in the diagnosis of the clinical disease entity. The other limitation concerns the possibility of diagnostic delay arising from the fact that the Saitama Cardiovascular and Respiratory Center is a specialised cardiovascular–respiratory hospital, and that the patients who had been followed by other rheumatologists were not admitted to this hospital until a respiratory symptom appeared. The majority of RA-LD occurs

within the first years after the initial diagnosis [1]. The present UIP subjects were diagnosed an average of 7.5 yrs after RA onset. This delay in diagnosis might affect median or 5-yr survival rates.

In summary, mortality rates were different among the various disease groups. Patients with DAD experienced the highest mortality, and, with UIP as the reference disease, the HR was estimated to be 2.892 (95% CI 1.134–7.736). In contrast, the NSIP group experienced the lowest mortality (HR 0.116; 95% CI 0.028–0.477), and this was significantly lower than that of the UIP group. Of patients with RA-LD, >80% died of pulmonary disease. Thus establishment of effective treatment for each RA-LD and improvement of treatment outcome for patients with pulmonary infections are necessary.

STATEMENT OF INTEREST

None declared.

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