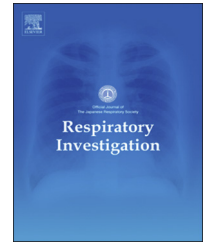


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## Original article

# Factors associated with the relapse of cryptogenic and secondary organizing pneumonia



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## ABSTRACT

**Background:** Organizing pneumonia (OP) is a histopathological response pattern to lung inflammation. It is clinically classified into cryptogenic OP and secondary OP, which is associated with various clinical conditions. Rapid resolution with corticosteroids and frequent relapses are common in OP. However, few studies have investigated the factors associated with OP relapse.

**Methods:** The medical records of 75 patients with biopsy-proven OP, diagnosed between January 2010 and August 2015, who underwent corticosteroid therapy were retrospectively reviewed. Initially, the patients were all treated successfully; however, 31 patients experienced relapse thereafter (R group), whereas the others did not (NR group; 44 patients). The clinical, radiological, and pathological characteristics and administered corticosteroid doses were compared between the two groups.

**Results:** The neutrophil percentage in the bronchoalveolar lavage (BAL) fluid and the level of fibrin deposition in lung biopsy specimens were higher in the R group than in the NR group ( $P=0.01$  and  $P=0.002$ , respectively). The multivariate analysis demonstrated that both factors were statistically significant predictors of OP relapse.

**Conclusions:** A high neutrophil percentage in the BAL and the level of fibrin deposition in lung biopsy specimens are considered predictive factors of OP relapse during the tapering or after the cessation of steroid therapy. Patients without these findings may be treated with low-dose corticosteroids.

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Abbreviations: OP, Organizing pneumonia; BAL, bronchoalveolar lavage; COP, Cryptogenic OP; SOP, secondary OP; SpO<sub>2</sub>, oxyhemoglobin saturation measured by pulse oximetry; WBC, white blood cells; LDH, lactate dehydrogenase; CRP, C reactive protein; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; RF, rheumatoid factor; ANA, antinuclear antibody; CT, computed tomography; HRCT, high-resolution computed tomography; GGO, ground-glass opacity; BALF, BAL fluid; OR, odds ratio; CI, confidence interval; NCA, neutrophil chemotactic activity

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## 1. Introduction

Organizing pneumonia (OP) is a nonspecific response to various stimuli or injuries that can be cryptogenic or secondary to several causes, such as collagen vascular diseases, infections, radiation therapy, drugs, and hematological malignancies. Cryptogenic OP (COP) is classified as idiopathic interstitial pneumonia because of its idiopathic nature and associated parenchymal inflammation and fibrosis [1,2]. Regardless of whether the patients have COP or secondary OP (SOP), almost all of them experience a subacute onset and show good response to corticosteroid therapy; however, relapses are frequently seen when corticosteroids are tapered or discontinued [3]. Lazor et al. reported that 58% of patients with COP experienced relapse and 27% had two or more relapses [4]. Previous studies have shown several possible factors related to OP relapse, but few studies have comprehensively investigated these factors. The aim of this study was to identify the factors related to relapse in patients with OP.

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## 2. Patients and methods

### 2.1. Patients

Patients with biopsy-proven OP diagnosed at the National Hospital Organization Himeji Medical Center between January 2010 and August 2015 were selected as candidates for our study. The histological diagnosis of OP was based on the presence of intraluminal organization in the alveolar ducts or alveoli. Among the candidates, patients who showed spontaneous remission were excluded; the remaining patients were selected as our subjects, and their medical records were retrospectively reviewed. The patients were treated with corticosteroids following our protocol. Specifically, the initial dose was 0.5–0.8 mg/kg/day depending on the clinical manifestations (patient's symptoms, extent of shadow, or clinical course); the treatment was tapered to 5–10 mg/day within 1–2 weeks, and the total administration period was 1–6 months. We grouped the patients whose OP had relapsed during the steroid treatment or after the cessation of treatment into the R group and the patients with no relapse into the NR group. The effect of the patients' baseline characteristics, clinical data, radiological findings, and the level of intraalveolar fibrin deposition in biopsy specimens on OP relapse was evaluated using univariate and multivariate analyses. In addition, patients were grouped into the H and L subgroups on the basis of the total corticosteroid dose that was administered in the first month of their initial treatment: a total corticosteroid dose of  $\geq 15$  mg/kg/month was administered to the H subgroup, and a dose of  $< 15$  mg/kg/month was administered to the L group. The threshold was based on the average dose of all of the patients (15.1 mg/kg/month). The relapse-free ratio between the H and L subgroup patients was assessed. The study design was approved by the Institutional Review Board of National Hospital Organization Himeji Medical Center (IRB No. 28-5 Jishu; approval date, June 28, 2016). The patient data were analyzed anonymously.

### 2.2. Data analysis

We studied the following variables: age, sex, symptoms, smoking status, oxyhemoglobin saturation measured by pulse oximetry (SpO<sub>2</sub>), serum biomarkers (white blood cells [WBC], lactate dehydrogenase [LDH], C-reactive protein [CRP], Krebs von den Lungen-6 [KL-6], surfactant protein D [SP-D], rheumatoid factor [RF], and antinuclear antibody [ANA] positivity), pulmonary function, bronchoalveolar lavage (BAL) findings, chest computed tomography (CT) imaging, days from symptom onset to initiation of corticosteroid treatment, initial steroid dose, total cumulative dose during the first month, and degree of fibrin deposition in the lung biopsy specimens.

High-resolution computed tomography (HRCT) findings of OP were independently and retrospectively reviewed by an experienced thoracic radiologist. The presence of traction bronchiectasis and the reversed halo sign, the propensity of ground-glass opacity (GGO) or consolidation, and the number of affected lung lobes were examined.

BAL was performed using the standard method, and the BAL fluid (BALF) was analyzed as reported previously [5]. The target site for BAL was determined on the basis of the findings of HRCT, which was performed within 2 weeks before BAL. Three 50-ml aliquots of normal saline were instilled in the target bronchus. The first aliquot was presented to the microorganism laboratory, while the second and third aliquots were used for cellular analysis.

Retrospective review of the hematoxylin and eosin-stained biopsy specimens was performed by an experienced pulmonary pathologist. Intraalveolar fibrin was identified by its eosinophilic appearance and divided into two groups as follows: "low" (no foci or discrete foci of fibrin deposition in a limited area) and "high" (multiple foci of fibrin filling the alveoli in a low-power field), according to the classification criteria reported by Nishino et al. [6] (Fig. 1). Relapse of OP was defined as a state with an appearance of new OP-related infiltration on chest imaging, with compatible clinical features and no other identified causes [4].

### 2.3. Statistical analysis

IBM SPSS Statistics 23 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Continuous variables are expressed as the mean  $\pm$  standard deviation. We used Student's *t*-test, the Mann-Whitney *U* test, or Fisher's exact test to compare continuous and categorical variables as appropriate. The log-rank test was used to evaluate the association of the relapse rate with the total corticosteroid dose in the first month. Multivariate logistic regression analysis was used to identify the significant factors related to OP relapse.

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## 3. Results

Of the 101 patients with biopsy-proven OP identified for the study, 26 were excluded because their disease resolved without corticosteroid therapy. The remaining 75 patients who underwent steroid therapy (43 men and 32 women) were studied. Their mean age was  $69.9 \pm 10.3$  years. Of these

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