Clinical Characteristics and Predictors of the Recurrence of Organising Pneumonia Associated with Rheumatoid Arthritis

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Abstract

Background: Organizing pneumonia (OP) accounts for ~10% of the interstitial lung diseases in patients diagnosed with rheumatoid arthritis (RA). There are only a few published studies that have described RA-associated OP (RA-OP), each with comparatively few study participants. Furthermore, despite the high frequency of secondary flareups, no studies to date have identified factors that predict RA-OP recurrence. This study aimed to clarify the clinical characteristics of RA-OP, to determine the relationship between OP and RA exacerbations, and to identify predictors of RA-OP disease recurrence.

Methods: The data of 33 patients with RA-OP admitted to our hospital between 2006 and 2016 were retrospectively analysed.

Results: RA onset preceded OP in 82% of patients; OP preceded or co-occurred with RA in 9% each. The median [Q1, Q3] age at first OP onset was 64.0 [55.0, 68.0] years and 5.5 [1.0, 19.3] years after RA onset. At OP onset, 42% of events exhibited unilateral shadows and 76% had normal KL-6; RA disease control remained good in 52% and was exacerbated in only 18%. Ten (30%) patients experienced OP recurrence with an interval of 13.0 [7.5, 22.5] months between events, with a rate of first recurrence of 127 per 1,000 person-years. Compared with 14 non-recurrent cases, 10 recurrent cases showed lower age at first OP (59.5 years vs. 67.1 years; $p = 0.043$) and shorter period from RA to first OP (6.4 vs. 14.2 years; $p = 0.047$) and included more OP-preceding patients (30% vs. 0%; $p = 0.029$) and more ever-smokers (80% vs. 36%; $p = 0.032$). OP-preceding patients showed shorter median recurrence-free survival time (15 vs. 136 months; $p = 0.009$) and higher recurrence risk (hazard ratio, 5.5; $p = 0.021$).

Conclusions: RA-OP showed a high recurrence rate but no association with RA exacerbation. Four predictors of RA-OP recurrence were identified.

Background

Rheumatoid arthritis (RA) is a systemic autoimmune disease with extra-articular involvement, with the lung being one of the most frequently affected organs. Several types of interstitial lung diseases (ILDs), reported in up to 58% of patients with RA [1–4], generally develop several years after the onset of RA and occasionally develop before or concomitantly with RA, significantly affecting the life prognoses of these patients and restricting therapeutic options for their arthritis [1–3, 5, 6]. The two main histopathological patterns of ILDs in RA are usual interstitial pneumonia and nonspecific interstitial pneumonia [7, 8]; however, organising pneumonia (OP) is also a substantial subtype, accounting for approximately 10% of ILDs in patients with RA [9–13]. In Japan, the estimated prevalence of OP in patients with RA (RA-OP) has been reported to be 1.9–4.8% [14].

OP, histologically characterised by intraluminal buds of granulation tissue within alveolar ducts and alveoli [15], starts usually with flu-like symptoms, such as fever, cough, fatigue, anorexia, and progressively mild dyspnoea [16]. Its radiographic manifestations are typically distinctive with bilateral, patchy or diffuse consolidation with or without ground-glass opacities [17]. OP is classified as

cryptogenic or secondary, the underlying causes of which include infections, drugs, radiation, and connective tissue diseases (CTDs), such as RA.

Most patients with OP recover fully either after glucocorticoid therapy or spontaneously; therefore, the prognosis of OP has been considered to be better than that of other types of ILDs [12, 18]. However, several studies have reported that the prognosis of OP associated with CTDs (CTD–OP), including RA–OP, is poorer than that of cryptogenic OP [19–21] and that while OP sometimes recurs after reduced glucocorticoid dosage, its recurrence rate is higher in CTD–OP than in cryptogenic OP [20, 21], suggesting the particularity of CTD–OP and indicating the importance of further research focussing specifically on CTD–OP.

Only a few studies have reported RA–OP’s clinical characteristics [14, 22], and further studies are required to understand the relationship between OP development and RA exacerbation. In addition, these studies did not exclude drug-induced and post-infectious OP in patients with RA, which may mask the true characteristics of RA–OP; therefore, they emphasise the need for studies focussing exclusively on RA–OP.

This retrospective cohort study aimed to investigate the clinical characteristics of RA–OP patients and RA–OP events, to examine the disease activity changes of RA at the development of OP, and specifically to clarify which characteristics at the first OP onset are predictors of the later OP recurrence.

Methods

Study population

Using either paper or electronic medical records, we retrospectively reviewed data of patients who were admitted to the Division of Rheumatic Diseases, National Center for Global Health and Medicine, Japan, between August 2006 and August 2016. RA–OP patients who fulfilled the following inclusion criteria were enrolled in this study: (1) diagnosis of RA according to the 1987 American College of Rheumatology (ACR) criteria [23] or the 2010 ACR/European League Against Rheumatism criteria [24]; (2) diagnosis of OP based on the criteria described in the section, Diagnosis of OP; and (3) clinical courses where the patient’s OP could not be explained by any underlying causes other than RA itself, such as causative infectious agents or drug usage. In total, 33 RA–OP patients were included in the study.

Diagnosis of OP

The diagnosis of OP was made according to the previously described criteria [14]. OP was diagnosed either when the pathological findings of lung biopsy samples were compatible with OP or when the patients fulfilled all of the following criteria: (a) the typical image findings on chest computed tomography (CT), determined to be OP by at least one rheumatologist and one radiologist; (b) no response to broad-spectrum antibiotics; and (c) substantial response to glucocorticoid therapy,

demonstrated by improvement in systemic and respiratory symptoms and chest infiltrates within two weeks.

Data collection

Clinical information, laboratory results, medication, lung biopsy findings, and CT images were collected from the patients' medical records. The follow-up data were abstracted until the time of death, dropout, or 30 October 2016. Rheumatoid factor and anti-citrullinated protein antibody were regarded as positive if positive findings were reported at least once during the follow-up.

RA disease activity at the time of and several months before the onset of OP were assessed according to the Clinical Disease Activity Index (CDAI) [25], and were divided into two categories: 'Low' if the CDAI score was ≤ 10 (i.e. low disease activity or remission) or 'High' if the CDAI score was > 10 (i.e. high or moderate disease activity). To analyse the relationship between OP development and RA exacerbation, each patient was categorised into one of following four groups based on the temporal changes of the RA disease activity along with OP development: 'Good Control,' where disease activity remained 'Low' both before and at the onset of OP; 'Poor Control,' where disease activity remained 'High' both before and at the onset of OP; 'Exacerbation,' where disease activity had been 'Low' before but became 'High' at the onset of OP; or 'Improvement,' where disease activity had been 'High' before but became 'Low' at the onset of OP.

For the examinations of the predictors of RA–OP recurrence, the OP recurrence was defined as the appearance of new infiltrates on chest imaging with compatible clinical features during or after the course of OP treatment, which required consideration of hospital treatment and a significant increase in the glucocorticoid dosage. In this analysis, the recurrence group included all of the patients who presented with recurrence at least once during follow-up, and the non-recurrence group included the patients who experienced no recurrence during follow-up for at least six months after the onset of OP. The cutoff value of the six-month follow-up was set before performing any statistical analysis and was chosen for two reasons. First, according to the standardised protocol of the OP treatment used in our division, the glucocorticoid dosage is increased at the onset of OP and is usually tapered to its maintenance dosage approximately six months later; therefore, the cutoff ensured that the patients in the non-recurrence group had completed the tapering period without recurrence. Second, some patients changed hospital or died from other causes within a few months after OP onset; therefore, the cutoff helped to exclude patients not fully followed up from the non-recurrence group.

Statistical analysis

The data were summarised using descriptive statistics, including medians (with first and third quartiles [Q1, Q3]), percentages, means, and confidence intervals (CIs). Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using Pearson's chi-square test or

Fisher's exact test. Recurrence-free survival times were calculated using the Kaplan–Meier method and were compared using the log-rank test. Cox proportional hazards regression analysis was performed to examine the associations between patients' characteristics and recurrence. All of the analyses were two-sided, and the level of significance was set at $p < 0.05$.

Results

Clinical characteristics of patients

The clinical features of the 33 RA–OP patients are summarised in **Table 1**. The median age at the RA onset and first OP onset was 53.0 [43.8, 61.3] years and 64.0 [55.0, 68.0] years, respectively. The median period from the RA onset to the first OP onset was 5.5 [1.0, 19.3] years (range, –1 to 45 years). The RA onset preceded the OP onset in 82% of the patients, RA and OP started simultaneously in 9% of the patients, and the OP onset preceded the RA onset in 9% of the patients. In addition, 44% of the patients had a history of smoking, and 49% of the patients had preexisting lung diseases, including one patient with an ILD other than OP, one patient with a history of a drug-induced ILD, six patients with RA-associated bronchial diseases (bronchiolitis or bronchiectasis), three patients with RA-associated pleuritis, three patients with a history of tuberculosis, and five patients with concomitant nontuberculous mycobacteriosis. The patients were followed up for a median of 23.0 [4.0, 80.0] months after the first OP onset.

Of the 33 patients, 10 (30%) patients experienced OP recurrence, with a total of 27 recurrence events; the median interval between two consecutive OP events was 13.0 [7.5, 22.5] months. The rate of the first recurrence of OP was 127 per 1,000 person-years.

Clinical characteristics of RA–OP events

We analysed a total of 60 RA–OP events, comprising 33 first OP events in each patient and 27 recurrences observed in 10 patients (**Table 2**). The most likely symptoms were coughing and fever, and dyspnoea was experienced during 39% of the events. Although the typical radiographic manifestation of OP is considered bilateral shadows, 42% of the events showed unilateral shadows. At the OP onset, the patients showed raised C-reactive protein (CRP) levels with a median of 10.2 [5.9, 16.9] mg/dL, and elevated erythrocyte sedimentation rate (ESR) levels of 109.0 [99.5, 124.5] mm/h. However, the median KL-6 titre, a serum marker for interstitial pneumonia, was 297.5 [233.3, 438.0] U/mL and remained within normal limits (<500 U/mL) in no fewer than 76% of the events. Nearly all of the events were treated with prednisolone (PSL), and steroid pulse therapy was performed concomitantly for 20% of the events. Focussing on the 36 RA–OP events, where OP occurred even with PSL treatment, the median PSL dosage at the OP onset was 6.5 [5.0, 10.3] mg/day.

Relationship between OP development and RA exacerbation

Changes in RA disease activity, along with OP development, were examined for each RA–OP event (**Table 2**). At the OP onset, the RA disease activity remained under good control in 52% of the events and was exacerbated in only 18%, suggesting that OP development is not accompanied by RA exacerbation. Consistently, the CRP and the ESR levels related to RA were not so high during a few months before the OP onset; the median CRP level was 0.5 [0.2, 1.4] mg/dL, and the ESR level was 24.0 [16.0, 52.0] mm/h.

Predictors of RA–OP recurrence

The predictors of RA–OP recurrence were determined among the patients' characteristics at the first OP onset, using analyses comparing the recurrence group (n = 10) and the non-recurrence group (n = 14), as defined in the **2.3 Data collection**. The age at the first OP onset was significantly lower in the recurrence group than in the non-recurrence group (59.5 years vs. 67.1 years; p = 0.043), with a significantly shorter period from the RA onset to the first OP onset (6.4 years vs. 14.2 years; p = 0.047) (**Table 3**). The receiver operating characteristic curves for these two predictors are shown in **Fig. 1**. A cutoff value of ≤ 66 years for age at the first OP onset predicted OP recurrence with a specificity of 57% and sensitivity of 90% (**Fig. 1A**). Similarly, a cutoff value of ≤ 4 years for the period from the RA onset to the first OP onset predicted the OP recurrence with a specificity of 69% and sensitivity of 80% (**Fig. 1B**).

The recurrence group included significantly more patients whose OP onset preceded the RA onset (the OP-preceding) than the non-recurrence group (30% vs. 0%; p = 0.029), and significantly more patients with a smoking history (80% vs. 36%; p = 0.032) (**Table 3**). Bilateral lung shadows at the first OP were more frequently observed in the recurrence group, although the difference was not statistically significant (p = 0.056). To estimate the recurrence-free survival time, the Kaplan–Meier method was applied to these two significant factors, the OP-preceding patients and the ever-smokers, for all of the 33 RA–OP patients (**Fig. 2**). The OP-preceding patients showed significantly shorter median recurrence-free survival time than the other: 15 (95% CI, 2–not available (NA)) vs. 136 (20–NA) months, p = 0.009, and showed a significantly higher risk for recurrence with a hazard ratio of 5.5 (1.3–23.0), p = 0.021 (**Fig. 2A**). The ever-smokers also exhibited shorter median recurrence-free survival time and higher risk for recurrence than the never-smokers, although these differences did not reach statistical significance: 34 (13–NA) vs. NA (13–NA) months, p = 0.15, with a hazard ratio of 3.0 (0.6–14.1), p = 0.17 (**Fig. 2B**).

There were no significant differences between the recurrence and the non-recurrence groups in the laboratory data at the first OP onset, such as CRP levels, rheumatoid factor titres, or KL-6 titres (**Table 3**). Importantly, the initial treatment for the first OP was similar in the two groups, including the initial PSL dosage and the concomitant use of steroid pulse therapy, and there was no significant difference in the minimum PSL dose without recurrence during the tapering process (4.7 mg/day vs. 5.4 mg/day, p = 0.37), which ensures the equivalent treatment in the two groups. Moreover, the mean follow-up period after the first OP did not differ significantly between the two groups (81.3 months vs. 47.4 months, p = 0.11), and

this follow-up period after the first OP in the non-recurrence group (47.4 months) was, on the contrary, longer than the mean recurrence-free follow-up period after the first OP in the recurrence group (27.1 months), indicating that the follow-up period was long enough to detect recurrence in the non-recurrence group.

Discussion

In this study, we clarified the clinical characteristics of RA–OP patients and events, showed that OP development is not associated with RA exacerbation, revealed the high rate of the first recurrence of RA–OP, and identified four predictive patient characteristics at the first OP onset for later OP recurrence: lower age at the first OP onset, shorter period from the RA onset to the first OP onset, OP-preceding, and history of smoking. This study is the third retrospective cohort study for RA–OP [14, 22] and the first to establish the predictors of RA–OP recurrence.

This study contributes to enhance our understanding and knowledge of the clinical characteristics of RA–OP. In our cohort, 9% of cases were the OP-preceding, who exhibited a higher risk for OP recurrence. This proportion of cases in our study is similar to those reported in previous studies: 11% [14] or 14% [22] of RA–OP patients. Meanwhile, the difficulty in differentiating RA–OP from bacterial pneumonia in clinical practice may be, in part, explained by our findings: 42% of the OP events showed unilateral shadows, 76% had normal KL-6 titres, and most patients presented with flu-like symptoms, all of which are the typical characteristics of bacterial pneumonia. In particular, this proportion of the unilaterality of lung shadows seems similar to 58% reported on RA–OP [14] and might be higher than 30% [26] or 27% [27] reported on cryptogenic OP.

Importantly, we revealed that OP development is not associated with RA exacerbation. In this study, the RA disease activity remained good in 52% of the patients and was exacerbated in only 18% at the OP onset, similar to those reported in the previous study, 57% and 14%, respectively [14], increasing the reliability of our results. That RA–OP develops even under good control of RA indicates the difficulty in foreseeing or preventing the occurrence of OP in patients with RA. This difficulty will be highlighted, considering our finding that the period from the RA onset to the first OP onset varied widely from –1 to 45 years.

Our study clarified that 30% of the patients with RA–OP experienced OP recurrence even with proper glucocorticoid treatment. This proportion corresponds to those in previous reports on RA–OP: 21% [14] or 10% [22]. These proportions of RA–OP might be lower than in those of cryptogenic OP: 58% [28], 56% [29], 30% [26], or 27% [27]. These lower proportions in RA–OP patients may reflect the effect of other immunosuppressive agents concomitantly administered for arthritis during the tapering process of glucocorticoid. This study also demonstrated the high rate of the first recurrence of RA–OP, 127 per 1,000 person-years. This rate is much higher than the reported rate of the total OP occurrence in RA patients, 2.72 per 1,000 person-years [14], indicating the need for the follow-up of RA–OP patients with careful

attention to the likelihood of recurrence and underscoring the importance of this study, in which the predictors of RA–OP recurrence were identified.

OP, in general, relapses frequently and, therefore, there have been several studies on the predictors for its recurrence. However, the majority of the studies have focussed on cryptogenic OP, and until this study, no study has analysed the RA–OP recurrence. The identified predictors of OP recurrence in previous reports and this study are summarised in **Table 4** [26-32]. This comparison emphasises the value of our data exclusively on RA–OP, and suggests the particularity of RA–OP compared with other forms of OP.

We identified four predictors of RA–OP recurrence. Three of them are related to the timing of OP onset: lower age at the first OP onset (especially ≤ 66 years), shorter period from the RA onset to the first OP onset (especially ≤ 4 years), and OP-preceding. However, the age at the first OP onset has not been identified as a predictor of recurrence in previous studies focussing mainly on cryptogenic OP (**Table 4**) [26-32]. This discrepancy may indicate the specialty of RA–OP and reflect the difference of underlying immunological mechanisms between RA–OP and cryptogenic OP.

There have been several case series on RA–OP, including recurrent cases. In reviewing the literature, we found that many of these reported cases fulfilled the identified predictors related to the timing. A retrospective cohort [22] included two patients with recurrence: a case whose period from the RA onset to the first OP onset was 0 year, fulfilling ≤ 4 years, and a patient whose first OP onset was at the age of 61 years, fulfilling ≤ 66 years. Another case series included a case whose first OP onset preceded the RA onset [33], fulfilling the OP-preceding, and the others included cases whose first OP onset was at age 21 years [19], 55 years [34], or 57 years [35], all fulfilling ≤ 66 years. This consistency may prove the validity of our predictors.

A history of smoking was the other predictor of RA–OP recurrence identified in this study. However, this characteristic has been previously reported as irrelevant to the recurrence of the other types of OP: cryptogenic OP [26, 28] or cryptogenic and secondary OP [32]. It is well established that smoking is a strong risk factor for RA [36] and even for ILDs in patients with RA [37, 38], and that smoking influences the severity of RA [39, 40]. Therefore, smoking may have some specific effects on the immunological status of RA–OP patients, resulting in its recurrence. This discrepancy again highlights the particularity of RA–OP, indicating the need for further studies that focus specifically on RA–OP, excluding cryptogenic OP or other types of secondary OP.

The identified predictors of RA–OP recurrence may help to improve the treatment strategy for RA–OP patients in the clinical practice. For patients with these predictors, the close follow-up with careful attention to their symptoms and the glucocorticoid tapering at a cautious pace can be considered. Given that the median PSL dosage at the OP onset under PSL administration was 6.5 mg/day in this study, RA–OP patients treated with such doses should be followed up with careful attention to the likelihood of recurrence. For patients with the predictors, the usage of azathioprine as a glucocorticoid-sparing agent, in addition to PSL, could also be considered, although the evidence supporting its effectiveness has been limited to a few case reports [41-43].

This study had several limitations. First, this study was single-centred and retrospective, indicating the need for a prospective multicentre cohort study, where patients with RA at the first OP onset or OP-preceding patients at the RA onset are registered and followed up. However, because this study is single-centred, it has advantages in some aspects; the starting dosage and the tapering rate of glucocorticoid were almost uniform for all of the RA–OP patients according to the standardised protocol in our division, which reduced the likelihood of recurrence due to the inadequate remedy or too rapid glucocorticoid tapering. Second, the number of subjects was so small that we could not conduct multivariate analyses to exclude confounding factors, even though our cohort was larger than in those of the previous reports on RA–OP [14, 22].

Conclusions

This study clarified the clinical characteristics of RA–OP and showed the absence of association between OP development and RA exacerbation. RA–OP showed a high recurrence rate, especially in patients with four predictors newly identified. These findings may help to improve the therapeutic strategy for RA–OP patients. Considering the specialty of RA–OP clarified in this study, additional studies exclusively focussing on RA–OP will be needed based on much larger cohorts to confirm our findings. While this study determined the predictors of recurrence, further research on the predictors of the first occurrence of OP in patients with RA is warranted.

Abbreviations

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CIs, confidence intervals; CRP, C-reactive protein; CT, computed tomography; CTDs, connective tissue diseases; ESR, erythrocyte sedimentation rate; ILDs, interstitial lung diseases; NA, not available; OP, organizing pneumonia; PSL, prednisolone; RA, rheumatoid arthritis.

Declarations

Ethics approval and consent to participate

This study was performed in compliance with the Declaration of Helsinki and was approved by the ethics committee of National Center for Global Health and Medicine (NCGM-G-003354-00). No additional consent form was needed for this retrospective non-interventional study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RK, HY, YT, and HK designed the study. RK acquired, analysed, and interpreted the patient data. RK and HY wrote the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Clinical characteristics of 33 patients with RA-OP

Characteristics	RA-OP patients
Number	33
Male (%)	33.3%
Age at the first OP onset (years)	64.0 [55.0, 68.0]*
Age at the RA onset (years)	53.0 [43.8, 61.3]*
Period from the RA onset to the first OP onset (years)	5.5 [1.0, 19.3]*
Sequence of the OP onset (%)	
RA-preceding	81.8%
Simultaneous	9.1%
OP-preceding	9.1%
Biopsy confirmation (%)	27.2%
Smoking history (%)	43.8%
Pre-existing lung disease (%)	48.5%
Follow-up period after the first OP onset (months)	23.0 [4.0, 80.0]*
Recurrence of OP (%)	30.3%
Number of recurrences	1.5 [1.5, 2.8]*
Time between two consecutive OP events (months)	13.0 [7.5, 22.5]*
ACPA positivity (%)	94.4%
RF positivity (%)	93.1%
Medication for RA at the first OP onset (%)	
PSL	42.4%
MTX	48.5%
CsDMARDs other than MTX	45.5%
Biologics	30.3%
No medication	18.2%

*Median [Q1, Q3]

ACPA, anti-citrullinated protein antibody; CsDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; MTX, methotrexate; OP, organizing pneumonia; PSL, prednisolone; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 2 Clinical characteristics of the 60 RA-OP events

Characteristics	RA-OP events
Number	60
Age at the onset of all the OP events (years)	61.0 [54.0, 68.0]*
Symptoms (%)	
Fever	61.1%
Coughing	79.6%
Chest pain	13.0%
Fatigue / loss of appetite	18.5%
Dyspnea	38.9%
Laterality of OP (%)	
Bilateral	58.2%
Unilateral	41.8%
OP in the lower lungs (%)	90.6%
CRP level at the OP onset (mg/dL)	10.2 [5.9, 16.9]*
ESR level at the OP onset (mm/h)	109.0 [99.5, 124.5]*
RF titre at the OP onset (U/mL)	146.9 [51.9, 372.0]*
KL-6 titre at the OP onset (U/mL)	297.5 [233.3, 438.0]*
Within normal limits (%)	76.2%
Treatment for OP (%)	
PSL	98.3%
Initial dosage (mg/day)	30.0 [30.0, 40.0]*
Concomitant use of steroid pulse therapy (%)	20.0%
No treatment	1.7%
Partial response to treatment (%)	3.3%
RA disease activity at the OP onset (%)	
Good Control	52.0%
Poor Control	30.0%
Exacerbation	18.0%
Improvement	0.0%
CRP level before the OP onset (mg/dL)	0.5 [0.2, 1.4]*
ESR level before the OP onset (mm/h)	24.0 [16.0, 52.0]*
Medication for RA at the onset of all the OP events (%)	
PSL	61.0%
MTX	62.7%
CsDMARDs other than MTX	50.8%
Biologics	39.0%
No medication	11.9%

*Median [Q1, Q3]

CRP, C-reactive protein; CsDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; MTX, methotrexate; OP, organizing pneumonia; PSL, prednisolone; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 3 Comparison of the characteristics between the recurrence and the non-recurrence groups

Characteristics	Recurrence	Non-recurrence	P-value
Number	10	14	
Male (%)	50.0%	35.7%	0.48
Age at the first OP onset (years)	59.5 (55.5 - 63.5)*	67.1 (62.0 - 72.3)*	0.043
Age at the RA onset (years)	53.0 (44.5 - 61.5)*	52.8 (46.1 - 59.6)*	0.98
Period from the RA onset to the first OP onset (years)	6.4 (-1.9 - 14.8)*	14.2 (7.5 - 20.9)*	0.047
Sequence of the OP onset: OP-preceding (%)	30.0%	0.0%	0.029
Smoking history (%)	80.0%	35.7%	0.032
Pre-existing lung disease (%)	40.0%	64.3%	0.24
Laterality of OP: bilateral (%)	88.9%	50.0%	0.056
OP in the lower lungs (%)	100.0%	92.9%	0.47
RA activity at the first OP onset (%)			0.80
Good Control	50.0%	38.5%	
Poor Control	37.5%	38.5%	
Exacerbation	12.5%	23.1%	
Improvement	0.0%	0.0%	
CRP level at the first OP onset (mg/dL)	13.9 (9.1 - 18.7)*	10.7 (6.4 - 15.0)*	0.54
ESR level at the first OP onset (mm/h)	105.7 (90.8 - 120.6)*	99.0 (77.7 - 120.3)*	0.92
ACPA positivity (%)	83.3%	87.5%	1
RF positivity (%)	87.5%	85.7%	0.91
RF titre at the first OP onset (U/mL)	411.3 (81.5 - 741.1)*	253.9 (89.3 - 418.4)*	0.68
KL-6 titre at the first OP onset (U/mL)	334.6 (205.9 - 463.3)*	520.6 (307.7 - 733.5)*	0.57
Treatment for the first OP (%)			
PSL	90.0%	100.0%	
Initial dosage (mg/day)	32.0 (22.8 - 41.2)*	32.5 (28.0 - 37.0)*	1
Concomitant use of steroid pulse therapy (%)	10.0%	7.1%	0.80
No treatment	10.0%	0.0%	0.23
Minimum dose of PSL without recurrence (mg/day)	4.7 (1.8 - 7.6)*	5.4 (4.1 - 6.8)*	0.37
Follow-up period after the first OP (months)	81.3 (51.9 - 110.7)*	47.4 (27.2 - 67.6)*	0.11

* Mean (95% CI)

ACPA, anti-citrullinated protein antibody; OP, organizing pneumonia; PSL, prednisolone; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 4 Literature review on the factors predictive of the recurrence of OP

	Objective	Recurrence/Non-recurrence (n)	Predictors of OP recurrence (p < 0.05)
The present study	RA-OP	10/14	Lower age at the first OP onset, shorter period from the RA onset to the OP onset, OP-preceding, and ever-smokers
Watanabe K, et al. (1998) [30]	COP + SOP including CTD-OP	7/11 2	Fever, lower serum TP, Alb, Na, or T-Cho levels, and lower PaO ₂
Lazor R, et al. (2000) [28]	COP	28/20	Longer delays between first symptoms and the start of treatment, and higher serum GGT or ALP levels.
Barroso E, et al. (2007) [29]	COP	18/14	Multifocal opacities on chest X-rays, a shorter time to chest X-ray normalization, and lower serum LDH or GGT levels.
Nishino M, et al. (2014) [27]	COP	7/19	Higher fibrin deposition in lung wedge biopsies.
Kim M, et al. (2015) [31]	COP + SOP including CTD-OP	20/46 7	Lower %FVC, higher P/F ratio, and lower serum TP levels
Onishi Y, et al. (2017) [32]	COP + SOP including CTD-OP	31/44 18	Higher neutrophil percentage in BALF, and higher fibrin deposition in lung biopsies
Saito Z, et al. (2019) [26]	COP	10/23	Bilateral shadow patterns or traction bronchiectasis on chest CT scans, and partial remission to steroid treatment

Alb, albumin; ALP, alkaline phosphatase; BALF, bronchoalveolar lavage fluid; COP, cryptogenic organizing pneumonia; CT, computed tomography; CTD-OP, organizing pneumonia associated with connective tissue diseases; GGT, gamma-glutamyltransferase; LDH, lactate dehydrogenase; OP, organizing pneumonia; P/F, PaO₂/FiO₂; %FVC, percent predicted forced vital capacity; RA, rheumatoid arthritis; SOP, secondary organizing pneumonia; T-Cho, total cholesterol; TP, total protein.

Figures

Figure 1

ROC curves for the predictors of the RA–OP recurrence. (A) ROC curve for the age at the first OP onset. (B) ROC curve for the period from the RA onset to the first OP onset. Optimal cutoff values, where the sum of sensitivity and specificity is maximal, are 66 years with a specificity of 57% and sensitivity of 90% in (A), and 4 years with a specificity of 69% and sensitivity of 80% in (B). The area under the curve was 0.75 (95% CI, 0.55–0.95) in (A) and 0.75 (0.53–0.97) in (B). CI, confidence interval; OP, organising pneumonia; RA, rheumatoid arthritis; ROC, receiver operating characteristic.

Figure 2

Kaplan–Meier estimates of recurrence-free survival in RA–OP patients. (A) Kaplan–Meier estimates stratified according to the sequence of the OP onset; patients whose OP onset preceded the RA onset (OP-preceding) vs. other patients (non-OP-preceding). (B) Kaplan–Meier estimates stratified according to a history of smoking: ever-smokers vs. never-smokers. Figures at the bottom refer to the number of patients still under observation at each time interval. Hazard ratios were calculated by Cox proportional hazards regression analysis. HR, hazard ratio; OP, organising pneumonia; RA, rheumatoid arthritis; RS, recurrence-free survival times.