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Original Article

Prognostic factors affecting respiratory-related death in patients with rheumatoid arthritis complicated by interstitial lung disease: an ANSWER cohort study

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Abstract

The aim of this multi-center retrospective study was to clarify the prognostic factors for respiratory-related death in patients with rheumatoid arthritis (RA) complicated interstitial lung disease (ILD). Patient background data, treatment regimen, and disease activity indicators of RA and ILD at baseline, 6 months after diagnosis of ILD, and at the last follow-up visit were extracted. A total of 312 patients with RA-ILD (17 patients who died from respiratory-related causes and 295 survivors) were included. Patients who died from respiratory-related causes had an older median age, higher proportion of males, and a higher anti-cyclic citrullinated peptide antibody positivity rate than survivors (P = 0.0001, 0.038, and 0.016, respectively); they also had significantly higher baseline serum levels of KL-6 than survivors (P = 0.013). Patients who died from respiratory-related causes showed significantly greater changes in serum KL-6 levels between the six-month timepoint and the last visit (ΔKL-6 [6m-last]) than survivors (P = 0.011). Multivariate analysis showed that the ΔKL-6 (6m-last) corrected by disease duration was a predictor of respiratory disease-related death in patients with RA-ILD (P <0.0001). Long-term increase in serum KL-6 levels is associated with respiratory disease-related death in patients with RA-ILD.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease that is characterized by polyarthritis [1]. Interstitial lung disease (ILD) occurs in 28%-67% of all RA cases [2-10]. It has been reported that the rate of ILD complication in RA has increased over the years, and that the mortality rate of RA-ILD has been on the rise [2]. Risk factors for ILD complication in RA are male sex, age older than 60 years, smoking history, and high levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA) [7], [11-14].

The main causes of death in patients with RA are malignant diseases and respiratory diseases, such as ILD

and pneumonia [15, 16]. Previous reports indicate that the poor prognostic factors for RA-ILD are male sex, older age, usual interstitial pneumonia (UIP)-like patterns in chest high-resolution computed tomography (HRCT) findings, and expanded and acute exacerbation of ILD [14, 17-19]. However, these reports were of studies conducted using a small number of cases or in a small number of institutions. Furthermore, the characteristics of respiratory-related deaths in patients with RA-ILD have not been fully elucidated. In particular, the relationship between disease activity, treatment regimen, these changes, and respiratory-related death in patients with RA-ILD have not been clarified. Therefore, this study investigated and clarified the factors that influence respiratory-related death in patients with RA-ILD.

Materials and Methods

Patients

This was a multicenter, observational, retrospective study conducted to clarify the prognostic factors of respiratory-related death in patients with RA-ILD. This study was conducted using the Kansai Consortium for Well-Being of Rheumatic Disease Patients (ANSWER) cohort. The ANSWER cohort is an observational multicenter registry of patients with RA in the Kansai district of Japan. Data from patients registered in seven institutes (Kyoto University, Osaka University, Osaka Medical and Pharmaceutical University, Kansai Medical University, Kobe University, Nara Medical University, and Osaka Red Cross Hospital) were included. RA patients enrolled in this cohort from 2009 to 2019 were included. The data of patients with RA who were diagnosed with ILD by a radiologist based on chest HRCT findings were retrospectively collected. RA was diagnosed based on either the 1987 RA classification criteria of the American College of Rheumatology (ACR) [20] or the 2010 ACR/European League Against Rheumatism criteria [21]. Baseline demographic data, including age, sex, smoking history, duration of RA, disease stage/class (Steinblocker's classification), RF positivity/titer, ACPA positivity/titer, disease activity (Disease Activity Score in 28 joints using C-reactive protein [DAS28-CRP]), simplified disease activity index (SDAI), clinical disease activity index (CDAI), serum levels of Krebs von den Lungen-6 (KL-6), treatments details, and prognosis, including respiratory-related death, were collected. In addition, data on disease activity of RA, serum KL-6 levels, and treatment regimen at six months after diagnosis of ILD (6 months) and at the last follow-up visit were obtained. The last follow-up visit was defined as the time of final observation for survivors and three months before death for patients who died. In RA-ILD patients, there is an increased risk of modification of each clinical parameter just before death due to other complications, such as infections and the effects of therapeutic drugs on these patients. In order to reduce

the influence of other factors on RA-ILD pathology, data from three months prior to death were extracted.

Ethics approval and consent to participate

The representative facility of the registry used for this is Kyoto University. This observational study was conducted in accordance with the Declaration of Helsinki and with approval from the ethics committee of each of the seven participating institutes (Kyoto University, Osaka University, Osaka Medical and Pharmaceutical University, Kansai Medical University, Kobe University, Nara Medical University, and Osaka Red Cross Hospital). The ethics committee of Osaka Medical and Pharmaceutical University approved this study (approval no. 1529) and waived the requirement for informed consent because of the anonymous nature of the study data. Written informed consent was obtained from participants in other institutes.

Respiratory-related death

The pathological conditions that each attending physician determined to be the cause of respiratory-related death were extracted; acute exacerbation of ILD, respiratory failure due to chronic progression of ILD, bacterial pneumonia, other infectious pneumonia (virus, *pneumocystis jirovecii*, fungal pneumonia, etc), and lung cancer, etc. Patients who died from non-respiratory-related causes were excluded from the analysis.

Statistical analysis

Data are presented as median (interquartile range). Fisher's exact test was used when appropriate, whereas the Wilcoxon signed-rank test was used to compare median values. Statistical significance was set at $P < 0.05$. Risk factors associated with respiratory-related death that had significant P values ($P < 0.05$) in univariable analyses were extracted and assessed using univariable and multivariable logistic regression analyses. The demographic and background characteristics of the respiratory-related death group and the survivor group were compared using univariable analysis. Thereafter, the odds ratios of patient outcomes were estimated using univariable and multivariable analysis with a logistic regression model. Data were analyzed using JMP version 14.0 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics, treatment details, and prognoses of patients with RA-ILD

The study population was selected from the patients with RA-ILD in the ANSWER cohort (n = 312) who

fulfilled the inclusion criteria. A total of 17 patients were included in the respiratory-related death group, whereas 295 patients with RA-ILD were included in the survivor group. The baseline characteristics, treatment details, and prognoses of the patients are shown in Table 1. The median age of the patients was 70 (64-76) years old and 65.4% of them were female. A smoking history was found in 106 (57.3%) of 185 patients who could recorded. The median duration of RA was 335.7 (99.4-825.7) weeks, RF positivity/titer was 93%/133.0 (59.0-340.0) U/mL, ACPA positivity/titer was 98.1%/297.0 (74.2-433.0) U/mL, DAS28-CRP score was 2.72 (1.82-3.93), SDAI was 8.6 (4.1-17.8), CDAI was 7.9 (3.6-16.2), and KL-6 level was 438.0 (282.0-705.8) U/mL. The concomitant medications used were methotrexate (MTX) 6 (4-8) mg/week (37.3%), tacrolimus (TAC) (15.9%), PSL 5.0 (4.0-10.0) mg/day (45.1%), tumor necrosis factor inhibitors (10.0%), interleukin 6 inhibitors (4.9%), abatacept (ABT) (9.1%), and janus kinase inhibitors (0.3%). Seventeen patients died due to respiratory-related causes. Of these, five patients died due to acute exacerbation of ILD, one died from respiratory failure due to chronic progression of ILD, five died due to pneumocystis pneumonia (PCP), three died due to bacterial pneumonia, and two died due to lung cancer.

Changes in the treatment regimen of patients with RA-ILD

Changes in the treatment regimen of patients with RA-ILD at baseline, 6 months, and at the last follow-up visit are presented in Table 2. Utilization of MTX tended to decrease six months after baseline and was significantly reduced towards the last visit. Utilization of TAC and ABT increased significantly after six months and towards the last visit compared to baseline.

Comparison of the baseline clinical characteristics and treatment regimens of patients who died from respiratory-related causes and survivors

We compared the baseline clinical characteristics and treatment regimens of the 17 patients in the respiratory-related death group and the 295 in the survivor group (Table 3). Median age was significantly older and the proportion of males was significantly higher in respiratory-related death group than in the survivor group ($P = 0.0001$ and 0.038, respectively). The RF positivity rate tended to be lower in the respiratory-related death group (78.6%) than in the survivor group (93.8%) ($P = 0.064$). The ACPA positivity rate was also significantly lower in the respiratory-related death group (81.8%) than in the survivor group (98.8%) ($P = 0.016$). The respiratory-related death group had significantly higher serum levels of KL-6 (754 [377-1713.5] U/mL) than the survivor group (425 [277.5-654.5] U/mL) ($P = 0.012$). MTX usage rate was significantly lower in the

respiratory-related death group (12.5%) than in the survivor group (38.7%) ($P = 0.036$). There were no differences between the two groups in terms of other clinical characteristics and treatment contents.

Comparison of the RA disease activities, serum KL-6 levels, and treatment regimens of patients who died of respiratory-related death causes and survivors at 6 months and at the last follow-up visit

There was no difference between the RA disease activities, serum KL-6 levels, and treatment regimens of the respiratory-related death and survivor groups at 6 months (Table 4). However, serum levels of KL-6 at the last visit were significantly higher in the respiratory-related death group (708.5 [468.5-1063.5] U/mL) than in the survivor group (444.0 [294.0-667.0] U/mL) ($P = 0.026$) (Table 5). There was no difference between the RA disease activities and the treatment regimens of the two groups at the last visit.

Comparison of changes in serum KL-6 levels and RA disease activities from baseline to the last visit between patients who died from respiratory-related death causes and survivors

Comparison of changes in serum KL-6 levels from baseline to the last visit between the respiratory-related death and survivor groups is shown in Figure 1. Changes in serum KL-6 levels between baseline and 6 months (ΔKL-6 [base-6m]) tended to be higher in the respiratory-related death group than in the survivor group ($P = 0.078$), whereas changes in serum KL-6 levels between 6 months and the last visit (ΔKL-6 [6m-last]) were significantly higher in the respiratory-related death group than in the survivor group ($P = 0.011$).

To correct for the influence of disease duration on the serum KL-6 level evolution rates, a numerical value was obtained by dividing the evolution rates by the disease duration (months) was used. The duration from 6 months to the last visit was 33 (12-50.5) months. The ΔKL-6 (6m-last), corrected by disease duration, was also significantly higher in the respiratory-related death group than in the survivor group ($P = 0.005$) (Supplementary Figure 1).

There was no difference in RA disease activity index between the two groups.

Logistic regression analyses of respiratory-related death in patients with RA-ILD

Age, male sex, RF and ACPA positivity, serum KL-6 levels at the initial and last visits, use of MTX, ΔKL-6 (base-6m), and ΔKL-6 (6m-last) corrected by disease duration were identified as risk factors for respiratory-related death. To confirm these findings, we performed univariate and multivariate analyses using logistic regression (Table 6). Serum KL-6 levels were divided by 10 to allow for the evaluation of sensitive changes in the

unit, which enables clinicians to interpret the impact of a 10-unit change in KL-6. Univariate analysis with a logistic regression model showed that age, male sex, RF and ACPA positivity, serum KL-6 levels at the last visit, and ΔKL-6 (6m-last) corrected by disease duration were predictors of respiratory-related death in patients with RA-ILD ($P \leq 0.0001$, 0.036, 0.043, 0.001, 0.004, and 0.0001, respectively). RF and ACPA were highly positive in patients with RA-ILD. In fact, 93% of cases in this study were positive for RF and 98.1% for ACPA, so RF and ACPA were excluded as explanatory variables for multivariate analysis. The use of MTX was excluded from multivariable analysis due to collinearity, as the initial KL-6 levels of the patients indicated the use of MTX. The KL-6 levels of the patients in the respiratory-related death group were naturally high at the last visit; thus, KL-6 level at the last visit was excluded from the multivariate analysis owing to its lack of clinical importance. Multivariate analysis with a logistic regression model showed that ΔKL-6 (6m-last) corrected by disease duration was a predictor of respiratory-related death in patients with RA-ILD ($P < 0.0001$).

Comparison of the clinical characteristics and treatment regimens of patients who died from infection-related causes and ILD-related causes

We compared the baseline clinical characteristics and treatment regimens of patients who died from infection-related causes and ILD-related causes (Supplementary Table 1). The PSL usage rate was significantly higher in the infection-related death group (100%) than in the ILD-related death group (33.3%) ($P = 0.011$). There were no other significant differences between the two groups in terms of other clinical characteristics or treatment contents. We also compared the RA disease activities, serum KL-6 levels, and treatment regimens of patients who died of infection-related causes and ILD-related causes at 6 months (Supplementary Table 2), and at the last follow-up visit (Supplementary Table 3). There were no significant differences between the two groups.

Discussion

This study investigated the prognostic factors for respiratory-related death in patients with RA-ILD. The male sex and elevation of serum KL-6 levels between 6 months and the last visit were independent factors associated with respiratory-related death in patients with RA-ILD.

Nakajima et al. examined the causes of death in 7926 Japanese patients with RA registered in the IORRA cohort database and found that respiratory-related diseases and malignant tumors were the most frequent causes of death (24.2%). In addition, pneumonia caused 12.1% of all deaths in that study, whereas another 12.1% of the

deaths were due to ILD-related causes [15]. Gao et al. investigated the causes of death in patients with RA-ILD using death certificate data from the Centers for Disease Control and Prevention. The results showed that the most common cause of death was joint disorder, followed by ILD, chronic respiratory depression, malignant tumor, and ischemic heart disease [16]. Respiratory-related causes of death were also common in the present study, with exacerbation of ILD being the most common, followed by lung infection and lung cancer, as in previous reports.

Previous reports indicate that the predictive factors for poor prognosis in RA-ILD include older age, male sex, history of smoking, lower predicted diffusing capacity of the lung for carbon monoxide, predicted forced vital capacity, UIP-like pattern on HRCT, extensive lung involvement on HRCT, and acute exacerbation of ILD [14] [17-19] [22, 23]. In the present study, elevation of serum KL-6 levels between 6 months and the last visit, corrected by disease duration, was an independent factor associated with respiratory-related death in patients with RA-ILD. Avouac et al. reported that in 15 RA-ILD cases, seven patients with advanced ILD on chest CT findings had significantly elevated serum KL-6 levels compared to eight patients without advanced ILD during a median observation period of three years [24]. Kim et al. retrospectively examined 84 patients with RA-ILD over a 5-year observation period and reported that a baseline serum KL-6 level ≥685 U/mL was an independent prognostic factor [25]. In addition, it has been reported that changes in serum KL-6 levels over time is associated with the prognosis of ILD in acute exacerbation of RA-ILD. Tanaka et al. reported that in 33 cases of RA-ILD with acute exacerbation of ILD, an increase in serum KL-6 level one year after the onset of acute exacerbation was an independent poor prognostic factor [26]. Although serum KL-6 levels at baseline and at 6 months were not associated with respiratory-related death in the present study, the results indicated that elevated serum KL-6 levels from 6 months to the last follow-up visit were independently related. Furthermore, the results of this study suggest that in patients with RA-ILD, changes in serum KL-6 levels over time, not serum KL-6 level at a single timepoint, are important indicators of the progression and prognosis of ILD.

There are various reports of MTX promoting [27], not affecting [28], and suppressing ILD [29] in patients with RA-ILD. As it is difficult to distinguish between hypersensitivity pneumonitis due to MTX and exacerbation of ILD, administration of MTX to patients with advanced RA-ILD is avoided. In the present study, utilization of MTX was significantly reduced after diagnosis of ILD. In addition, the MTX usage rate at baseline was significantly lower in the respiratory-related death group than in survivor group. This is probably because the use of MTX for the treatment of patients with RA-ILD was avoided by the attending physicians. Furthermore, the TAC and ABT usage rates increased significantly after the diagnosis of ILD. TAC has been used for the treatment of connective tissue disease-associated interstitial lung disease, including polymyositis/dermatomyositis

in cases of ILD [30], which suggests its efficacy for RA-ILD [31]. In recent years, it has been reported that ABT may have a suppressive effect on RA-ILD [32, 33]. For these reasons, we considered that TAC and ABT may have been more likely to be selected for patients with RA-ILD.

In the present study, there was no difference in RA disease activity and its changes over time between the respiratory-related death and survival groups. This finding suggests that arthritis and ILD progression may not be parallel in patients with RA-ILD. However, it has been reported that high disease activity of RA is a risk factor for poor prognosis in patients with RA-ILD [34]. As mentioned above, patients with RA-ILD have a limited choice of treatment because of the tendency of physicians to avoid MTX. In addition, existing lung lesions, including ILD, are at risk of developing lung infections [35, 36]. It is speculated that it may be difficult to adequately suppress RA disease activity in patients with RA-ILD leading to respiratory-related death.

High RF and ACPA levels were not associated with respiratory-related death in the present study. This suggests that high RF and ACPA levels are predictive indicators of ILD complications in patients with RA but may not be predictive indicators of respiratory-related death. In contrast, elevated ACPA has been reported to be an independent risk factor for ILD progression in patients with RA-ILD [37]. It has also been reported that spread of semi-quantified ground-glass opacities and fibrosis on the chest HRCT of patients with RA-ILD is correlated with elevated ACPA levels [38]. In the pathogenesis of RA, local trauma and inflammation in the lungs trigger an increase in peptidylarginine deiminase isoforms, leading to citrullination of the lung tissue peptides and bacterial peptides. These citrullinated antigens that are on the cell surface and/or externalized by NETosis are recognized by antigen-presenting cells, and ACPA is generated by a mechanism that presents citrullinated antigens to autoreactive T cells [39]. Autoreactive lymphocytes accumulate in the inducible bronchus-associated lymphoid tissue of RA-ILD lungs, and are involved in its pathogenesis [40]. Since ACPA may be involved in the pathogenesis of ILD in patients with RA, the relationship between high RF and ACPA levels and ILD prognosis warrants further investigation.

A recent systematic review reported the presence of pulmonary lesions and corticosteroid use as risk factors for respiratory infections in RA patients [41]. PCP was the most frequent cause of death from respiratory infections in this study, and other studies have also reported that the use of corticosteroids along with the presence of lung lesions is a risk factor for PCP complications [42, 43]. It was suggested that the use of corticosteroids in RA-ILD patients requires attention to pulmonary infections with a poor prognoses.

As this was a multicenter cohort study, it has some limitations related to clinical data extraction. First, in the cohort database used in this study, the presence or absence of other complicated connective tissue diseases were

not registered. Therefore, the influence of other complicated connective tissue diseases on ILD could not be investigated. Second, detailed data on respiratory conditions, such as respiratory symptoms, respiratory function test findings, SpO2, and arterial blood gas findings, could not be extracted. Third, the details of chest HRCT findings, including ILD disease type classification, such as UIP-like, non-UIP-like, or NSIP-like pathology, were not examined. Fourth, some data were missing because the data that could be obtained differed depending on the institution. Despite these limitations, this study is significant in that it is the first case-scale multicenter cohort study of Japanese patients with RA-ILD. In addition, this study is the first study of the relationship between changes in treatment regimen over time or changes in RA disease activity and respiratory-related death in patients with RA-ILD. In the future, we will conduct a prospective multicenter cohort study using detailed information, including respiratory function test findings and chest HRCT findings, to further investigate the factors that affect respiratory-related death in patients with RA-ILD.

Conclusion

This multicentre cohort study of Japanese patients with RA demonstrated that a long-term increase in serum KL-6 levels is an independent factor associated with respiratory-related death in patients with RA-ILD.

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Contributions

TK designed the study; HM, TK, and DN analysed the data; HM, TK, and DN wrote the manuscript; and TK, KH, AO, TH, MH, and TT revised the manuscript. All authors including other authors contributed to the collection of data.

Conflicts of interest

HM, TK, KH, AY, YW, YH, HS, KN, and TT are affiliated with a department that is financially supported by six pharmaceutical companies (Mitsubishi-Tanabe, Asahi-Kasei, Abbvie, Chugai, Eisai, and Takeda). TK has received payments for lectures from Abbvie, Bristol-Myers Squibb, Chugai, Eisai, Eli Lilly, and Pfizer. KH has received payments for lectures from Abbvie, Asahi-Kasei, Chugai, Janssen, Mitsubishi-Tanabe, and Eisai. YS

has received payments for lectures from Bristol-Myers Squibb, Chugai, Janssen, Eisai, and Abbvie, HA has received payments for lectures from Chugai. AO reports grants from Pfizer Inc., Bristol-Myers Squibb., Advantest, personal fees from Asahi Kasei Pharma, Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K, Ono Pharmaceutical Co., Mitsubishi Tanabe Pharma, Takeda Pharmaceutical Company Limited, and Daiichi Sankyo Co. Ltd. AO belong to the department that is financially supported by five pharmaceutical companies (Tanabe-Mitsubishi, Chugai, Ayumi, UCB-Japan and Asahi-Kasei), Nagahama city and Toyooka city. RH has received payments for lectures from Abbvie and Eisai. TH has received payments for lectures from Mitsubishi-Tanabe, Chugai, Astellas, GlaxoSmithKline, and Sanofi. MH received research grants and/or speaker fee from Abbvie, Asahi Kasei, Astellas, Ayumi, Brystol Meyers, Chugai, EA Pharma, Eisai, Daiichi Sankyo, Eli Lilly, Nihon Shinyaku, Novartis Pharma, Tanabe Mitsubishi. TT received research grants and/or speaker fee from Abbvie, Asahi Kasei, Astellas, Brystol-Meyers Squibb, Chugai, Eisai, Eli Lilly, Janssen pharma, Nihon Shinyaku, Mitsubishi-Tanabe, Takeda, and Pfizer. Other authors (DN, WY, MK, and KA) do not have any conflict of interest.

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Availability of Data and Materials

Regarding the submission of raw data, since it is difficult to protect personal information, information will be disclosed only for reasonable offers. If someone wants to request the data from this study, the contact should be the corresponding author.

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Figure legends

Figure 1 Comparison of changes in serum KL-6 levels from baseline to the last follow-up visit between the respiratory-related death group and survivor group.

ΔKL-6 (base-6m), changes in serum KL-6 levels from baseline to 6 months; ΔKL-6 (base-last), changes in serum KL-6 levels from baseline to the last visit; ΔKL-6 (6m-last), changes in serum KL-6 levels from 6 months to the last visit. * $P < 0.05$.

Supplementary Figure 1 Comparison of changes in serum KL-6 levels corrected by disease duration from baseline to the last follow-up visit between the respiratory-related death group and survivor group.

ΔKL-6 (base-last)/DD, changes in serum KL-6 levels divided by disease duration (months) from baseline to the last visit; ΔKL-6 (6m-last)/DD, changes in serum KL-6 levels divided by disease duration (months) from 6 months to the last visit. * $P < 0.05$.

Table 1. Characteristics and treatments of RA-ILD patients (N = 312)

Characteristics and treatments	Values
Age, years	70 (64–76)
Female, n (%)	204 (65.4)
Smoking history (N = 185), n (%)	106 (57.3)
Disease duration of RA, weeks	335.7 (94.4–825.7)
Steinbrocker stage (N = 51), n	I; 11, II; 22, III; 12, IV; 6
Steinbrocker class (N = 52), n	1; 22, 2; 17, 3; 11, 4; 2
RF positive, n (%)	267 (93.0)
RF, IU/mL	133.0 (59.0-340.0)
ACPA positive, n (%)	252 (98.1)
ACPA, U/mL	297.0 (74.2-433.0)
Disease activity of RA	
DAS28-CRP	2.72 (1.82-3.93)
SDAI	8.6 (4.1-17.8)
CDAI	7.9 (3.6-16.2)
KL-6, U/mL	438.0 (282.0-705.8)
Treatments	
MTX use, n (%)	115 (37.3)
MTX dose, mg/week	6.0 (4.0-8.0)
TAC use, n (%)	49 (15.9)
PSL use, n (%)	139 (45.1)
PSL dose, mg/day	5.0 (4.0-10.0)
TNF-i use, n (%)	31 (10.0)
IL-6-i use, n (%)	15 (4.9)
ABT use, n (%)	28 (9,1)
JAK-i use, n (%)	1 (0.3)
Respiratory related death, n (%)	17 (5.4)

Continuous values indicate the median (interquartile range). RA, rheumatoid arthritis; ILD, interstitial lung disease; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptides antibody; CRP, C-reactive protein; DAS28-CRP, disease activity score-28-CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; KL-6, krebs von den lungen 6; MTX, methotrexate; TAC, tacrolimus; PSL, prednisolone; TNF-i, tumor necrosis factor inhibitors; IL-6-i, interleukin 6 inhibitors; ABT, abatacept; JAK-i, janus kinase inhibitors.

Table 2. Changes in the contents of teratments in RA-ILD patients

Medications	Baseline (N = 312)	6 months (N = 291)	Last visit (N = 307)	*P* (baseline vs 6 months)	*P* (baseline vs last visit)	*P* (6 months vs last visit)
MTX use, n (%)	115 (37.3)	89 (30.6)	80 (26.1)	0.085	0.003**	0.239
MTX dose, mg/week	6.0 (4.0-8.0)	6.0 (6.0-8.0)	6.0 (4.0-8.0)	0.815	0.639	0.461
TAC use, n (%)	49 (15.9)	72 (24.7)	98 (32.0)	0.008**	< 0.0001***	0.057
PSL use, n (%)	1439 (45.1)	142 (48.8)	148 (48.4)	0.413	0.467	0.935
PSL dose, mg/day	5.0 (4.0-10.0)	5.0 (3.0-9.0)	5.0 (3.0-8.0)	0.368	0.06	0.253
TNF-i use, n (%)	31 (10.0)	20 (6.9)	22 (7.2)	0.19	0.251	1
IL-6-i use, n (%)	15 (4.9)	19 (6.6)	25 (8.2)	0.383	0.104	0.531
ABT use, n (%)	28 (9.1)	49 (16.9)	66 (21.2)	0.005**	< 0.0001***	0.211
JAK-i use, n (%)	1 (0.3)	1 (0.3)	3 (1.0)	1	0.371	0.624

Continuous values indicate the median (interquartile range). *P < 0.05, **P < 0.01, ***P < 0.001. RA, rheumatoid arthritis; ILD, interstitial lung disease; 6 months, 6 months after diagnosis of ILD; MTX, methotrexate; TAC, tacrolimus; PSL, prednisolone; TNF-i, tumour necrosis factor inhibitors; IL-6-i, interleukin 6 inhibitors; ABT, abatacept; JAK-i, Janus kinase inhibitors.

Table 3. Comparison of clinical characteristics, and treatments between respiratory related deaths and survivors in RA-ILD patients at base line.

Characteristics and treatments	Respiratory related death (N = 17)	Survivors (N= 295)	*P*
Age, years	77 (72–83.5)	70 (64-75)	0.0001***
Female, n (%)	7 (41.2)	197 (66.8)	0.038*
Smoking history, n (%)	6 (46.2)	100 (58.1)	0.562
Disease duration of RA, weeks	188.5 (71.9–543.4)	341.4 (95-881.1)	0.333
RF positive, n (%)	11 (78.6)	256 (93.8)	0.064
RF, IU/mL	110.0 (71.0-756.0)	133.0 (56.5-326.9)	0.489
ACPA positive, n (%)	9 (81.8)	243 (98.8)	0.016*
ACPA, U/mL	196.0 (97.5-265.0)	198.0 (66.8-454)	0.753
Disease activity of RA			
DAS28-CRP	2.91 (1.65–4.01)	2.72 (1.83-3.93)	0.935
SDAI	14.1 (3.9–20.1)	8.3 (4.1-17.9)	0.677
CDAI	9.1 (3.8–16.6)	7.9 (3.5-16.3)	0.987
KL-6, U/mL	754.0 (377.0-1713.5)	425 (277.5-654.5)	0.012*
Treatments			
MTX use, n (%)	2 (12.5)	113 (38.7)	0.036*
MTX dose, mg/week	7.0 (4.0-10.0)	6 (4-8)	0.913
TAC use, n (%)	3 (18.8)	46 (15.7)	0.726
PSL use, n (%)	11 (68.8)	128 (43.8)	0.07
PSL dose, mg/day	5.0 (0.0-26.3)	5 (4-10)	0.57
TNF-i use, n (%)	1 (6.3)	30 (10.2)	1
IL-6-i use, n (%)	1 (6.3)	14 (4.8)	0.558
ABT use, n (%)	1(6..3)	27(9.2)	1
JAK-i use, n (%)	0(0.0)	1(0.3)	1

Continuous values indicate the median (interquartile range). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. RA, rheumatoid arthritis; ILD, interstitial lung disease; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptides antibody; CRP, C-reactive protein; DAS28-CRP, disease activity score-28-CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; KL-6, krebs von den lungen 6; MTX, methotrexate; TAC, tacrolimus; PSL, prednisolone; TNF-i, tumour necrosis factor inhibitors; IL-6-i, interleukin 6 inhibitors; ABT, abatacept; JAK-i, janus kinase inhibitors.

Table 4. Comparison of disease activities of RA, serum KL-6 levels, and treatments between respiratory related deaths and survivors in RA-ILD patients at 6 months after diagnosis of ILD.

Characteristics and treatments	Respiratory related death (N = 10)	Survivors (N = 281)	*P*
Disease activity of RA			
DAS28-CRP	3.5 (2.0–4.2)	2.3 (1.7-3.1)	0.109
SDAI	11.6 (5.7-21.4)	6.6 (2.7-10.9)	0.079
CDAI	10.6 (5.5-15.4)	5.9 (2.4-10.2)	0.096
KL-6, U/mL	593 (377.5-737.5)	483.0 (298.0-734.0)	0.583
Treatments			
MTX use, n (%)	1 (10.0)	98 (31.3)	0.293
MTX dose, mg/week	6	6.0 (6.0-8.0)	0.717
TAC use, n (%)	2 (20.0)	70 (24.9)	1
PSL use, n (%)	6 (60.0)	136 (48.4)	0.533
PSL dose, mg/day	5.0 (3.3-11.9)	5.0 (3.0-9.0)	0.939
TNF-i use, n (%)	0 (0.00)	20 (7.2)	1
IL-6-i use, n (%)	0 (0.00)	19 (6.8)	1
ABT use, n (%)	2 (20.0)	47 (16.8)	0.679
JAK-i use, n (%)	0 (0.0)	1 (0.4)	1

Continuous values indicate the median (interquartile range). **P* < 0.05, ***P* < 0.01, ****P* < 0.001. RA, rheumatoid arthritis; ILD, interstitial lung disease; CRP, C-reactive protein; DAS28-CRP, disease activity score-28-CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; KL-6, krebs von den lungen 6; MTX, methotrexate; TAC, tacrolimus; PSL, prednisolone; TNF-i, tumour necrosis factor inhibitors; IL-6-i, interleukin 6 inhibitors; ABT, abatacept; JAK-i, Janus kinase inhibitors.

Table 5. Comparison of disease activities of RA, serum KL-6 levels, and treatment contents between respiratory related deaths and survivors in RA-ILD patients at last visit.

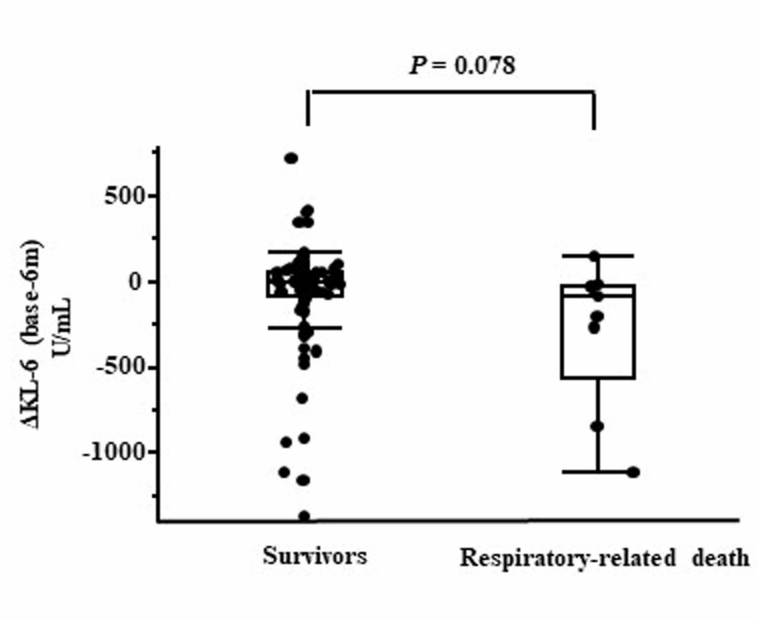
Characteristics and treatments	Respiratory related death (N = 12)	Survivors (N = 295)	*P*
Disease activity of RA			
DAS28-CRP	2.2 (1.9-4.4)	2.3 (1.6-3.4)	0.306
SDAI	8.1 (4.4-20.8)	6.7 (2.7-12.9)	0.232
CDAI	6.4 (3.3-17.9)	6.0 (1.9-11.4)	0.333
KL-6, U/mL	708.5 (468.5-1063.5)	444.0 (294.0-667.0)	0.026*
Treatments			
MTX use, n (%)	1 (9.1)	79 (26.8)	0.299
MTX dose, mg/week	4.0 (4.0-4.0)	6.0 (4.0-8.0)	0.276
TAC use, n (%)	2 (18.2)	96 (32.5)	0.512
PSL use, n (%)	6 (54.6)	142 (48.1)	0.764
PSL dose, mg/day	10.0 (4.8-10.8)	5.0 (3.0-8.0)	0.063
TNF-i use, n (%)	0 (0.0)	22 (7.5)	1
IL-6-i use, n (%)	0 (0.0)	25 (8.5)	0.609
ABT use, n (%)	3 (27.3)	63 (21.0)	0.706
JAK-i use, n (%)	0 (0.0)	3 (1.0)	1

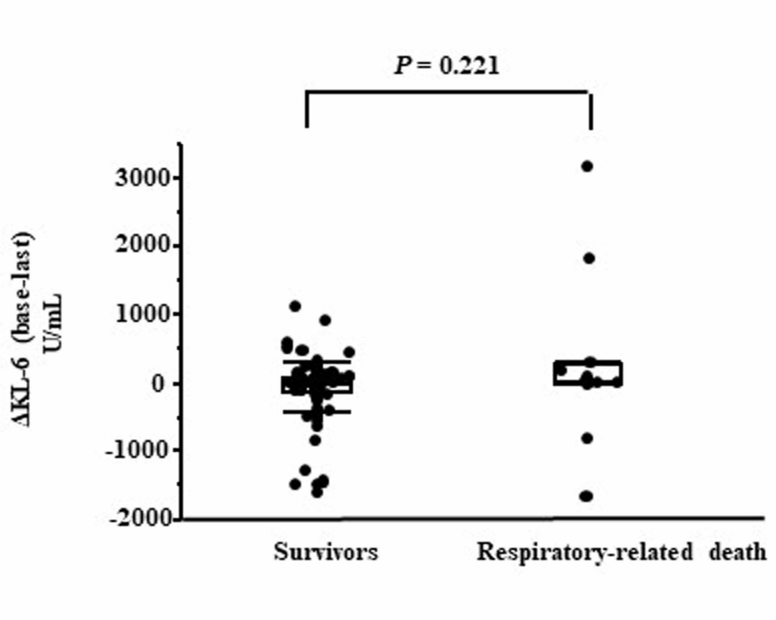
Continuous values indicate the median (interquartile range). *$P < 0.05$. RA, rheumatoid arthritis; ILD, interstitial lung disease; CRP, C-reactive protein; DAS28-CRP, disease activity score-28-CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; KL-6, krebs von den lungen 6; MTX, methotrexate; TAC, tacrolimus; PSL, prednisolone; TNF-i, tumour necrosis factor inhibitors; IL-6-i, interleukin 6 inhibitors; ABT, abatacept; JAK-i, Janus kinase inhibitors.

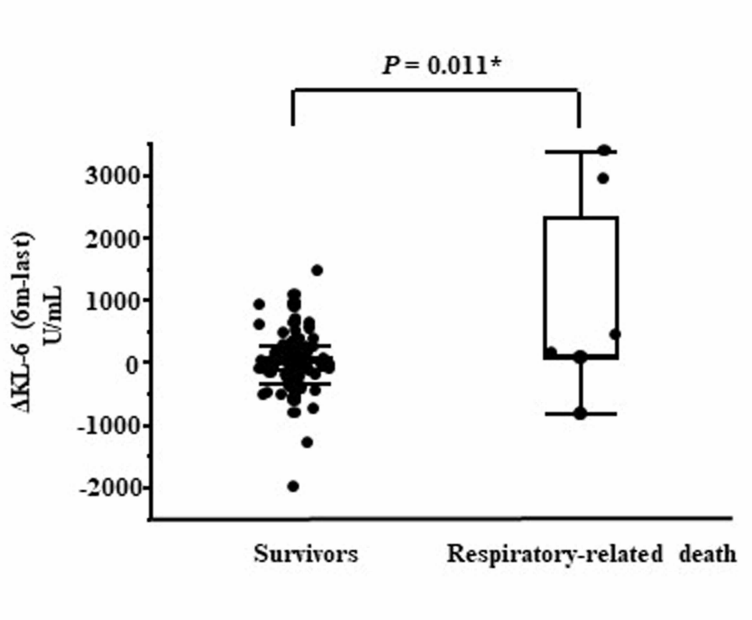
Table 6. The resutlts of logistic regression analyses of respiratory-related deaths in RA-ILD

	Univarible analysis			Multivariable analysis		
Risk factors	Crude odd's ratio	95% CI	*P*	Adjusted odd's ratio	95% CI	*P*
Age (by year)	1.155	1.0727-1.2426	< 0.0001***	1.124	0.9642-1.3115	0.085
Male (Ref: female)	2.872	1.0609-7.7735	0.036*	33.262	0.6251-1769.9973	0.084
RF positive (Ref: negative)	4.107	1.046-16.126	0.043*	-	-	-
ACPA positive (Ref: negative)	18.000	2.6684-121.420	0.001**	-	-	-
KL-6 at initial (by 10 unit)	1.005	0.9992-1.0097	0.097	1.000	0.9995-1.0010	0.518
KL-6 at last point (by 10 unit)	1.011	1.0039-1.0185	0.004**	-	-	-
ΔKL-6 (6m-last) (by DD)	1.077	1.0199-1.1364	0.0001***	1.113	1.0247-1.2081	<0.0001***
MTX use (Ref: non-use)	4.419	0.986-19.808	0.052	-	-	-

The odd's ratios of respiratory-related death were derived from univariable and multivariable logistic regression analyses. CI, confidence interval; Ref, reference; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; RA, rheumatoid arthritis; ILD, interstitial lung disease; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; KL-6, krebs von den lungen-6; ΔKL-6 (base-6m), change of serum KL-6 levels between baseline to 6 months after diagnosis of ILD; ΔKL-6 (6m-last), change of serum KL-6 levels between 6 months after diagnosis of ILD to last visit; DD, disease duration (months); MTX, methotrexate.


P = 0.078
ΔKL-6 (base-6m) U/mL
500
0
-500
-1000
Survivors
Respiratory-related death


P = 0.221
ΔKL-6 (base-last) U/mL
3000
2000
1000
0
-1000
-2000
Survivors
Respiratory-related death


P = 0.011*
ΔKL-6 (6m-last) U/mL
3000
2000
1000
0
-1000
-2000
Survivors
Respiratory-related death

Supplementary Table 1. Comparison of clinical characteristics, and treatments between infection-related deaths and ILD-related deaths in RA-ILD patients at base line.

Characteristics and treatments	Infection-related death (N = 9)	ILD -related death (N = 6)	*P*
Age, years	80 (74.5-83)	79.5 (71.5-85.3)	0.953
Female, n (%)	5 (55.6)	2 (33.3)	0.608
Smoking history, n (%)	3 (50.0)	2 (40.0)	1
Disease duration of RA, weeks	197.1 (135.8-531.7)	71.9 (18.3-880.6)	0.306
RF positive, n (%)	4 (66.7)	5 (83.3)	1
RF, IU/mL	48.5 (0.85-108.8)	192 (46-471.8)	0.301
ACPA positive, n (%)	4 (80.0)	4 (80.0)	1
ACPA, U/mL	197 (32.1-573)	189.5 (121.5-221.5)	1
Disease activity of RA			
DAS28-CRP	2.22 (1.37-3.03)	4.35 (3.67-5.04)	0.064
SDAI	9.45 (1.96-15.8)	22.7 (14.2-31.2)	0.165
CDAI	5 (1.85-11)	19.3 (13.8-24.8)	0.064
KL-6, U/mL	754 (253-1330)	851.5 (570-1987.5)	0.637
Treatments			
MTX use, n (%)	2 (22.2)	0 (0.0)	0.486
MTX dose, mg/week	7.0 (4.0-10.0)	-	-
TAC use, n (%)	3 (33.3)	0 (0.0)	0.229
PSL use, n (%)	9 (100.0)	2 (33.3)	0.011*
PSL dose, mg/day	10.0 (4.5-37.5)	0.0 (0.0-52.5)	0.161
TNF-i use, n (%)	0 (0.0)	1 (16.7)	0.4
IL-6-i use, n (%)	0 (0.0)	1 (16.7)	0.4
ABT use, n (%)	0 (0.0)	1 (16.7)	0.4
JAK-i use, n (%)	0 (0.0)	0 (0.0)	-

Continuous values indicate the median (interquartile range). *$P < 0.05$. RA, rheumatoid arthritis; ILD, interstitial lung disease; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptides antibody; CRP, C-reactive protein; DAS28-CRP, disease activity score-28-CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; KL-6, krebs von den lungen 6; MTX, methotrexate; TAC, tacrolimus; PSL, prednisolone; TNF-i, tumour necrosis factor inhibitors; IL-6-i, interleukin 6 inhibitors; ABT, abatacept; JAK-i, janus kinase inhibitors.

Supplementary Table 2. Comparison of disease activities of RA, serum KL-6 levels, and treatments between infection-related deaths and ILD-related deaths in RA-ILD patients at 6 months after diagnosis of ILD.

Characteristics and treatments	Infection-related death (N = 5)	ILD-related death (N = 4)	*P*
Disease activity of RA			
DAS28-CRP	2.9 (1.7-3.7)	4.2 (2.0-4.4)	0.289
SDAI	8.8 (5.8-19.0)	20.2 (5.7-21.4)	0.858
CDAI	8.1 (5.4-11.8)	15.4 (5.5-18.6)	0.212
KL-6, U/mL	598 (380-691)	491 (378.5-736.3)	0.724
Treatments			
MTX use, n (%)	1 (20.0)	0 (0.0)	1
MTX dose, mg/week	6	-	-
TAC use, n (%)	1 (20.0)	1 (25.0)	1
PSL use, n (%)	4 (80.0)	1 (25.0)	0.143
PSL dose, mg/day	4.5 (1.8-5.0)	10	0.147
TNF-I use, n (%)	0 (0.0)	0 (0.0)	-
IL-6-I use, n (%)	0 (0.0)	0 (0.0)	-
ABT use, n (%)	0 (0.0)	0 (0.0)	-
JAK-I use, n (%)	0 (0.0)	0 (0.0)	-

Continuous values indicate the median (interquartile range). RA, rheumatoid arthritis; ILD, interstitial lung disease; CRP, C-reactive protein; DAS28-CRP, disease activity score-28-CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; KL-6, krebs von den lungen 6; MTX, methotrexate; TAC, tacrolimus; PSL, prednisolone; TNF-I, tumour necrosis factor inhibitors; IL-6-I, interleukin 6 inhibitors; ABT, abatacept; JAK-I, Janus kinase inhibitors.

Supplementary Table 3. Comparison of disease activities of RA, serum KL-6 levels, and treatment contents between infection-related deaths and ILD-related deaths in RA-ILD patients at last visit.

Characteristics and treatments	Infection-related death (N = 9)	ILD-related death (N = 6)	*P*
Disease activity of RA			
DAS28-CRP	3.1 (1.8-4.4)	2.2 (1.9-4.4)	1
SDAI	12.9 (4.6-23.9)	5.9 (4.4-20.8)	0.724
CDAI	11.1 (4.1-17.4)	3.9 (3.0-18.6)	0.724
KL-6, U/mL	714 (542-1140)	834 (444-3734)	0.732
Treatments			
MTX use, n (%)	1 (11.1)	0 (0.0)	1
MTX dose, mg/week	4	-	-
TAC use, n (%)	2 (22.2)	0 (0.0)	0.444
PSL use, n (%)	4 (44.4)	1 (16.7)	0.206
PSL dose, mg/day	7.5 (4.3-12.3)	10	0.717
TNF-i use, n (%)	0 (0.0)	0 (0.0)	-
IL-6-i use, n (%)	0 (0.0)	0 (0.0)	-
ABT use, n (%)	1 (11.1)	2 (50.0)	0.524
JAK-i use, n (%)	0 (0.0)	0 (0.0)	-

Continuous values indicate the median (interquartile range). RA, rheumatoid arthritis; ILD, interstitial lung disease; CRP, C-reactive protein; DAS28-CRP, disease activity score-28-CRP; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; KL-6, krebs von den lungen 6; MTX, methotrexate; TAC, tacrolimus; PSL, prednisolone; TNF-i, tumour necrosis factor inhibitors; IL-6-i, interleukin 6 inhibitors; ABT, abatacept; JAK-i, Janus kinase inhibitors.