

Article

Comparison of clinical features and prognosis in patients with cryptogenic and secondary organizing pneumonia

Keum-Ju Choi¹, Eun-Hyung Yoo², Kyung Chan Kim¹ and Eun Jin Kim^{1,*}

¹ Department of Internal Medicine, Daegu Catholic University Medical Center, Daegu Catholic University College of Medicine, Daegu, Korea; tvbogo@naver.com (K-J. C.); solar903@chol.com (K.C.K.)

² Department of Laboratory Medicine, Daegu Catholic University Medical Center, Daegu Catholic University School of Medicine, Daegu, South Korea; yooeh@cu.ac.kr (E-H. Y.)

* Correspondence: ejkim77@cu.ac.kr; Tel.: +82-53-650-4274 (E.J.K.)

Abstract: Organizing pneumonia (OP) can be diagnosed pathologically, and cryptogenic OP (COP) and secondary OP (SOP) have been classified by cause and underlying context. Because it is clinically difficult to differentiate between COP and SOP, this study investigated characteristics that could distinguish between COP and SOP. The medical records of patients who underwent lung biopsy from 2016 to 2018 were retrospectively reviewed. Eighty-five patients had pathologically proven OP, including 16 diagnosed with COP and 69 diagnosed with SOP. The most common cause of SOP was infectious pneumonia, observed in 57 (82.6%) of the 69 patients. Median time from symptom onset to hospital admission is shorter ($P=0.006$) and fever was more common ($P=0.021$) in the SOP. Some laboratory results differed significantly between the two groups. Lymphocyte in bronchoalveolar lavage fluid were higher in the COP ($P=0.012$). Radiologic findings showed that effusion was more common in the SOP ($P=0.043$). There were no between-group differences in steroid use, 30 day and in-hospital mortality rates, and rates of OP outcomes and recurrences. Infection is the main cause of SOP. Symptom onset is more rapid in patients with SOP. Pleural effusion was more common in the SOP but there were no differences in clinical course.

Keywords: Organizing pneumonia; Cryptogenic organizing pneumonia; Secondary organizing pneumonia

1. Introduction

Organizing pneumonia (OP) is an interstitial lung disease histologically characterized by patchy filling of the lung alveoli and respiratory bronchioles by loose plugs of granulation tissue [1, 2]. OP was first described histologically during the early 20th century [3] and has been regarded as a distinct pathological entity since the 1980s [1, 4]. Histological, clinical, and radiological advances have increased understanding of OP, which is presently classified as an interstitial lung disease [5, 6].

OP is initiated by lung injuries, with the alveolar epithelium reacting to produce granulation tissue [6]. Despite having the same pathologic patterns, OP can be classified as either cryptogenic OP (COP) or secondary OP (SOP). SOP can be caused by infection, drug toxicity, drug intoxication, inhalation of toxic gases, aspiration of gastric contents, connective tissue diseases, organ transplantation, radiotherapy, vasculitis, tumors, pulmonary infarction, hypersensitivity pneumonitis, eosinophilic pneumonia, and other interstitial lung diseases [2, 7]. COP can be diagnosed by excluding SOP, based on clinical history, characteristics, laboratory tests, radiologic findings, and associated pathologic findings [8, 9]. Clinical confusion has arisen in the differential diagnosis of COP or SOP, as differences in their characteristics have not been clearly identified [10-15]. The present study investigated whether any characteristics could distinguish between COP and SOP.

The causes, clinical characteristics, laboratory results, radiologic findings, and prognosis were therefore compared in patients with pathologically proven SOP and COP.

2. Materials and Methods

2.1. Study design

The medical records of all patients who underwent lung biopsy at a single tertiary medical institution, Daegu Catholic University Medical Center, South Korea, from January 2016 to December 2018 were retrospectively reviewed. OP was diagnosed by the presence of intraluminal granulation tissue in the alveolar ducts, alveoli, and bronchiolar lumen, as confirmed pathologically by lung biopsy results. A total of 85 patients were identified.

Basic clinical characteristics, including clinical history, symptoms, comorbidities, and concomitant drug use; radiologic findings, including computed tomography (CT) results; biopsy methods and patterns, laboratory data, results of sputum and bronchioloalveolar lavage (BAL) fluid tests, culture findings, and polymerase chain reaction (PCR) results on admission and at biopsy were recorded, as were the results of pulmonary function tests (PFT), treatment-associated data, and follow-up data. The clinical diagnosis was confirmed before the biopsy was performed. The predominant pattern of each biopsy specimen was also determined.

The study protocol was approved by the Institutional Review Board of Daegu Catholic University Hospital (IRB No. CR-21-097).

2.2 Definitions

COP was defined as OP in the absence of an established clinical cause, based on correlations of underlying diseases, concomitant drugs, and microbiological data with a predominant histological pattern. SOP was defined as OP secondary to lung injury of known etiology. For example, a patient with another predominant pattern on biopsy, or with a cause identified by patient history or laboratory data-like culture, was classified as having SOP. Radiologically, focal OP was defined as a solitary focal and nodular opacity. Recurrence was defined as worsening of chest X ray after prior improvement; in such cases, re-biopsy was not performed.

2.3 Methods

2.3.1. Lung biopsy

Lung tissue samples were obtained by bronchoscopic transbronchial lung biopsy (TBLB), CT-guided lung biopsy, or video-associated surgical lung biopsy. Patients with OP diagnosed by TBLB or CT-guided lung biopsy did not require surgical lung biopsy. Of the 85 patients, 77 (90.6%) were diagnosed by TBLB, including 59 (68.2%) by radial probe and 19 (22.4%) by blind TBLB. Seven (8.2%) patients underwent CT-guided lung biopsy and one (1.2%) underwent surgical lung biopsy. All patients underwent bronchoscopy, even those who underwent CT-guided or surgical lung biopsy, with BAL fluid samples obtained from 43 (50.6%) patients.

2.3.2. Microbiological and molecular methods

The quality of sputum and BAL fluid specimens was assessed microscopically using Gram stain smears, as determined by the Murray–Washington grouping system [16]. Specimens were processed and cultured according to standard laboratory procedures. The most purulent portion of each specimen was inoculated onto blood, chocolate, and

MacConkey's agar plates, and incubated at 35°C in 5% CO₂ for 48 hours. Agar plates were examined at 16–24 and 48 hours, and the predominant organisms were identified and quantified. Biochemical identification and antibiotic susceptibility tests were performed using the VITEK 2 System (bioMérieux, Durham, NC, USA) or Microscan WalkAway 96 SI Plus (Beckman Coulter, Brea, CA, USA) according to the manufacturer's instructions. In some cases, sputum, bronchial washing, and BAL fluid samples were subjected to Acid fast bacilli (AFB) smear and culture and fungal culture.

Mycoplasma pneumoniae, *Legionella pneumophila*, *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Bordetella pertussis*, and *Chlamydophila pneumoniae* were detected in respiratory samples by multiplex real-time PCR tests. To detect viruses, RNA was extracted from clinical samples with Nextractor NX-48 kits (Biosewoom, Seoul, Korea) according to the manufacturer's instructions. Real-time RT-PCR assays were performed to detect 14 respiratory viruses (adenovirus; human rhinovirus, human coronaviruses (CoV) NL63/HKU1, 229E, and OC43; influenza A and B viruses; parainfluenza viruses (PIV) 1, 2, and 3; respiratory syncytial viruses A and B; human bocavirus, and metapneumovirus) using Real-Q RV Detection kits (Biosewoom) and the CFX96 Real-Time System (Bio-Rad, Hercules, CA, USA). Respiratory samples were also analyzed using the BioFire™ Diagnostics Respiratory Panel and FilmArray™ multiplex PCR System (bioMérieux) to detect the following pathogens: adenovirus, CoV 229E, CoV HKU1, CoV NL63, CoV OC43, human metapneumovirus, human rhinovirus/enterovirus, influenza A H1 virus, influenza A H1 2009 virus, influenza A H3 virus, influenza B virus, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 4, respiratory syncytial virus, *Bordetella pertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*.

2.3.3. PFT and chest CT

Forty-one (48.2%) patients were assessed by PFTs, with results reported as absolute values and % of predicted values. PFT results were interpreted as normal, restrictive, obstructive, and mixed patterns according to American Thoracic Society criteria [17]. All patients were evaluated by chest CT to assess the patterns and distribution of pulmonary abnormalities. Pulmonary patterns were classified as consolidations, ground glass opacities, nodules, and masses, with pleural effusions, cavitations, and migratory signs also identified.

2.3.4. Treatment and follow-up

Each patient was started on treatment with antibiotics and steroids at the discretion of each physician based on the clinical condition of the patient. Most patients were started on methylprednisolone 0.75 mg/kg/day or higher [8, 18], with the duration and dose depending on the judgment of each physician. Patients were followed-up and recurrence monitored for at least 2 years.

2.4. Statistical analysis

Normally distributed continuous variables were expressed as numbers and percentages or as means or medians and interquartile ranges (IQRs), whereas non-normally distributed continuous variables were expressed as medians and IQRs. Results in the COP and SOP groups were compared by Mann–Whitney U-tests. Qualitative variables between the two groups were compared using chi-square (χ^2) tests. All statistical analyses were performed using SPSS version 25 (SPSS, Inc., Chicago, IL, USA), with statistical significance set at $P < 0.05$.

3. Results

3.1. Diseases associated with secondary organizing pneumonia

Of the 85 patients with pathologically confirmed OP on lung biopsy, 16 (18.8%) were diagnosed with COP and 69 (81.2%) with SOP. Infectious pneumonia was the most frequent cause of SOP, occurring in 57 patients (82.6%), followed by cancer and radiation pneumonitis. The bacteria causing infectious pneumonia were confirmed in 45 patients (65.2%), either by culture or PCR testing. *Acinetobacter baumannii* was the most frequently identified, followed by *Stenotrophomonas*, *Tuberculosis*, *Streptococcus*, *Staphylococcus*, *Klebsiella*, and fungi (Table 1). In one patient each, SOP was caused by connective tissue disease, hypersensitivity pneumonitis, and chronic eosinophilic pneumonia, and was drug-related in one patient.

Table 1. Diseases associated with secondary organizing pneumonia

Associated diseases (n=69)	No. (%)
Infectious pneumonia	57 (82.6)
Acinetobacter	8 (11.6)
Tuberculosis	7 (10.1)
Stenotrophomonas	7 (10.1)
Streptococcus	6 (9.7)
Staphylococcus	5 (7.2)
Klebsiella	4 (5.8)
Fungus infection	3 (4.3)
Pneumocystis jiroveci pneumonia	1 (1.4)
Pseudomonas	1 (1.4)
Enterobacter	1 (1.4)
Influenza virus	1 (1.4)
Hemophilus influenzae	1 (1.4)
Cancer	6 (8.7)
Radiation pneumonitis	2 (2.9)
Connected tissue disease	1 (1.4)
Hypersensitivity pneumonitis	1 (1.4)
Drug (adalimumab)	1 (1.4)
Chronic eosinophilic pneumonia	1 (1.4)

3.2. Patient characteristics

Median ages of patients in the COP and SOP groups were 64 and 71 years, respectively, with no significant between-group difference. The percentages of men were higher than those of women in both groups, but the difference in gender distribution was not significant. Reasons for biopsy included the pneumonia pattern in 61 patients (71.8%) and the mass form in 24 (28.2%). Median body mass index (BMI) was significantly higher in the COP than in the SOP group (24.1 kg/m² vs. 21.7 kg/m², P=0.030). The median time from the first visit to diagnosis was 13 days in both groups, whereas the median time from symptom onset to hospital admission was significantly longer in the COP than in the SOP group (4 weeks vs. 1 week, P=0.006). Fever was significantly more common in the SOP group (P=0.021), whereas chest pain was significantly more common in the COP group (P=0.043). The most common symptoms in all patients were cough, sputum, shortness of breath, fever, hemoptysis, and chest pain. Chronic liver disease was signifi-

cantly more frequent in the COP group ($P=0.003$), but there were no other differences in comorbidities or in CURB-65 score, an index of the severity of pneumonia (Table 2).

Table 2. Baseline demographic and clinical characteristics of patients with cryptogenic and secondary organizing pneumonia

	COP (n=16)	SOP (n=69)	Total OP (n=85)	P
Age, yr	64 (62–74)	71 (61–78)	70.0 (61–77)	0.303
Male : Female	11:5	58:11	69:16	0.158
Smoking				0.533
Non-smoker	6 (37.5)	25 (36.2)	31 (36.5)	
Ex-smoker	6 (37.5)	34 (49.3)	40 (47.1)	
Smoker	4 (25.0)	10 (14.5)	14 (16.5)	
Reason for biopsy				0.126
Pneumonic lesion	9 (56.3)	52 (75.4)	61 (71.8)	
Mass lesion	7 (43.8)	17 (24.6)	24 (28.2)	
Duration between first visit and biopsy, days	13 (9-23)	13 (8-20)	13 (8-20)	0.875
BMI, kg/m ²	24.1 (21.3–25.5)	21.7 (19.7–24.2)	22.0 (19.8–24.5)	0.030**
Symptom duration, weeks	4 (2–5) (n=13)	1 (1–4) (n=63)	2 (1–4) (n=76)	0.006**
Symptom				
Cough	12 (75.0)	50 (72.5)	62 (72.9)	0.837
Sputum	9 (56.3)	37 (53.6)	46 (54.1)	0.849
Dyspnea	9 (56.3)	25 (36.2)	34 (40.0)	0.141
Fever	2 (6.3)	30 (43.5)	32 (37.6)	0.021*
Hemoptysis	2 (12.5)	6 (8.7)	8 (9.4)	0.639
Chest pain	3 (18.8)	3 (4.3)	6 (7.1)	0.043*
Mental status change	0	3 (4.3)	3 (3.5)	0.396
Underlying diseases				
Hypertension	4 (25.0)	31 (44.9)	35 (41.2)	0.144
Diabetes mellitus	4 (25.0)	22 (31.9)	26 (30.6)	0.590
Chronic airway disease	3 (18.8)	15 (21.7)	18 (21.2)	0.792
Ischemic heart disease	2 (12.5)	11 (15.9)	13 (15.3)	0.730
Cerebrovascular disease	0	11 (15.9)	11 (12.9)	0.087
Active cancer	1 (6.3)	7 (10.1)	8 (9.4)	0.631
Immune suppression	0	7 (10.1)	7 (8.2)	0.184
Bed bound state	0	7 (10.1)	7 (8.2)	0.184
Atrial fibrillation	2 (12.5)	4 (5.8)	6 (7.1)	0.346
Chronic kidney disease	0	5 (7.2)	5 (5.9)	0.267
Chronic liver disease	3 (18.8)	1 (1.4)	4 (4.7)	0.003*
Other interstitial lung diseases	0	1 (1.4)	1 (1.2)	0.628
Connective tissue diseases	0	1 (1.4)	1 (1.2)	0.628
CURB-65[26]				0.123
0	7 (43.8)	12 (17.4)	19(22.4)	
1	7 (43.8)	29 (42.0)	36(42.4)	
2	2 (12.5)	20 (29.0)	22(25.9)	
3	0	7 (10.1)	7(8.2)	
4	0	1 (1.4)	1(1.2)	

Data are presented as number (%) or median (interquartile range [IQR]). * $P<0.05$ by chi-square tests for comparisons between the COP and SOP groups. ** $P<0.05$ by Mann–Whitney U-tests for comparisons between the COP and SOP groups. Abbreviations: COP = cryptogenic organizing pneumonia; SOP = secondary organizing pneumonia; OP = organizing pneumonia; BMI = body mass index.

3.3. Clinical, laboratory, bronchoalveolar fluid and PFT findings

Vital signs and PF ratios did not differ between the two groups, nor did leukocyte and neutrophil counts and concentrations of C-reactive protein (CRP). By contrast, eosinophil counts and concentrations of procalcitonin, pro-brain natriuretic peptide (proBNP), D-dimer, creatinine, and lactate differed significantly between the two groups at admission. Lymphocyte counts in BAL fluid were significantly higher in the COP than in the SOP group ($P=0.012$). Of the 41 (48.2%) patients who underwent PFT, 16 (39.0%) had normal lung function, 12 (29.3%) had a restrictive ventilator defect, nine (22.0%) had an obstructive ventilator defect, and four (9.8%) had mixed defects. PFT results, however, did not differ significantly between these two groups (Table 3).

Table 3. Laboratory and clinical findings in patients with cryptogenic and secondary organizing pneumonia

	COP (n=16)	SOP (n=69)	Total OP (n=85)	P
PF ratio	297 (270–330)			
(n=6)	281 (250–375)			
(n=45)	281 (254–367)			
(n=51)	0.853			
SBP, mmHg	110 (100–120)	120 (110–130)	120 (110–130)	0.100
DBP, mmHg	70 (60–80)	70 (60–80)	70 (60–80)	0.861
PR, /min	85 (76–99)	90 (80–98)	89 (79–99)	0.582
RR, /min	20 (20–20)	20 (20–20)	20 (20–20)	0.401
BT, °C	37.0 (36.8–37.5)	37.0 (36.7–37.4)	37.0 (36.7–37.4)	0.744
Day on admission				
Leukocyte, 103/ul	6.1 (5.1–9.4)	8.7 (6.6–13.7)	8.7 (6.2–13.6)	0.197
Neutrophil, %	71 (66–79)	80 (72–86)	80 (71–85)	0.088
Eosinophil, %	3 (2–3)	1 (0–2)	1 (0–2)	0.012**
CRP, mg/l	11 (3–49)	108 (24–210)	83 (21–208)	0.067
Procalcitonin, ng/ml	0.05 (0.03–0.05)	0.26 (0.11–1.45)	0.23 (0.08–1.53)	0.018**
proBNP, pg/ml	223 (112–325)	985 (307–2387)	881 (251–2287)	0.035**
D-dimer, ug/ml	0.9 (0.3–1.3)	2.0 (1.3–2.8)	1.9(1.0–2.7)	0.015**
Albumin, g/dl	3.6 (3.3–3.8)	3.3 (3.1–3.7)	3.3 (3.1–3.7)	0.260
Creatinine, mg/dl	0.7 (0.6–0.8)	1.0 (0.7–1.3)	1.0 (0.7–1.3)	0.012**
Lactate, mmol/l	1.0 (1.0–1.1)	1.4 (1.1–1.9)	1.4 (1.0–1.9)	0.047**
Bronchoalveolar fluid	COP (n=9)	SOP (n=35)	OP (n=44)	P
Leukocyte, /ul	380 (200–600)	270 (150–850)	300 (150–700)	0.895
Neutrophil, %	7 (4–13)	15 (5–67)	10 (4–56)	0.132
Lymphocyte, %	60 (38–83)	31 (7–56)	36 (9–61)	0.012**
Eosinophil, %	0 (0–1)	1 (1–3)	1 (0–2)	0.007**
Pulmonary function tests***	COP (n=10)	SOP (n=31)	OP (n=41)	0.303
Normal	6 (60.0)	10 (32.3)	16 (39.0)	
Obstructive ventilatory defect	1 (10.0)	8 (25.8)	9 (22.0)	
Restrictive ventilatory defect	3 (30.0)	9 (29.0)	12 (29.3)	
Mixed ventilatory defect	0	4 (12.9)	4 (9.8)	

Data are presented as number (%) or median (interquartile range [IQR]). * $P<0.05$ by chi-square tests for comparisons between the COP and SOP groups. ** $P<0.05$ by Mann–Whitney U-tests for comparisons between the COP and SOP groups. ***Classified as normal, restrictive, obstructive, and mixed pattern according to American Thoracic Society criteria [17]. Abbreviations: COP = cryptogenic organizing pneumonia; SOP = secondary organizing pneumonia; OP = organizing pneumonia; PF ratio = arterial partial pressure of oxygen (PaO₂)/fraction of inspired oxygen (FiO₂) ratio; CRP = C-reactive protein; proBNP = pro-brain natriuretic peptide; ESR = erythrocyte sedimentation rate; FVC = forced vital capacity; FEV₁ = forced expiratory volume in the first second; TLC = total lung capacity; DLCO = diffusing capacity of the lung for carbon monoxide.

3.4 Chest CT findings

Chest CT showed no between-group differences in the extent or pattern of pneumonia, whereas effusion was more common in the SOP group ($P=0.043$; Table 4). Chest CT identified 12 patients with focal OP, including seven (43.8%) in the COP group and five (7.2%) in the SOP group ($P<0.001$).

Table 4. Computed tomography findings in patients with cryptogenic and secondary organizing pneumonia, including 12 patients with focal organizing pneumonia

	COP (n=16)	SOP (n=69)	Total OP (n=85)	P
Number of involved lobes				0.056
1	7 (43.8)	19 (27.5)	26 (30.6)	
2	1 (6.3)	16 (23.2)	17 (20.0)	
3	5 (31.3)	9 (13.0)	14 (16.5)	
4	3 (18.8)	10 (14.5)	13 (15.3)	
5	0	15 (21.7)	15(17.6)	
Characters				
Consolidation	5 (31.3)	29 (42.0)	34 (40.0)	0.428
Effusion	2 (12.5)	27 (39.1)	29 (34.1)	0.043*
Both of consolidation and ground glass opacities	4 (25.0)	23 (33.3)	27 (31.8)	0.519
Nodule or mass	6 (37.5)	12 (17.4)	18 (21.2)	0.076
Focal solitary nodule	7 (43.8)	5 (7.2)	12 (14.1)	<0.001*
Cavity	0	10 (14.5)	10 (11.8)	0.1.05
Ground glass opacities	1 (6.3)	5 (7.2)	6 (7.1)	0.889

Data are presented as number (%) or median (interquartile range [IQR]). * $P<0.05$ by chi-square tests for comparisons between the COP and SOP groups. Abbreviations: COP = crypto-genic organizing pneumonia; SOP = secondary organizing pneumonia; OP = organizing pneumonia

3.5. Treatment and prognosis

Four patients (5.8%) in the SOP group required ventilator use and five (7.2%) in this group required inotropics, but there were between-group differences. Antibiotic use was significantly higher in the SOP than in the COP group ($P=0.013$), but there was no between-group difference in steroid use. The 30 day and in-hospital mortality rates, as well as outcome and recurrence rates, did not differ between the two groups (Table 5).

Table 5. Treatment and prognosis in patients with cryptogenic and secondary organizing pneumonia

	COP (n=16)	SOP (n=69)	Total OP (n=85)	P
Antibiotics	11 (73.3)	65 (94.2)	76 (90.5)	0.013*
Steroid	9 (56.3)	31 (44.9)	40 (47.1)	0.414
Inotropics or vasopressors	0	5 (7.2)	5 (5.9)	0.267
Ventilator	0	4 (5.8)	4 (4.7)	0.324
30 day mortality				0.615
Death	0	3 (4.3)	3 (3.5)	
Loss of follow-up	0	1 (1.4)	1 (1.2)	
In-hospital mortality	0	4 (5.8)	4 (4.7)	0.324
Outcome of OP				0.308
Improvement	14 (89.5)	56 (81.2)	70 (82.4)	
Fail	0	8 (11.6)	8 (9.4)	
Loss of follow-up	2 (12.5)	5 (7.2)	7 (8.2)	
Recur	2 (12.5)	10 (14.5)	12 (14.1)	0.837

Data are presented as number (%) or median (interquartile range [IQR]). * $P<0.05$ by chi-square tests for comparisons between the COP and SOP groups. Abbreviations: COP = cryptogenic organizing pneumonia; SOP = secondary organizing pneumonia; OP = organizing pneumonia.

3.6 Clinical outcomes in SOP

Subgrouping of the 69 patients with SOP cases into those who were (n=31) and were not (n=38), treated with steroids showed that pneumonia recurrence was significantly more frequent in the former group ($P=0.016$). However, there were no differences between these subgroups in 30 day and in-hospital mortality rates and in outcome of OP (Table 6). Median neutrophil counts on complete blood count (CBC) were significantly higher in the recur group (80.2 %) than in the non-recur group (66.0 %) ($p=0.027$). Lymphocyte count on CBC was also significantly lower in the recur group (5.6 %) than in the non-recur group (7.9%) ($p=0.005$). (Data not shown)

Table 6. Treatment and prognosis in patients with cryptogenic and secondary organizing pneumonia

	Steroid using group (n=38)	Non-steroid using group (n=31)	Total (n=69)	P
OP outcome				
Improve	32 (84.2)	24 (77.4)	56 (81.2)	0.118
Fail	2 (5.3)	6 (19.4)	8 (11.6)	
f/u loss	4 (10.5)	1 (3.2)	5 (7.2)	
In-hospital mortality	1 (2.6)	3 (9.7)	4 (5.8)	0.213
30 day mortality	1 (2.6)	2 (6.5)	3 (4.3)	0.499
Recur	2 (5.3)	8 (25.8)	10 (14.5)	0.016*

Data are presented as number (%) or median (interquartile range [IQR]). * $P<0.05$ by chi-square tests for comparisons between the steroid using and non-steroid using SOP subgroups. Abbreviations: SOP = secondary organizing pneumonia; OP = organizing pneumonia.

4. Discussion

This study found that the most frequent cause of SOP was infection, with symptoms progressing more rapidly in patients with SOP than with COP. Several parameters in blood and BAL fluid differed significantly in the SOP and COP groups. Pleural effusion was more common in the SOP than in the COP group. PFT results, response to treatment, and treatment results were similar between these two groups. Subanalysis of the SOP group showed that the recurrence rate was higher in those who were than were not treated with steroids.

OP is a pathologic diagnosis term, defined as the presence of means polypoid intraluminal plugs of proliferating fibroblasts and myofibroblasts within alveolar ducts and spaces with varying degrees of bronchiolar involvement. OP can be regarded as a non-specific pathological pattern of lung responses to injury [6]. In the absence of a specific cause, this condition is diagnosed as COP [9]. The 2002 ATS/ERS classification recommended using COP rather than the term bronchiolitis obliterans organizing pneumonia (BOOP) because BOOP may be confused with airway disease and, histologically, bronchiolitis obliterans may be concomitant or absent [19]. OP may be a clinical manifestation of a nonspecific repair process in response to a local or distant injury [12]. Based on this definition, SOP was diagnosed in patients with a pathologic OP pattern resulting from identified causes. Distinguishing between COP and SOP is important because the underlying disease, not OP itself, must be managed in patients with SOP. Descriptions of OP are based on an autopsy study of patients with unresolved bacterial pneumonia prior to the advent of antimicrobial therapy [20-22]. Although OP was thought to be due to infection alone, it was later recognized as a variety of conditions, including interstitial disease, drug toxicity, and connective tissue disorders. Several studies have described the differences between COP and SOP [10-15].

The major difference between these earlier studies and the present study is that the SOP group in the latter included a high percentage of patients with infectious pneumonia. Because the clinical symptoms of COP and SOP are similar, it is difficult to diagnose SOP, especially infectious pneumonia, based only on clinical symptoms. In a previous study of 57 patients, 27 were diagnosed with SOP, with eight patients having SOP due to infection, the most frequent cause of SOP in that study [11]. The present study also found that infectious pneumonia was the most frequent cause of SOP. In our center, patients who experience slow clinical improvement after being diagnosed with infectious pneumonia are evaluated by lung biopsy to determine whether other conditions may have accompanied infection. Moreover, many patients with infection in the present study were evaluated by lung biopsy, which may have led to the high rate of infection-related SOP diagnoses. In addition, our study was performed after the development of more recent diagnostic techniques, including culture of respiratory samples, multiplex PCR, and respiratory virus panel tests, enabling more accurate identification of bacteria and viruses, and thus the increased diagnosis of SOP. A study performed from 2001 to 2008 found that only two (9.5%) of 21 patients had SOP caused by infections [12]. However, the difficulty of distinguishing between SOP and COP, and the inability to identify a pathogen, may have resulted in some patients with SOP being diagnosed with COP.

The median age of patients in the present study was 70 years, higher than the average ages reported in previous studies. Moreover, BMI was significantly lower ($P=0.030$) and the duration of clinical symptoms before admission significantly shorter ($P=0.006$) in the SOP group. The latter was likely due to the more rapid onset and progression of clinical symptoms in the SOP group, resulting in a shorter duration of symptoms. Among the symptoms, fever was more frequent in the SOP group ($P=0.021$). A previous study reported that, although most secondary BOOPs were related to chemotherapy and radiotherapy, the clinical symptoms of secondary BOOP were more evident [14]. Our study also found that chronic liver disease was more frequent in the COP group ($P=0.003$).

Advanced liver disease in the pulmonary parenchyme has been reported to lead to lymphocytic or OP [23], which may explain this result. CURB-65, an index of pneumonia severity, did not differ between these two groups.

Serum concentrations of procalcitonin, proBNP, D-dimer, creatinine, and lactate were found to be significantly higher in the SOP than in the COP groups, with these increases thought to be due to the underlying disease in patients with SOP. Lymphocyte counts in BAL fluid were significantly higher in the COP than in the SOP group ($P=0.012$). Lymphocytosis $>25\%$ in BAL fluid is considered a marker of COP [24]. Although a previous study reported that lymphocyte counts in BAL fluid were significantly lower in patients with COP than with SOP, BAL fluid was assessed in only five patients with SOP and 27 patients with COP, with the mean lymphocyte counts in the BAL fluid of the COP group being much lower, 16%, than reported elsewhere [12]. As in previous studies, we found that PFT did not differ between the COP and SOP groups.

CT evaluation showed that pleural effusion was significantly more frequent in the SOP than in the COP group ($P=0.043$). This finding is in good agreement with the results of previous studies, with effusion being more frequent in patients with SOP than in those with COP [12, 14].

Antibiotic use was significantly greater in the SOP group ($P=0.013$), although there was no between-group difference in steroid use. Although COP was found to improve more rapidly with corticosteroids, relapses were more common when treatment was discontinued [8, 13, 18, 25]. Several studies have reported no significant difference in treatment response and clinical course between COP and SOP [10, 12], although one study found a higher mortality rate in patients with SOP, narrowly defined as OP due to a connective tissue disorder, hematologic malignant neoplasms, chemotherapy, or leukemia, than in those with COP [13], suggesting that the underlying disease affects patient prognosis. The present study found no difference in treatment-related outcomes between the COP and SOP groups. Pneumonia recurrence in the SOP group, however, was significantly more frequent in patients who were than were not treated with steroids ($P=0.016$). This finding was likely due to the low rate of lymphocytosis in the BAL fluid of patients with SOP, which may have reduced responses to steroids and increased the recurrence of pneumonia due to underlying diseases. Among patients with SOP, those who experienced pneumonia recurrence had a significantly higher neutrophil count ($P=0.027$) and a significantly lower lymphocyte count ($P=0.005$) than those who did not experience recurrence. High neutrophil counts in patients with infectious SOP cases indicate that infection control is poor, with SOP recurring because of a lack of improvement in the underlying disease.

There were some limitations in this study. Because this was a retrospective study of OP diagnosed by lung biopsy, critically ill patients were excluded if lung biopsy was difficult. Because steroids tend to be used only in patients with relatively severe pneumonia, there was likely a selection bias regarding the steroid effect. In this study, steroid dose, duration, and criteria for use were not standardized, making it difficult to interpret treatment-related outcomes. Moreover, recurrence could not be confirmed as a recurrence of OP, as it was not determined histologically by re-biopsy.

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References

1. Epler GR, Colby TV, McCloud TC, Carrington CB, Gaensler EA: Bronchiolitis obliterans organizing pneumonia. *New England Journal of Medicine* 1985, 312(3):152-158.
2. Epler GR: Bronchiolitis obliterans organizing pneumonia, 25 years: a variety of causes, but what are the treatment options? *Expert review of respiratory medicine* 2011, 5(3):353-361.
3. Tripier R: *Traité d'anatomie pathologique générale*: Masson; 1904.
4. Davison A, Heard B, McAllister W: STEROID-RESPONSIVE RELAPSING CRYPTOGENIC ORGANIZING PNEUMONITIS. In: *Thorax: 1982: BRITISH MED JOURNAL PUBL GROUP BRITISH MED ASSOC HOUSE, TAVISTOCK SQUARE ...*; 1982: 785-786.
5. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002, 165(2):277-304.
6. Baque-Juston M, Pellegrin A, Leroy S, Marquette CH, Padovani B: Organizing pneumonia: what is it? A conceptual approach and pictorial review. *Diagnostic and interventional imaging* 2014, 95(9):771-777.
7. Roberton BJ, Hansell DM: Organizing pneumonia: a kaleidoscope of concepts and morphologies. *Eur Radiol* 2011, 21(11):2244-2254.
8. Cordier J: Cryptogenic organising pneumonia. *The European respiratory journal* 2006, 28(2):422.
9. Flaherty KR, King TE, Raghu G, Lynch JP, Colby TV, Travis WD, Gross BH, Kazerooni EA, Toews GB, Long Q et al: Idiopathic Interstitial Pneumonia. *American Journal of Respiratory and Critical Care Medicine* 2004, 170(8):904-910.
10. Baha A, Yıldırım F, Köktürk N, Galata Z, Akyürek N, Demirci NY, Türkteş H: Cryptogenic and secondary organizing pneumonia: clinical presentation, radiological and laboratory findings, treatment, and prognosis in 56 cases. *Turkish thoracic journal* 2018, 19(4):201.
11. Basarakodu KR, Aronow WS, Nair CK, Lakkireddy D, Kondur A, Korlakunta H, Valasareddi SL, Lem V, Schuller D: Differences in treatment and in outcomes between idiopathic and secondary forms of organizing pneumonia. *Am J Ther* 2007, 14(5):422-426.
12. Drakopanagiotakis F, Paschalaki K, Abu-Hijleh M, Aswad B, Karagianidis N, Kastanakis E, Braman SS, Polychronopoulos V: Cryptogenic and Secondary Organizing Pneumonia: Clinical Presentation, Radiographic Findings, Treatment Response, and Prognosis. *Chest* 2011, 139(4):893-900.
13. Lohr RH, Boland BJ, Douglas WW, Dockrell DH, Colby TV, Swensen SJ, Wollan PC, Silverstein MD: Organizing pneumonia: features and prognosis of cryptogenic, secondary, and focal variants. *Archives of internal medicine* 1997, 157(12):1323-1329.
14. Vasu TS, Cavallazzi R, Hirani A, Sharma D, Weibel SB, Kane GC: Clinical and radiologic distinctions between secondary bronchiolitis obliterans organizing pneumonia and cryptogenic organizing pneumonia. *Respir Care* 2009, 54(8):1028-1032.
15. Chang J, Han J, Kim DW, Lee I, Lee KY, Jung S, Han HS, Chun BK, Cho SJ, Lee K et al: Bronchiolitis Obliterans Organizing Pneumonia: Clinicopathologic Review of a Series of 45 Korean Patients Including Rapidly Progressive form. *J Korean Med Sci* 2002, 17(2):179-186.
16. Murray PR, Washington JA: Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975, 50(6):339-344.
17. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CPM, Gustafsson P, Hankinson J et al: Interpretative strategies for lung function tests. *European Respiratory Journal* 2005, 26(5):948-968.
18. Lazor R, Vandevenne A, Pelletier A, Leclerc P, Court-Fortune I, Cordier JF: Cryptogenic organizing pneumonia. Characteristics of relapses in a series of 48 patients. *The Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P)*. *Am J Respir Crit Care Med* 2000, 162(2 Pt 1):571-577.
19. Demedts M, Costabel U: ATS/ERS international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. In: *Eur Respiratory Soc*; 2002.
20. FLOYD R: Organization of pneumonic exudates. *Medical and Surgical Report* 1925:110.
21. Milne LS: Chronic pneumonia (including a discussion of two cases of syphilis of the lung). *The American Journal of the Medical Sciences (1827-1924)* 1911, 142(3):408.
22. Roberton BJ, Hansell DM: Organizing pneumonia: a kaleidoscope of concepts and morphologies. *European radiology* 2011, 21(11):2244.
23. Rodríguez-Roisin R, Krowka MJ: Hepatopulmonary Syndrome — A Liver-Induced Lung Vascular Disorder. *New England Journal of Medicine* 2008, 358(22):2378-2387.

24. Poletti V, Cazzato S, Minicuci N, Zompatori M, Burzi M, Schiattone M: The diagnostic value of bronchoalveolar lavage and transbronchial lung biopsy in cryptogenic organizing pneumonia. *European Respiratory Journal* 1996, 9(12):2513-2516.
25. Wells AU: Cryptogenic organizing pneumonia. *Semin Respir Crit Care Med* 2001, 22(4):449-460.
26. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT: Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003, 58(5):377-382.