# Clinical, radiological, and pathological evaluation of “NSIP with OP overlap” pattern compared with NSIP in patients with idiopathic interstitial pneumonias

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## Author contributions

NE and TS contributed to the study conception and design. NE, HS, HS, MK, TT, HH, and TF contributed acquisition of data. NE, HH, and TF analyzed and interpreted the data. NE drafted the manuscript. NE, HS, HS, MK, TT, TF, and TS contributed to critical revision for important intellectual content. NE, HS, HS, MK, TT, HH, TF, and TS approved the final version of manuscript to be published.

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## Summary

***Background:*** Nonspecific interstitial pneumonia (NSIP) and organizing pneumonia (OP) are major subtypes of idiopathic interstitial pneumonias (IIPs) and closely related to connective tissue diseases (CTDs). "NSIP with OP overlap" is a controversial finding that has recently appeared in the criteria of interstitial pneumonia with autoimmune features (IPAF). However, details of this controversial entity are not well known.

***Objective:*** To determine the frequency of "NSIP with OP overlap" pattern in IIPs and to identify differences from idiopathic NSIP (iNSIP).

***Methods:*** In 524 patients with interstitial pneumonia from 39 institutes who underwent surgical lung biopsy, 444 were diagnosed as IIPs by a multidisciplinary discussion meeting via a cloud-based integrated database. Among these patients, 44 (9.9%) who had iNSIP and 21 (4.7%) with histopathologically-defined "NSIP with OP overlap" pattern (a pathological NSIP and OP pattern, but without a UIP pattern) were retrospectively studied.

***Results:*** Patients with "NSIP with OP overlap" pattern showed a significantly greater extent of consolidation ($p<0.001$), more subpleural ground glass attenuation ($p=0.036$), and more peripheral+bronchovascular distribution ($p=0.009$) on high-resolution computed tomography than those with iNSIP. The incidences of newly-developed CTDs during follow-up was similar between the groups and polymyositis/dermatomyositis was the most frequent CTD in both groups. Nearly half of the patients fulfilled IPAF criteria, but no significant difference was found between iNSIP and "NSIP with OP overlap" pattern (47.7% vs. 42.9, $p=0.712$). The incidence of acute exacerbation and the survival rates were similar between the groups.

***Conclusions:*** The incidence of "NSIP with OP overlap" pattern is 4.7% in IIPs. The frequency of newly-developed CTDs during follow-up, mainly polymyositis/dermatomyositis, the frequency of acute exacerbation, and the survival rate in "NSIP with OP overlap" pattern are

similar to those of iNSIP.

**Key words:** idiopathic interstitial pneumonia; interstitial pneumonia with autoimmune features; nonspecific interstitial pneumonia; organizing pneumonia; unclassifiable interstitial pneumonia

## Introduction

Idiopathic nonspecific interstitial pneumonia (iNSIP) is the second most common idiopathic interstitial pneumonia (IIP) after idiopathic pulmonary fibrosis (IPF) [1] [2]. Additionally, NSIP is sometimes related to underlying connective tissue diseases (CTDs), hypersensitivity pneumonitis, or drug toxicity [2-4]. Cryptogenic organizing pneumonia is also one of the IIPs, in which fibroblast plugs fill the alveolar space [2]. Organizing pneumonia (OP) is also sometimes related to other aetiologies such as CTDs, similar to NSIP [4]. Histopathologically, NSIP does not have prominent OP components that involve 20% or more of the overall biopsy specimen [3], but 52% of them also had mild OP components [3]. In addition, a median proportion of OP components of 9% (range, 1%-40%) was found in a previous study [5]. Therefore, overlapping findings of NSIP and mild OP components are not uncommon.

As mentioned above, NSIP and OP are closely related to CTDs. NSIP is frequently found in patients with polymyositis/dermatomyositis (PM/DM) or systemic sclerosis (SSc) [4, 6]. Similarly, OP is often found in patients with PM/DM [4] [7]. Therefore, NSIP and OP may have a common aetiology, such as PM/DM.

Some patients with IIPs have rheumatological “flavor”, but do not meet any criteria of CTDs. These patients meet the criteria of interstitial pneumonia with autoimmune features (IPAF), which were proposed by the European Respiratory Society/American Thoracic Society “Task Force on Undifferentiated Form of Connective Tissue Disease-associated Interstitial Lung Disease” [8]. The concepts in the research statement were intended to provide a platform for the prospective study of these patients and were not intended as guidelines for clinical care. In that statement, Fischer et al. described the newly proposed classification criteria for IPAF, which consist of clinical, serologic, and morphologic domains [8]. “NSIP with OP overlap” pattern is a controversial finding on high-resolution computed tomography (HRCT) or surgical lung biopsy (SLB) specimens that has appeared in the

morphologic domain of the IPAF criteria, and it has attracted attention [8]. However, the incidence of "NSIP with OP overlap" pattern in IIPs, and its characteristics, findings on HRCT or SLB specimens, development of CTDs, and prognosis are not well known. Recently, we developed a cloud-based integrated database containing the clinical, radiological, and pathological data, along with outcomes, in a large number of patients who underwent SLB and were diagnosed with IIPs by multidisciplinary discussion (MDD) [1]. We conducted secondary analyses using this database to determine the frequency of "NSIP with OP overlap" pattern in IIPs and to identify differences from iNSIP. To the best of our knowledge, this is the first study to show the results of comprehensive analysis, including HRCT and SLB specimens, of long-term prognostic information in patients with "NSIP with OP overlap" pattern.

## Methods

### Study design and patients

This study was conducted on the basis of our previous study [1]. Briefly, in 39 institutions that were certified by the Japanese Respiratory Society, patients with IIPs who underwent HRCT and SLB from April 2009 to March 2014 were registered in the cloud-based integrated database, and were retrospectively assessed. The period of observation was calculated from the date of SLB until the date of the last visit or death. "Acute", "subacute", and "chronic" were defined as duration of <1 month, 1–3 months, and ≥3 months, respectively, from the onset of respiratory symptoms to the diagnosis of IIPs. This study was approved by the Institutional Review Board of the Hamamatsu University School of Medicine (approval number: E14-360).

**Conducting web-based MDD using cloud-based integrated database**

Clinical, radiological, and pathological data files were uploaded to each web server separately, and web-based MDD was performed for all cases as described by Fujisawa et al. [1]. Briefly, a clinician, radiologist, and pathologist, all experts in interstitial lung diseases, each used the database to examine the case records by themselves, after which they discussed the case via video-conferencing (Arcstar Web Conferencing: NTT Communications Co., Ltd, Tokyo, Japan), leading to a multidisciplinary diagnosis. We had four MDD teams. All experts have a minimum of 10 years of experience in the diagnosis of interstitial lung diseases including IIPs, and they are each currently working in university hospitals or interstitial lung disease centers [1]. If CTDs newly developed earlier than 6 months after the first diagnosis of IIPs by MDD, such patients were excluded from this study.

**Definition of "NSIP with OP overlap" pattern based on pathological findings on SLB specimens**

In patients with unclassifiable IIP (UCIIP) according to the web-based MDD diagnosis [1], those who had an NSIP and OP pattern without a UIP pattern on SLB specimens were defined as "NSIP with OP overlap" pattern. Precise definition was described in Supplementary material. In addition to pathological findings, which the MDD teams assessed, two pulmonary pathologists (MK and TT) reviewed specimens of "NSIP with OP overlap" pattern or iNSIP, and added further assessments. The basic definitions of the pathological findings are shown in Supplementary material. Furthermore, two lung radiologists (HS and HS) reviewed HRCT scans and added further assessments. When the score differed between observers, a consensus was reached after discussion.

**Definitions of HRCT findings**

The definitions of HRCT findings were followed to the Glossary of Terms by Fleischner Society [9]. In the HRCT findings, the presence of subpleural ground-glass attenuation (GGA), fibrotic cysts, honeycombing, traction bronchiectasis, volume loss, findings of PPFE and emphysema were evaluated. Fibrotic cysts were defined as cystic lesion caused by fibrosis and surrounded by GGA, reticular opacity and/or traction bronchiectasis. Findings of PPFE was defined as subpleural consolidation of upper lung such as main radiological findings of idiopathic PPFE [10]. And the extent of total lung lesion, fibrotic lesion (such as ground-glass opacity with traction bronchiectasis, reticular opacity and fibrotic cysts) and air-space consolidation were scored using following five scales; 0: none, 1: less than 5%, 2: 5-25%, 3: 25-50%, 4: more than 50%. The distribution was evaluated for left-right difference, craniocaudal and transverse axis predominant. The distribution in transvers axis was classified to 7 groups: none, peripheral, peripheral and peribronchovascular, peribronchovascular, diffuse, patchy, no dominancy. Peripheral predominant distribution was classified as a predominance of findings in the outer third of the lung. Peribronchovascular predominant distribution was classified as a predominance of findings along the bronchi and vessels. Diffuse distribution was classified as extensive lesions that occupied most of the lung field and showed no zonal predominance. Patchy distribution was classified as patchy distribution that scattered in the lung field. No dominancy was classified as the distribution that did not apply to the distribution listed above. The distribution in craniocaudal axis was classified to upper-predominant, equivalent and lower-predominant. The upper predominant was considered when the abnormalities were the most extensive above the level of the tracheal carina, and the lower predominant distribution was considered when the abnormalities were most extensive below the level of the tracheal carina.

**Statistical analysis**

Statistical analysis was performed using JMP-13.1.0 (SAS Institute Inc., Cary, NC, USA) and EZR 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [11]. Categorical data were compared using the $\chi^2$ test or Fisher's exact probability test for independence, and continuous data were compared using the Wilcoxon rank sum test. Occurrence of acute exacerbation (AE) of IIPs was estimated considering the death before AE as a competing event, and analysed using Gray's method. Occurrence of CTDs during the observation period and overall survival of patient groups were estimated using Kaplan-Meier curves and the log-rank test. All tests were two-sided and statistical significance was set at $p < 0.05$.

## Results

### Incidence of "NSIP with OP overlap" pattern and iNSIP in patients with IIPs

Among 524 participants who were enrolled from 39 institutes, 444 patients with IIPs after MDD diagnosis were included (Figure 1). Among these patients, 21 with "NSIP with OP overlap" pattern and 44 patients with iNSIP were thoroughly evaluated. Patients with "NSIP with OP overlap" pattern were basically classified as UCIIP after diagnosis by MDD. The incidence of "NSIP with OP overlap" pattern in all patients with IIPs was 4.7% (21/444) and that of iNSIP was 9.9% (44/444). The incidence of "NSIP with OP overlap" pattern in UCIIP was 12.5% (21/168).

### Demographic data, physiologic and laboratory data, bronchoalveolar lavage, and treatment in patients with "NSIP with OP overlap" pattern or iNSIP

Clinical characteristics of all patients with "NSIP with OP overlap" pattern, including physiological examination findings and treatments, were compared with those in patients with

iNSIP (Table 1). The median age of patients with "NSIP with OP overlap" pattern was 60 years old, and these patients were predominantly women (57.1%, 12/21) and ex-smoker (57.1%, 12/21), but these characteristics were not significantly different from those of iNSIP. In patients with "NSIP with OP overlap" pattern, chronic onset was the most common type of onset (57.1%). However, there was a tendency for a higher incidence of subacute onset in patients with "NSIP with OP overlap" pattern than in those of iNSIP (33.3% vs. 11.4%, p=0.058). The proportion of lymphocytes and eosinophils in bronchoalveolar lavage were significantly higher in patients with "NSIP with OP overlap" pattern than in those with iNSIP (28% vs. 11%, p=0.024; 4.5% vs. 1%, p=0.016, respectively). Administration of corticosteroids or immunosuppressants was not different between the groups. Nearly half of the patients fulfilled IPAF criteria, but no significant difference was found between iNSIP and "NSIP with OP overlap" pattern (47.7% vs. 42.9, p=0.712). As show in Table 1, 9 of 21 patients with "NSIP with OP overlap" pattern met IPAF criteria. In these 9 patients, 6 fulfilled serologic domain and morphologic domain, 2 fulfilled clinical domain and morphologic domain, and one fulfilled all 3 domains.

**Symptoms, physical findings, and autoantibodies**

Symptoms, physical findings, and results of autoantibodies are shown in Table 2. Respiratory symptoms or CTD-related symptoms and physical findings were not different between the two groups. No significant differences in any of the antibodies tested were found between iNSIP and those with "NSIP with OP overlap" pattern. Positive rates were found for antinuclear antibody ≥1:160 (35% vs. 50%, respectively) and anti-aminoacyl tRNA synthetase antibody (9.8% vs. 11%, respectively).

**Comparison of findings on HRCT**

Representative HRCT images in patients with iNSIP or "NSIP with OP overlap" pattern are shown in Figure 2A and 2B, respectively. HRCT of iNSIP showed that bilateral, symmetrical, reticular, and ground glass attenuation (GGA) with lower lobe predominance (Figure 2A). Traction bronchiectasis without honeycombing was also observed. However, HRCT of "NSIP with OP overlap" pattern showed bilateral, symmetrical, and consolidation with lower lobe predominance (Figure 2B). Peripheral+peribronchovascular distribution and traction bronchiectasis without honeycombing were also observed. Comparisons of detailed HRCT findings between iNSIP and "NSIP with OP overlap" pattern is shown in Table 3. Patients with iNSIP had a significantly greater extent of fibrotic lung lesion ($p=0.024$), fibrotic cysts ($p=0.038$), and diffuse distribution in the transverse axis ($p=0.009$) than patients with "NSIP with OP overlap" pattern. In contrast, patients with "NSIP with OP overlap" pattern had a significantly greater extent of consolidation ($p<0.001$), more subpleural GGA ($p=0.036$), and more peripheral+peribronchovascular distribution in the transverse axis ($p=0.009$) than patients with iNSIP. Other findings, such as traction bronchiectasis or emphysematous change, were not different between the groups.

**Comparison of findings in SLB specimens**

Representative histopathologic images in patients with iNSIP or "NSIP with OP overlap" pattern are shown in Figure 2C and 2D, respectively. In 44 patients with iNSIP, 42 were pathologically diagnosed as fibrotic NSIP pattern and 2 were done as cellular NSIP pattern. Patients with iNSIP showed a temporally and spatially uniform mixture of interstitial fibrosis and infiltration of mononuclear cells (Figure 2C; stained with Hematoxylin-Eosin (HE) and Elastica-van Gieson (EVG)). However, patients with "NSIP with OP overlap" pattern showed fibroblast plugs in the alveolar space (Figure 2D; stained with HE and EVG). Temporally and spatially uniform interstitial lung lesions were also observed, similar to iNSIP. Comparison of

detailed pathological findings between iNSIP and "NSIP with OP overlap" pattern is shown in Table 4. A significantly higher incidence of mild-bronchiolitis was found in patients with iNSIP than in those with "NSIP with OP overlap" pattern (p=0.036). However, presence of bronchiolitis was not related with the development of CTD (p=0.963). Findings that suggested CTD, such as lymphoid aggregation with a germinal center, plasma cell infiltration, perivascular collagen deposition, and pleuritis [12], were often observed, but there were no significant differences between the groups.

**Newly-developed CTDs during follow-up**

Patients were followed up for a median of 70.9 months from diagnosis of IIPs. During follow-up, CTDs newly developed in 9 of 44 (3.3%/year) patients with iNSIP and in 2 of 21 (1.6%/year) patients with "NSIP with OP overlap" pattern. The cumulative incidence of CTD was not significantly different between iNSIP and "NSIP with OP overlap" pattern (log-rank, p=0.378; Figure 3A). However, the incidence of CTDs in patients with iNSIP was significantly higher than that of patients with IPF or UCIIP other than "NSIP with OP overlap" pattern (Figure 3B; p<0.01). On the other hand, the incidence of CTD was not significantly different between iNSIP and "NSIP with OP overlap" pattern (p=0.304; Figure 3B). In patients with iNSIP, DM accounted for 56% (5/9 patients, Figure 3B). In patients with "NSIP with OP overlap" pattern, only PM and DM developed (one patient each). However, in patients with IPF, rheumatoid arthritis (5/8 patients) and microscopic polyangiitis (2/8 patients) were the dominant CTDs. In patients with UCIIP other than "NSIP with OP overlap" pattern, Sjogren's syndrome (4/8 patients) and rheumatoid arthritis (3/8 patients) were the dominant CTDs. Patients meeting IPAF criteria tended to have more newly-developed CTDs than those with non-IPAF, but the frequencies were not significantly different between IPAF and non-IPAF (25.0% and 11.8%, p=0.175).

**Changes in physiologic functions, development of AE of IP, and mortality**

During follow-up period from diagnosis of IIPs, changes in %forced vital capacity were not significantly different between patients with iNSIP and those with "NSIP with OP overlap" pattern (median 6.4% and 10.3%, respectively, p=0.335; Figure 4A). In addition, changes in %diffusion lung capacity for carbon monoxide were also not significantly different between patients with iNSIP and those with "NSIP with OP overlap" pattern (median 6.1% and 7.0%, respectively, p=0.594; Figure 4B). During follow-up period, acute exacerbation of IP (AE-IP) appeared in 7 of 44 (2.6%/year) patients with iNSIP and in 5 of 21 (4.1%/year) patients with "NSIP with OP overlap" pattern. The cumulative incidence of AE-IP was not significantly different between patients with iNSIP and those with "NSIP with OP overlap" pattern (Gray's test, p=0.493; Figure 4C). Significant differences were not found between onset forms and the development of AE (p=0.262), or between exudate of fibrin on lung histopathology and the development of AE (p=0.221). The survival rates were also not significantly different between the groups (log-rank test, p=0.683; Figure 4D). In patients with iNSIP or "NSIP with OP overlap" pattern, the 5-year survival rates were as high as 91.2% and 100%, respectively.

## Discussion

In the present study, we retrospectively studied 444 patients with IIPs who underwent surgical lung biopsy and diagnosis by MDD, and found 44 (9.9%) patients with iNSIP and 21 (4.7%) patients with "NSIP with OP overlap" pattern. Although no difference in demographic data was found, patients with "NSIP with OP overlap" pattern showed a greater extent of consolidation, more subpleural GGA, and more peripheral+bronchovascular distribution on

HRCT than those with iNSIP. More than 40% of these patients in both groups met IPAF criteria. The frequency of new CTDs after the diagnosis of IIPs was similar between the iNSIP and "NSIP with OP overlap" pattern groups, and PM/DM were the most frequent CTDs in both groups. The incidence of AE-IP and the survival rates were similar in both groups. Therefore, although "NSIP with OP overlap" pattern is basically included in UCIIP and has several different findings from iNSIP, it shows similar relationships with CTDs, especially PM/DM, and has similar clinical characteristics to those of iNSIP.

Either an NSIP- or OP-pattern is often found as CTD-related IP [2-4, 13], and mutual CTDs that is related to NSIP and OP are PM/DM. These findings led us to hypothesize that "NSIP with OP overlap" pattern can precede lung manifestation of PM/DM. Furthermore, NSIP, OP, and "NSIP with OP overlap" pattern are included in the criteria of IPAF [8], and "NSIP with OP overlap" pattern has attracted attention. In fact, we previously reported that 17.1% of patients with iNSIP later developed CTDs and half of them were DM [14]. Furthermore, "NSIP with OP overlap" pattern was reported to be associated with CTDs [15]. In the present study, the incidence of IPAF was as high as 42.9% in "NSIP with OP overlap" pattern, which appears higher than that in a previous report [16, 17]. In previous studies regarding treatment response and prognosis of "NSIP with OP overlap" pattern, although two cases of "NSIP with OP overlap" pattern were improved by steroid treatment [18], "NSIP with OP overlap" pattern was related to unfavorable disease progression compared with OP [19]. However, the difference in prognosis between iNSIP and "NSIP with OP overlap" pattern is unknown. In the present study, the profile of immunosuppressive treatments was not different between iNSIP and "NSIP with OP overlap" pattern. Additionally, the incidence of AE-IP was low in iNSIP and "NSIP with OP overlap" pattern compared to that of IPF [20], and the survival rate was also similarly favorable between these groups. Therefore, patients with "NSIP with OP overlap" pattern may not have to be strictly distinguished from those with iNSIP in terms of

clinical treatment and prognosis.

"NSIP with OP overlap" pattern was classified as UCIIP according to the web-based MDD diagnosis. The presence of overlapping findings that are common to multiple distinct ILD subtypes leads UCIIP in MDD diagnosis of IIPs [21]. In the present study, SLB specimens that had an NSIP and OP pattern simultaneously without a UIP pattern were searchingly defined as "NSIP with OP overlap" pattern, and 4.7% in all patients with IIPs and 12.5% in those with UCIIP were classified as "NSIP with OP overlap" pattern. Consequently, patients with "NSIP with OP overlap" pattern had similar clinical characteristics, incidence of CTDs and AE-IP, and prognosis to those with iNSIP, whereas each pattern showed different HRCT findings. Similarly, Huo et al. also reported that OP components did not affect the prognosis of patients with iNSIP [5]. Therefore, patients with "NSIP with OP overlap" pattern, which is basically classified as UCIIPs, may have to be strictly distinguished from other UCIIPs to receive proper treatments.

This study has several limitations. First, the data were retrospectively analysed. Therefore, there were some missing data in each patient. Second, only a small number of patients with "NSIP with OP overlap" pattern were included in those with UCIIP. Re-examination of all cases of COP, NSIP, and UCIIP may be necessary if this controversial entity of "NSIP with OP overlap" pattern is established in the future. Third, the number of patients with cryptogenic OP was only five and this was too small for comparison because the integrated database included only patients who underwent SLB. Fourth, the location of SLB may not have been adequate and not reflected representative pathology in all patients. Therefore, a larger prospective study with less selection bias taking advantage of HRCT is required to accurately evaluate the clinical features and treatment responses in patients with "NSIP with OP overlap" pattern.

In conclusion, we retrospectively studied 444 patients with IIPs and found 44 (9.9%)

patients with iNSIP and 21 (4.7%) patients with “NSIP with OP overlap” pattern who were basically diagnosed as UCIIP by MDD. The incidence of new CTDs after the diagnosis of IIPs was similar between the groups and PM/DM were the most frequent CTDs in both groups. Nearly half of the patients with “NSIP with OP overlap” pattern fulfilled IPAF criteria. The incidence of AE-IP was low and the survival rate was favorable, and these were similar between the groups. These findings should be useful for understanding “NSIP with OP overlap” pattern in clinical practice. Further evaluation is required to precisely describe “NSIP with OP overlap” pattern and its relationship to CTDs, especially PM/DM.

## Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Figure Legends

**Figure 1** Study profile. Among 524 participants who were enrolled from 39 institutes, 444 patients with IIPs after web-based MDD diagnosis were studied. Among these patients, 44 with iNSIP and 21 with "NSIP with OP overlap" pattern were thoroughly evaluated. Three hundred seventy-four patients with other IIPs included 200 patients with idiopathic pulmonary fibrosis and 147 patients with unclassifiable IIP. Abbreviations; IIPs: idiopathic interstitial pneumonias, MDD: multidisciplinary discussion, iNSIP: idiopathic nonspecific interstitial pneumonia, OP: organizing pneumonia.

**Figure 2** Representative HRCT and histopathology of SLB specimens. HRCT images of a patient with iNSIP (A) and a patient with "NSIP with OP overlap" pattern (B) are shown. A representative HRCT image of iNSIP shows that reticular and GGA with lower lobe predominance (A). Traction bronchiectasis without honeycombing can also be seen. A representative HRCT image of "NSIP with OP overlap" pattern shows consolidation with lower lobe predominance (B). Peripheral (arrowhead)+peribronchovascular distribution and traction bronchiectasis (arrow) without honeycombing can also be seen. Representative histopathological images in patients with iNSIP (C; stained with Hematoxylin-Eosin (HE) and Elastica-van Gieson (EVG)) or "NSIP with OP overlap" pattern (D; stained with HE and EVG) are shown. Representative histopathological images of iNSIP show a temporally and spatially uniform mixture of interstitial fibrosis and infiltration of mononuclear cells (C). Representative histopathological images of "NSIP with OP overlap" pattern show fibroblast plugs in the alveolar space (D, black arrows). Temporally and spatially uniform interstitial lung lesion can also be seen. Abbreviations; HRCT: high-resolution computed tomography, SLB: surgical lung biopsy, IIPs: idiopathic interstitial pneumonias, MDD: multidisciplinary

discussion, iNSIP: idiopathic nonspecific interstitial pneumonia, OP: organizing pneumonia, GGA: ground glass attenuation, HE: haematoxylin-eosin.

**Figure 3** Cumulative incidence of newly-developed CTDs during follow-up and types of CTDs. During the follow-up period, CTDs developed in 9 of 44 (3.3%/year) patients with iNSIP and 2 of 21 (1.6%/year) patients with "NSIP with OP overlap" pattern. The cumulative incidence of CTDs was not significantly different between iNSIP and "NSIP with OP overlap" pattern (A, log-rank test, p=0.378). However, the incidence of CTDs in iNSIP was significantly higher than that of IPF or UCIIP other than "NSIP with OP overlap" pattern (B, p<0.01). In patients with iNSIP, dermatomyositis accounted for 56% (5/9 patients). In patients with "NSIP with OP overlap" pattern, only PM and DM developed (one patient each). In patients with IPF, RA (5/8 patients) and MPA (2/8 patients) were the dominant CTDs developed. In UCIIP other than "NSIP with OP overlap" pattern, SjS (4/8 patients) and RA (3/8 patients) were the dominant CTDs. Abbreviations; CTD: connective tissue disease, IIPs: idiopathic interstitial pneumonias, iNSIP: idiopathic nonspecific interstitial pneumonia, OP: organizing pneumonia, IPF: idiopathic pulmonary fibrosis, UCIIP: unclassifiable IIP, PM/DM: polymyositis/dermatomyositis, RA: rheumatoid arthritis, MPA: microscopic polyangiitis, SLE: systemic lupus erythematosus, SjS: Sjogren's syndrome.

**Figure 4** Changes in physiologic functions, appearance of acute exacerbation of interstitial pneumonia, and mortality. During follow-up period from diagnosis of IIPs, changes in % FVC were not significantly different between patients with iNSIP and those with "NSIP with OP overlap" pattern (A, median 6.4% and 10.3%, respectively, p=0.335). In addition, changes in % $DL_{CO}$ were also not significantly different between patients with iNSIP and those with "NSIP with OP overlap" pattern (B, median 6.1% and 7.0%, respectively, p=0.594). During

the follow-up period, AE-IP appeared in 7 of 44 (2.6%/year) patients with iNSIP and 5 of 21 (4.1%/year) patients with "NSIP with OP overlap" pattern. The cumulative incidence of AE-IP was not significantly difference between iNSIP and "NSIP with OP overlap" pattern (C, Gray's test, p=0.493). The survival rate was not different between iNSIP and "NSIP with OP overlap" pattern (D, log-rank test, p=0.683). In patients with iNSIP and those with "NSIP with OP overlap" pattern, the 5-yare survival rates were 91.2% and 100%, respectively. Abbreviations; FVC: forced vital capacity, $DL_{CO}$: diffusion lung capacity for carbon monoxide, AE-IP: acute exacerbation of interstitial pneumonia, iNSIP: idiopathic nonspecific interstitial pneumonia, OP: organizing pneumonia.

# Highlights

- A controversial disease entity of “NSIP with OP overlap” pattern attracts attention in IPAF criteria.
- In 444 patients with IIPs, 21 (4.7%) were classified as histopathologically-defined “NSIP with OP overlap” pattern.
- The frequency of CTDs, mainly PM/DM, and that of acute exacerbation in “NSIP with OP overlap” pattern were similar to those of idiopathic NSIP.
- Prognosis in patients with “NSIP with OP overlap” pattern was favorable and also similar to that of idiopathic NSIP.

# Methods

### Causes of unclassifiable idiopathic interstitial pneumonia (UCIIP)

Causes of UCIIP include the following situations [1]: (1) major discordance between clinical, radiologic, and pathologic findings that may occur in the following situations: (a) previous therapy resulting in substantial alteration of radiologic or histologic findings; (b) new entity, or unusual variant of recognized entity, not adequately characterized by the current American Thoracic Society (ATS)/European Respiratory Society (ERS) classification; and (c) multiple high-resolution computed tomography (HRCT) and/or pathologic patterns that may be encountered in patients with idiopathic interstitial pneumonia, and (2) inadequate clinical, radiologic, or pathologic data.

### Precise definition of "NSIP with OP overlap" pattern

Unclassifiable idiopathic interstitial pneumonia (UCIIP) was diagnosed based on web-based multidisciplinary discussion (MDD) [2]. Histological pattern/component was evaluated based on 2011 ATS/ERS/JRS/ALAT idiopathic pulmonary fibrosis (IPF) statement [3] and 2013 ATS/ERS idiopathic interstitial pneumonia (IIP) classification statement [1]. The MDD diagnosis category included IPF, idiopathic nonspecific interstitial pneumonia (iNSIP), cryptogenic organizing pneumonia (COP), desquamative interstitial pneumonia/respiratory bronchiolitis-associated interstitial lung disease, acute interstitial pneumonia, lymphoid interstitial pneumonia, idiopathic pleuroparenchymal fibroelastosis, and UCIIP.

The database also includes histological pattern/component including usual interstitial pneumonia pattern, NSIP pattern, OP pattern, diffuse alveolar pattern, desquamative interstitial pneumonia pattern, respiratory bronchiolitis pattern, lymphocytic interstitial pneumonia pattern, pleuroparenchymal fibroelastosis pattern, and others.

The entry criteria of "NSIP with OP overlap" pattern include (i) patient was diagnosed with UCIIP by MDD, (ii) it has histological pattern/component of NSIP pattern/component as well as OP pattern/component, (iii) it does not have UIP pattern/component.

**Definitions of pathological findings**

- Fibroblastic focus: The fibroplasia/granulation tissue with background of chronic dense fibrosis.
- Organizing pneumonia: The loose fibroplasia/granulation tissue. Mainly polypoid type fibroplasia/granulation tissue are stated inside the alveolar spaces, and in some case, the fibroplasia/granulation tissue incorporated with alveolar spaces. Note that the incorporated fibroplasia/granulation tissue are NOT adjacent to chronic dense fibrosis.
- Microscopic honeycombing: The multiple cystic lesions surrounded by chronic dense fibrosis.
- Aggregation of alveolar macrophages: The macrophages seen in alveolar spaces, which sometimes demonstrate aggregation.
- Exudate of fibrin: The eosinophilic exudate material inside the alveolar space as well as organizing pneumonia. Note that dense membranous eosinophilic material was excluded as hyaline membrane.
- Granuloma: The various inflammatory cell accumulation/nodule mainly including epithelioid histiocytes.
- Bronchiolitis: The lymphocytic infiltration around the small airway with or without mild airway centered fibrosis.
- Lymphoid aggregation with germinal center: The nodular accumulation of lymphocytes with pale round area of centrocytes. Same as the lymphoid follicle with germinal center seen in lymph nodes.

- Plasma cell infiltration: The plasma cells infiltration on alveolar septum and /or fibrous area.
- Perivascular collagen deposition: The concentric collagen fiber deposition around the middle sized pulmonary vain.
- Pleuritis: The inflammatory cell infiltration in the visceral pleura with or without fibrous change.
- Fibroelastosis: Accumulation of elastic fiber in the dense fibrosis, mainly seen beneath the pleura and interlobular septum.
- Cyst: The unclassifiable cystic lesions other than honeycombing, bullae, and emphysematous change.

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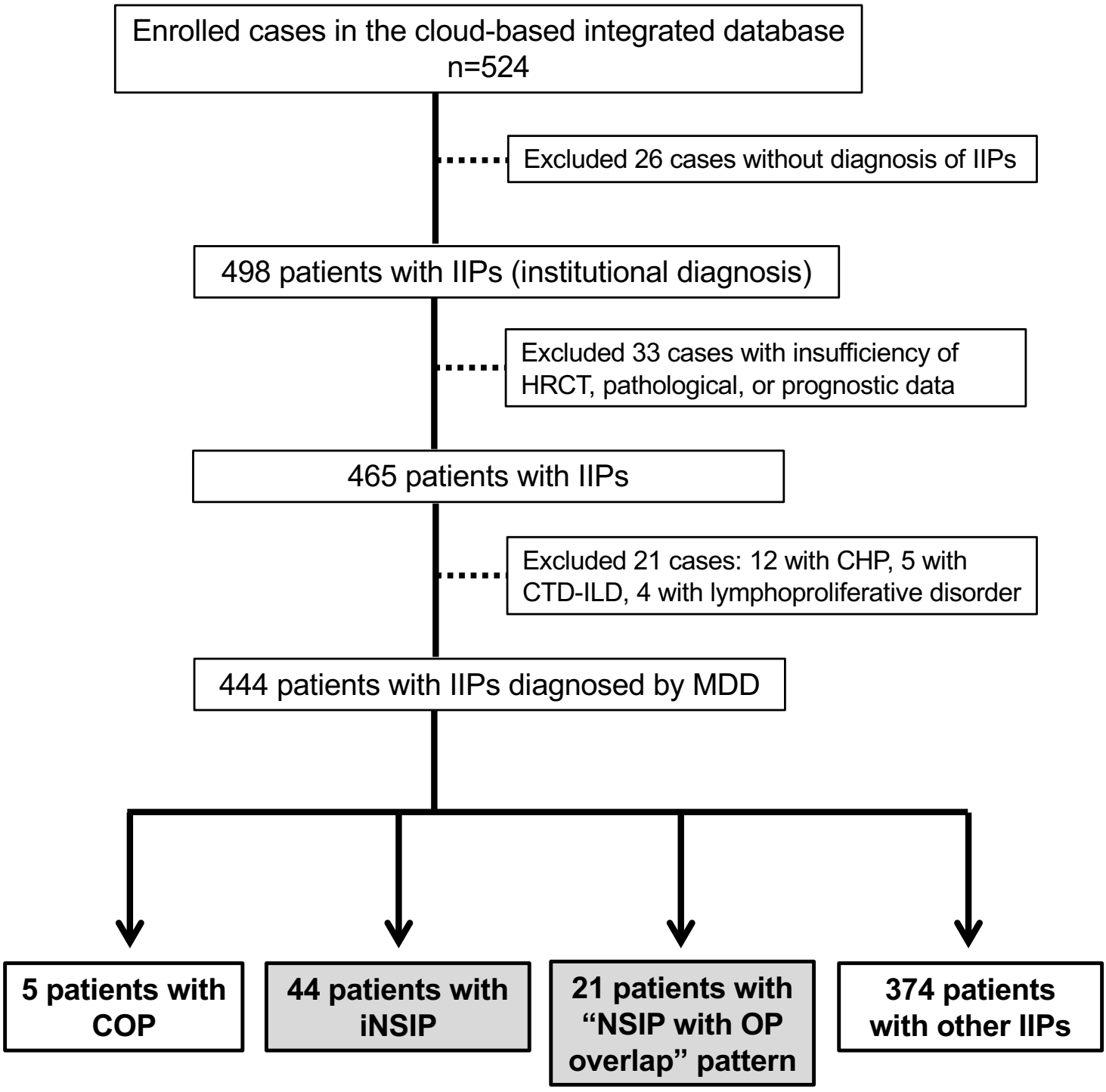
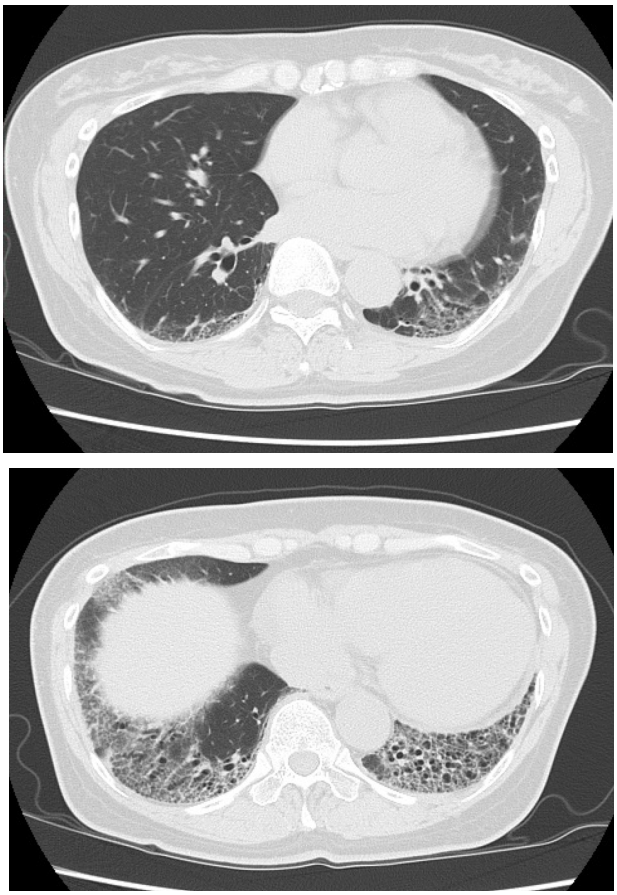
# Figure 1

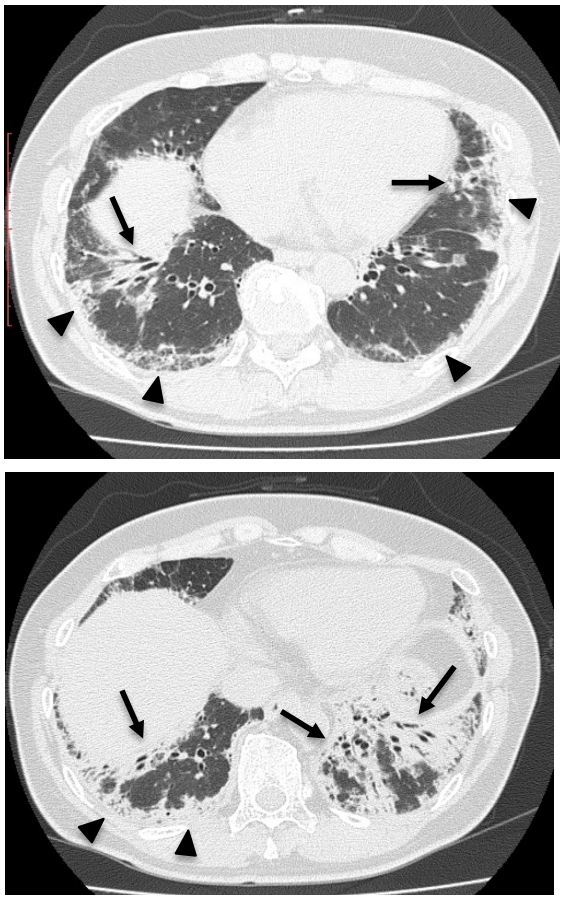

Enrolled cases in the cloud-based integrated database
n=524
Excluded 26 cases without diagnosis of IIPs
498 patients with IIPs (institutional diagnosis)
Excluded 33 cases with insufficiency of HRCT, pathological, or prognostic data
465 patients with IIPs
Excluded 21 cases: 12 with CHP, 5 with CTD-ILD, 4 with lymphoproliferative disorder
444 patients with IIPs diagnosed by MDD
5 patients with COP
44 patients with iNSIP
21 patients with "NSIP with OP overlap" pattern
374 patients with other IIPs

# Figure 2

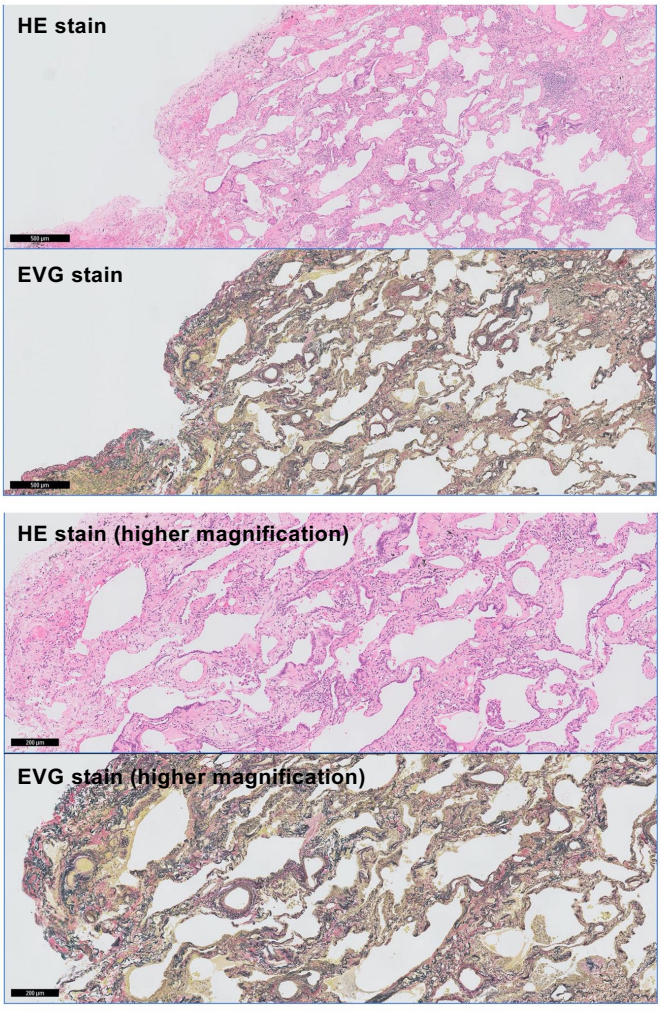
## A iNSIP



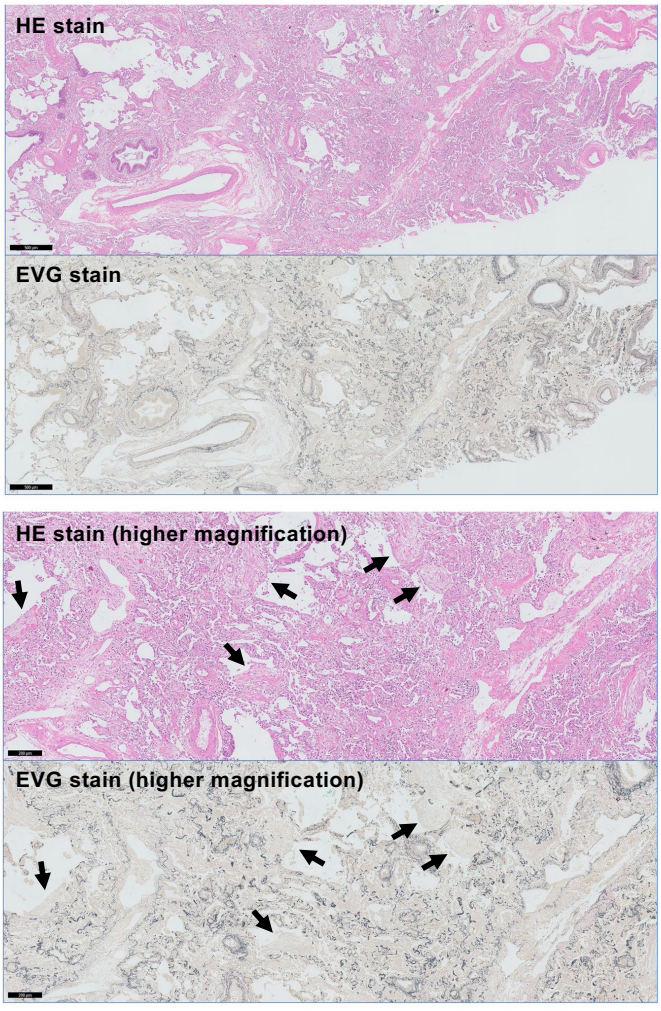
## B NSIP with OP overlap pattern



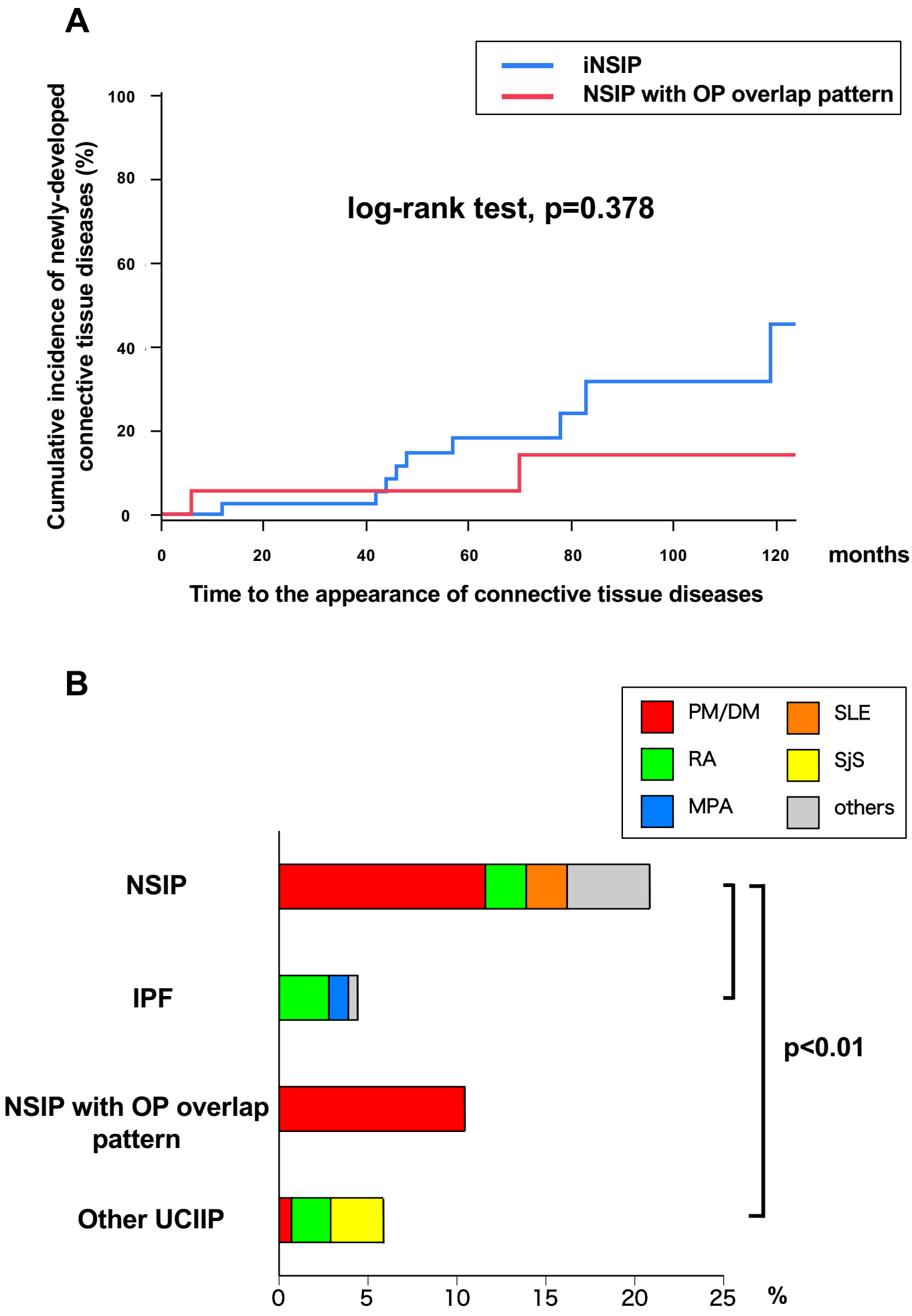
## C iNSIP




## D NSIP with OP overlap pattern



# Figure 3


A
iNSIP
NSIP with OP overlap pattern
log-rank test, p=0.378
Cumulative incidence of newly-developed connective tissue diseases (%)
100
80
60
40
20
0
0
20
40
60
80
100
120
months
Time to the appearance of connective tissue diseases
B
PM/DM
SLE
RA
SjS
MPA
others
NSIP
IPF
NSIP with OP overlap pattern
Other UCIIP
p<0.01
0
5
10
15
20
25
%

# Figure 4

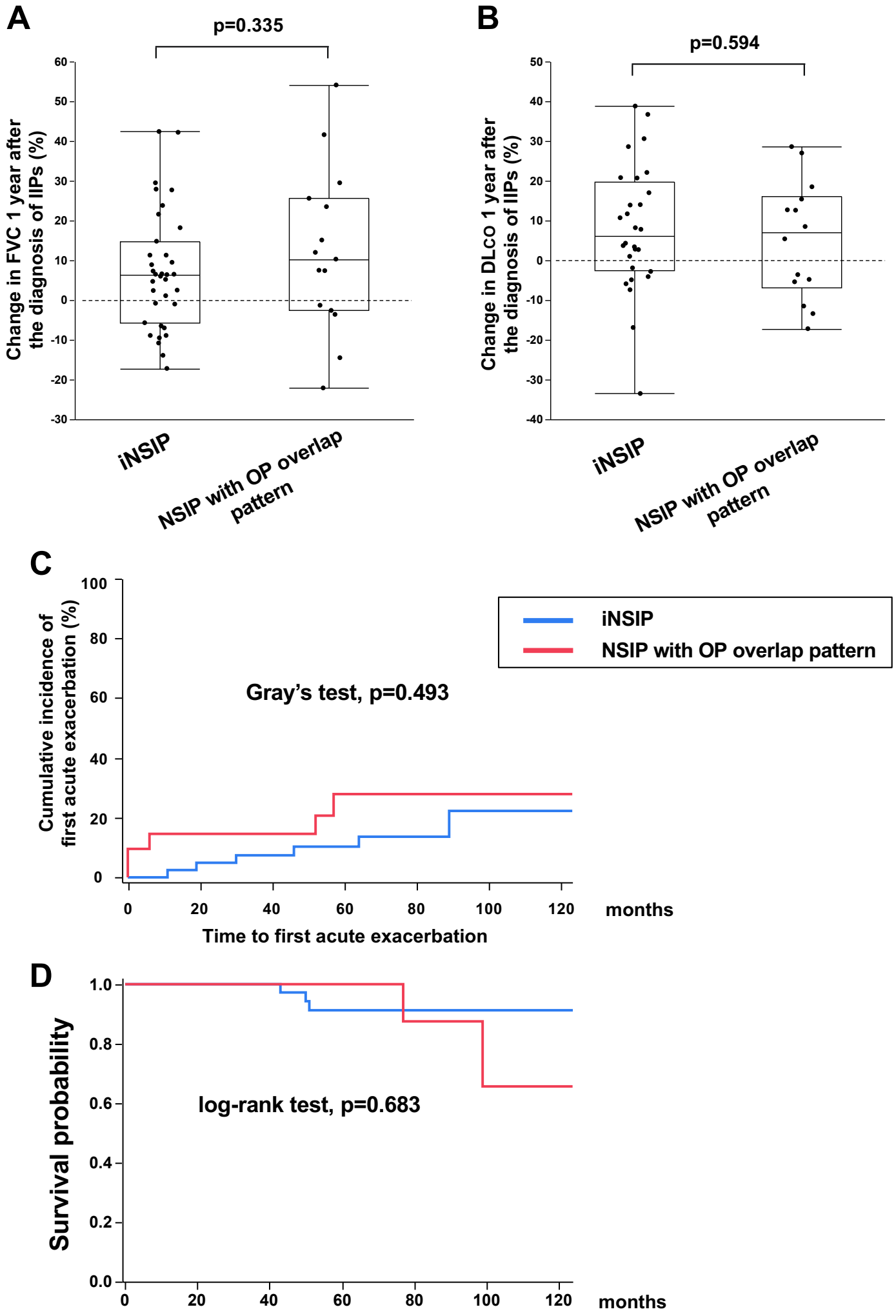

A
p=0.335
Change in FVC 1 year after the diagnosis of IIPs (%)
60
50
40
30
20
10
0
-10
-20
-30
iNSIP
NSIP with OP overlap pattern
B
p=0.594
Change in DLco 1 year after the diagnosis of IIPs (%)
50
40
30
20
10
0
-10
-20
-30
-40
iNSIP
NSIP with OP overlap pattern
C
Cumulative incidence of first acute exacerbation (%)
100
80
60
40
20
0
iNSIP
NSIP with OP overlap pattern
Gray's test, p=0.493
0
20
40
60
80
100
120
months
Time to first acute exacerbation
D
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
log-rank test, p=0.683
0
20
40
60
80
100
120
months

**Table 1** Demographic data, physiologic and laboratory data, bronchoalveolar lavage, and treatments in patients with iNSIP or "NSIP with OP overlap"

| | **iNSIP** (median (range)) | **NSIP with OP overlap pattern** (median (range)) | **p-value** |
|---|---|---|---|
| Number of patients in IIPs (%) | 44 (9.9) | 21 (4.7) | – |
| Age, years old | 63 (28, 82) | 60 (20, 76) | 0.710 |
| Sex, male / female | 20 / 24 | 9 /12 | 0.844 |
| Familial history of IP, + / – / unknown | 1 / 38 / 5 | 0 / 17 / 4 | 0.495 |
| Dust inhalation history, + / – / unknown | 3 / 35 / 6 | 5 / 14 / 2 | 0.182 |
| Smoking history, current / ex / never / unknown | 3 / 18 / 21 / 2 | 2 / 6 / 12 / 1 | 0.473 |
| Smoking, Brinkman Index | 9 (0, 1760) | 0 (0, 2250) | 0.771 |
| Onset forms, Acute / subacute / chronic / unknown | 2 / 5 / 35 / 2 | 0 / 7 / 12 / 2 | 0.058 |
| IPAF, + / – (%) | 21 / 23 (47.7) | 9 /12 (42.9) | 0.712 |
| FVC, % predicted | 74.6 (46.4, 114.7) | 70.0 (41.4, 101.7) | 0.162 |
| $DL_{CO}$, % predicted | 55.4 (24.5, 131) | 58.6 (34.3, 85.5) | 0.975 |
| $PaO_2$, Torr | 81.8 (63.5, 150) | 83.3 (69.6, 96.1) | 0.645 |
| 6MWD, m | 486 (220, 893) | 438 (226, 680) | 0.192 |
| $mSpO_2$ in 6MWT, m | 90 (66, 98) | 88 (81, 97) | 0.838 |
| KL-6, U/mL | 1642 (404, 8512) | 1772 (339, 5541) | 0.752 |
| SP-D, ng/mL | 214 (17, 1540) | 207 (29, 409) | 0.926 |
| LDH, U/L | 229 (135, 368) | 239 (171, 372) | 0.337 |
| BAL Lymphocyte, % | 11 (0, 61.3) | 28 (4, 85) | 0.024 |
| Neutrophil, % | 2.2 (0, 30.6) | 2.8 (0, 16) | 0.478 |
| Eosinophil, % | 1 (0, 9) | 4.5 (0, 23) | 0.016 |
| CD4/8 ratio | 0.7 (0.1, 1.7) | 0.5 (0.3, 1.7) | 0.547 |
| Administration of corticosteroids, + / – / unknown | 36 / 7 / 1 | 18 / 2 / 1 | 0.496 |
| Administration of Immunosuppressants, + / – / unknown | 26 / 17 / 1 | 10 / 10 / 1 | 0.436 |
| Observation period from the IP diagnosis, months | 74.5 (1, 347) | 70 (4, 211) | 0.801 |

Abbreviations; IP: interstitial pneumonia, COP: cryptogenic organizing pneumonia, iNSIP: idiopathic nonspecific interstitial pneumonia, IPAF: interstitial pneumonia with autoimmune features, FVC: forced vital capacity, $DL_{CO}$: diffusion lung capacity for carbon monoxide, 6MWD: 6-minute walk distance, KL-6: Krebs von den Lungen-6, SP-D: surfactant protein D, LDH: lactate dehydrogenase, BAL: bronchoalveolar lavage.

**Table 2** Comparison of symptoms, physical findings, and autoantibodies between patients with iNSIP and those with "NSIP with OP overlap" pattern

| | **iNSIP** (n=44) | **NSIP with OP overlap pattern** (n=21) | **p-value** |
|---|---|---|---|
| Cough, + / – / unknown (%) | 30 / 14 / 0 (68) | 16 / 3 / 2 (89) | 0.173 |
| Sputum, + / – (%) | 8 / 35 (19) | 5 / 14 (26) | 0.498 |
| Dyspnea on exertion, mMRC, 0 / 1 / 2 / 3 / 4 | 12 / 19 / 4 / 3 / 1 | 5 / 10 / 2 / 1 / 0 | 0.909 |
| Mechanic hands, + / – (%) | 3 / 36 (7.7) | 0 / 19 (0) | 0.117 |
| Gottron's sign or papules, + / – (%) | 1 / 38 (2.5%) | 1 / 18 (5.3%) | 0.608 |
| Fingertip ulceration, + / – (%) | 0 / 39 (0) | 0 / 19 (0) | NS. |
| Raynaud's phenomenon, + / – (%) | 3 / 37 (7.5) | 2 / 16 (11.1) | 0.657 |
| Digital edema, + / – (%) | 1 / 37 (2.6) | 0 / 19 (0) | 0.365 |
| Palmar telangiectagia, + / – (%) | 1 / 36 (2.7) | 1 / 17 (5.6) | 0.607 |
| Dry symptoms, + / – (%) | 4 / 36 (10) | 1 / 18 (5.2) | 0.526 |
| ANA, ≥ 1:160; + / – (%) | 8 / 15 (35) | 3 / 3 (50) | 0.499 |
| Rheumatoid factor, + / – (%) | 6 / 35 (15) | 6 / 13 (32) | 0.137 |
| Anti-ARS antibody, + / – (%) | 4 / 37 (9.8) | 2 / 16 (11) | 0.875 |
| Anti-Scl-70 antibody, + / – (%) | 2 / 34 (5.6) | 0 / 18 (0) | 0.198 |
| Anti-centromere antibody, + / – (%) | 0 / 26 (0) | 0 / 13 (0) | NS. |
| Anti-SS-A antibody, + / – (%) | 3 / 34 (8.1) | 0 / 19 (0) | 0.109 |
| Anti-SS-B antibody, + / – (%) | 0 / 37 (0) | 0 / 19 (0) | NS. |
| Anti-CCP antibody, + / – (%) | 1 / 24 (4) | 1 / 11 (8.3) | 0.597 |
| Anti-U1-RNP antibody, + / – (%) | 0 / 30 (0) | 0 / 18 (0) | NS. |
| MPO-ANCA, + / – (%) | 2 / 37 (5.1) | 0 / 19 (0) | 0.203 |
| PR3-ANCA, + / – (%) | 0 / 36 (0) | 0 / 18 (0) | NS. |

Abbreviations; iNSIP: idiopathic nonspecific interstitial pneumonia, OP: organizing pneumonia, mMRC: modified medical research council, ANA: antinuclear antibody, ARS: aminoacyl tRNA synthetase, CCP: cyclic citrullinated peptide, RNP: ribonucleoprotein, ANCA: antineutrophil cytoplasmic antibodies. NS: not significant.

**Table 3** Comparison of HRCT findings between patients with iNSIP and those with "NSIP with OP overlap" pattern

| | **iNSIP** (n=44) | **NSIP with OP overlap pattern** (n=21) | **p-value** |
|---|---|---|---|
| Extent of total lung lesion, none / <5% / 5-25% / 25-50% / ≥50% | 0 / 0 / 8 / 25 / 11 | 0 / 0 / 5 / 12 / 4 | 0.801 |
| Extent of fibrotic lung lesion, none / <5% / 5-25% / 25-50% / ≥50% | 0 / 3 / 17 / 17 / 7 | 1 / 5 / 9 / 6 / 0 | 0.024 |
| Extent of consolidation, none / <5% / 5-25% / 25-50% / ≥50% | 23 / 14 / 6 / 1 / 0 | 2 / 6 / 9 / 4 / 0 | <0.001 |
| Subpleural GGA, + / – (%) | 13 / 31 (29.5) | 12 / 9 (57.1) | 0.036 |
| Fibrotic cysts, + / – (%) | 14 / 30 (31.8) | 2 / 19 (9.5) | 0.038 |
| Honeycombing, + / – (%) | 0 / 44 (0) | 0 / 21 (0) | NS. |
| Traction bronchiectasis, + / – (%) | 37 / 7 (84.1%) | 17 / 4 (80.9%) | 0.754 |
| Volume loss (upper lobe), + / – (%) | 4 / 40 (9.1) | 3 / 18 (14.3) | 0.536 |
| Volume loss (lower lobe), + / – (%) | 41 / 3 (93.2) | 20 / 1 (95.2) | 0.742 |
| Findings of PPFE, + / – (%) | 2 / 42 (4.5) | 0 / 21 (0) | 0.216 |
| Distribution in left-right axis bilateral / right-dominant / left-dominant | 38 / 3 / 3 | 19 / 2 / 0 | 0.287 |
| Distribution in craniocaudal axis lower-dominant / equivalent / upper-dominant | 40 / 4 / 0 | 18 / 3 / 0 | 0.536 |
| Distribution in transverse axis none / peripheral-dominant / peripheral+peribrochovascular / peribrochovascular / diffuse / patchy / no dominancy | 0 / 12 / 4 / 7 / 21 / 0 / 0 | 0 / 7 / 8 / 1 / 4 / 0 / 1 | 0.009 |
| Emphysematous finding, + / – (%) | 8 / 36 (18.2) | 2 / 19 (10) | 0.349 |

Abbreviations; HRCT: high-resolution computed tomography, iNSIP: idiopathic nonspecific interstitial pneumonia, OP: organizing pneumonia, GGA: ground glass attenuation, PPFE: pleuroparenchymal fibroelastosis. NS: not significant.

**Table 4** Comparison of pathological findings on surgical lung biopsy specimens between patients with iNSIP and those with "NSIP with OP overlap" pattern

| | **iNSIP** (n=44) | **NSIP with OP overlap pattern** (n=21) | **p-value** |
|---|---|---|---|
| Fibroblastic foci, none / mild / moderate / severe | 23 / 14 / 5 / 0 | 14 / 6 / 0 / 0 | 0.108 |
| Microscopic honeycombing, none / mild / moderate / severe | 34 / 4 / 2 / 0 | 19 / 1 / 0 / 0 | 0.332 |
| Aggregation of alveolar macrophages, none / mild / moderate / severe | 4 / 30 / 8 / 0 | 3 / 13 / 5 / 0 | 0.736 |
| Exudate of Fibrin, + / – (%) | 11 / 33 (25.0) | 9 / 12 (42.8) | 0.149 |
| Granuloma, + / – (%) | 7 / 33 (17.5) | 1 / 20 (4.8) | 0.132 |
| Bronchocentric fibrosis, + / – (%) | 15 / 25 (37.5) | 6 / 14 (30.0) | 0.563 |
| Bronchiolitis, none / mild / moderate / severe | 17 / 20 / 3 / 0 | 11 / 4 / 5 / 0 | 0.036 |
| Lymphoid aggregation with germinal center, none / mild / moderate / severe | 10 / 19 / 11 / 1 | 6 / 12 / 2 / 1 | 0.408 |
| Plasma cell infiltration, none / mild / moderate / severe | 0 / 23 / 18 / 3 | 0 / 11 / 6 / 4 | 0.296 |
| Perivascular collagen deposition, + / – (%) | 8 / 36 (18.2) | 6 / 15 (28.5) | 0.349 |
| Pleuritis, none / mild / moderate / severe | 23 / 15 / 1 / 0 | 11 / 10 / 0 / 0 | 0.539 |
| Fibroelastosis, none / mild / moderate / severe | 38 / 3 / 1 / 0 | 19 / 1 / 0 / 0 | 0.539 |
| Cyst, none / mild / moderate / severe | 33 / 7 / 2 / 0 | 19 / 2 / 0 / 0 | 0.302 |

Abbreviations; iNSIP: idiopathic nonspecific interstitial pneumonia, OP: organizing pneumonia.