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Korean Guidelines for Diagnosis and Management of Idiopathic Nonspecific Interstitial Pneumonia

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Abstract

Idiopathic nonspecific interstitial pneumonia (iNSIP) is recognized as a distinct entity among various types of idiopathic interstitial pneumonias. It is identified histologically by the nonspecific interstitial pneumonia pattern. A diagnosis of iNSIP is feasible once secondary causes or underlying diseases are ruled out. Usually presenting with respiratory symptoms such as shortness of breath and cough, iNSIP has a subacute or chronic course. It predominantly affects females aged 50 to 60 years who are non-smokers. Key imaging findings on chest high-resolution computed tomography include bilateral reticular opacities in lower lungs, traction bronchiectasis, reduced lung volumes and, ground-glass opacities. Abnormalities are typically diffuse across both lungs with subpleural distributions. Treatment often involves systemic steroids, either alone or in combination with other immunosuppressants, although evidence supporting effectiveness of these treatments is limited. Prognosis is generally more favorable for iNSIP than for idiopathic pulmonary fibrosis, with many studies reporting a 5-year survival rate above 70%. Antifibrotic agents should be considered in a condition, termed progressive pulmonary fibrosis, where pulmonary fibrosis progressively worsens.

Keywords: Interstitial Lung Disease; Idiopathic Nonspecific Interstitial Pneumonia; Diagnosis; Management

Introduction

Historically, idiopathic nonspecific interstitial pneumonia (iNSIP) was not recognized as a discrete disease entity but merely as a provisional grouping within various interstitial pneumonias. However, it is currently acknowledged as an independent disease distinguished by unique clinical characteristics from other interstitial lung diseases (ILDs)[1,2]. Diagnosis of iNSIP is achieved histologically through lung biopsy by identifying the nonspecific interstitial pneumonia (NSIP) pattern and excluding the possibility of other secondary causes or diseases.

The initial classification of NSIP as a distinct type of interstitial pneumonia was proposed by Katzenstein and Fiorelli[3] in 1994. They highlighted distinctive histopathological features of NSIP, which can be differentiated from usual interstitial pneumonia (UIP) by the

presence of both inflammation and fibrosis within the interstitium. Initially, recognition of NSIP as an independent disease was challenging due to its association with a variety of causes including connective tissue disease (CTD), environmental exposures to organic dust, and prior pulmonary damage. However, subsequent studies raised the possibility that it could be an independent disease. In 2002, the American Thoracic Society (ATS)/European Respiratory Society (ERS) international consensus classification tentatively categorized idiopathic interstitial pneumonia (IIP) into seven subtypes, with NSIP being provisionally categorized as a distinct type of IIP[4]. In 2008, According to a study by Travis et al.[2] in 2008 investigating 67 patients with iNSIP, this distinct clinical entity was more common among middle-aged, nonsmoking women and was associated with a favorable prognosis. The 2013 revision of the ATS/ERS international consensus classification definitively recognized iNSIP as an independent disease entity[1]. Histological findings similar to those of NSIP can also be seen in other conditions such as hypersensitivity pneumonitis (HP). To diagnose iNSIP, it is crucial to excluding other secondary causes or disease. A multidisciplinary approach is needed for its diagnosis.

Epidemiology

The incidence or prevalence of iNSIP is not clearly known. However, several retrospective cohort studies have estimated that its prevalence is about 1 to 9 per 100,000 people[5] or about 3 per million people[6].

Among IIPs, iNSIP is the second most prevalent form, constituting 14%–36%[7] of cases. A national survey conducted by the Korean Society of Tuberculosis and Respiratory Medicine in 2008 reported that iNSIP comprised 11.9% of 2,186 IIP patients, making it the second most common one after idiopathic pulmonary fibrosis (IPF)[8]. A cohort study from a Danish university hospital examined 431 cases of ILD between 2003 and 2009 and found that 7% of cases were iNSIP, ranking it fourth after IPF, CTD-ILD, and HP[6]. iNSIP showed a noted higher prevalence in females than in males, with a greater likelihood of occurrence in non-smokers and an earlier age of onset than IPF[2,8].

Recent studies have also identified radiological and pathological similarities between interstitial lung abnormality, a precursor of interstitial pneumonia, and iNSIP[9]. This correlation underscores the need for further research to explore these association more deeply.

Clinical Characteristics

Clinical symptoms of iNSIP usually display a subacute or chronic course, manifesting as shortness of breath and coughing over an average duration of 6 months. These symptoms are most frequently observed in women aged 50 to 60. While bilateral inspiratory crackles are commonly audible, the majority of physical examination findings remain nonspecific. Affected individuals are predominantly non-smokers. Pulmonary function tests often reveal a pattern of restrictive impairment[2]. Given the similarity in clinical presentation between iNSIP and other conditions (such as HP, early stage of IPF and cryptogenic organizing pneumonia [OP]) and drug or occupational exposures, it is imperative to conduct a systematic questionnaire to ascertain a history of exposure to specific antigens, including contact with birds, medication use, or occupational history.

Among various CTDs, NSIP is notably a prevalent type of ILD. The hypothesis that NSIP could represent an initial manifestation of CTD was first proposed by Sato et al.[10]. Subsequently, Kinder et al.[11] reported that 80% of 28 NSIP patients met the diagnostic criteria for undifferentiated connective tissue disease (UCTD) and Park et al.[12] observed that CTD developed in eight of 83 patients (10%) initially diagnosed with NSIP during follow-up. Despite a substantial proportion of NSIP patients exhibiting positive autoantibody tests, many do not fulfill the specific diagnostic criteria for CTD[2,11,13-15]. These patients have been variously described as having UCTD-associated ILD, lung-dominant CTD, or autoimmune-featured ILD. Recently, the ATS/ERS recommended the term 'interstitial pneumonia with autoimmune features' for such cases[16]. In patients presenting with a NSIP pattern, it is crucial to evaluate clinical symptoms suggestive of CTD, such as Raynaud's phenomenon, joint pain or arthritis, skin rash, dry mouth or eyes, and muscle pain. The presence or development of CTD during follow-up should be cautiously monitored.

Diagnosis

Similar to other interstitial pneumonias, a multidisciplinary approach diagnosis (MDD) is needed in the diagnosis of NSIP. This involves consultations among respiratory physicians, radiologists, and pathologists who collectively deliberate and determine the diagnosis. NSIP pattern primarily found in images can manifest in various clinical conditions. Thus, a thorough investigation into potential underlying causes is needed. Diseases that must be distinguished from iNSIP are

summarized in Table 1.

1. Radiologic findings

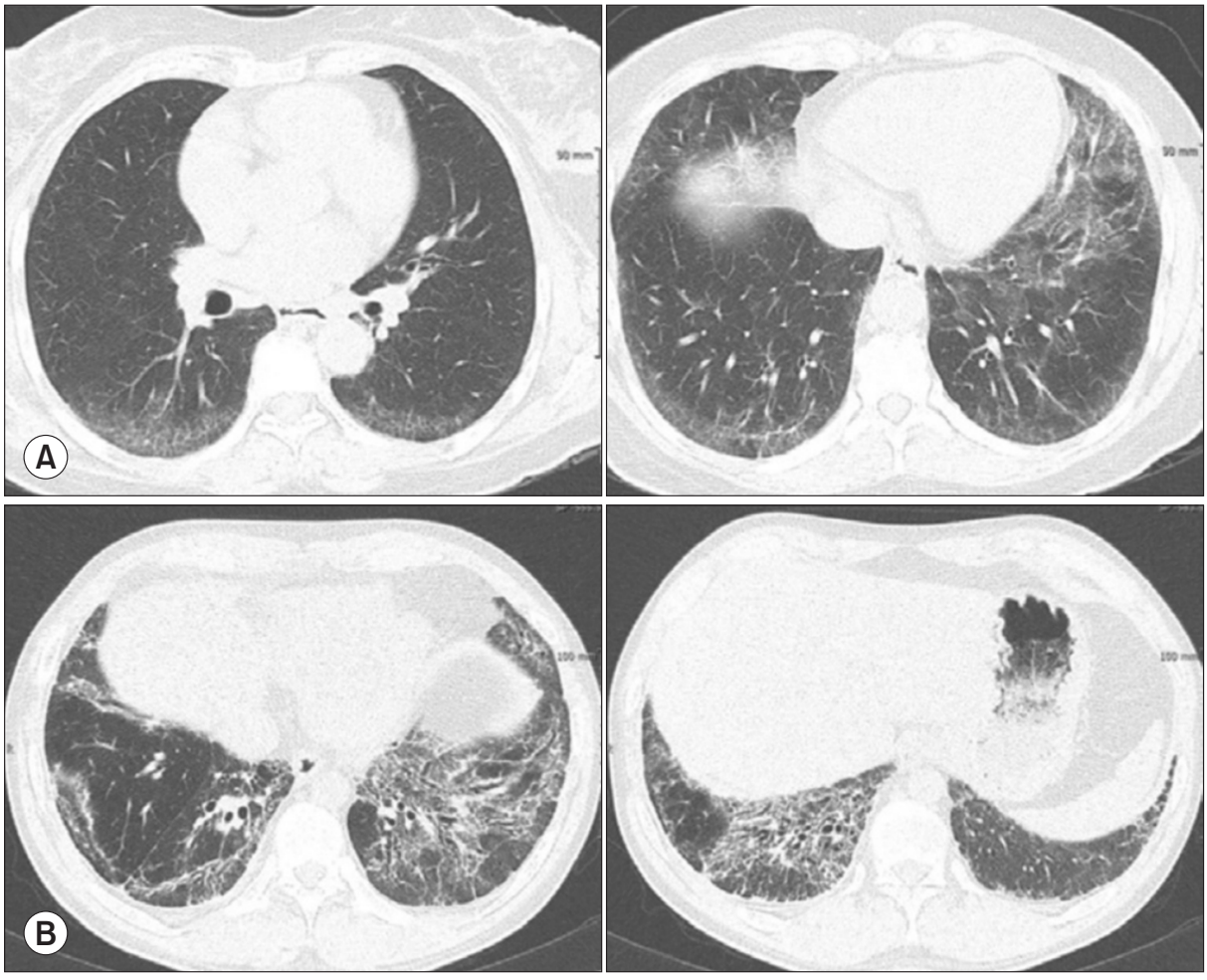
The most prevalent findings on chest high-resolution computed tomography (HRCT) include bilateral reticular shadows mainly in lower lungs, traction bronchiectasis, reduced lung volume, and ground-glass opacities[2,17-19]. These lesions predominantly appear diffusely in both lungs or manifest subpleurally. In approximately 20% of cases, areas just below the pleura are lesion-free and preserved (subpleural sparing), aiding in differentiation from IPF. Unlike the UIP pattern, honeycombing is either absent or extremely rare (Figure 1). Lung parenchymal consolidation suggestive of OP might also coexist. It might be linked to CTD. Unlike IPF, which could be diagnosed based on imaging findings of UIP or probable UIP alone through an MDD,

Table 1. Diseases to be differentiated from idiopathic nonspecific interstitial pneumonia

CTD-ILD
Hypersensitivity pneumonitis (HP)
Other ILDs, particularly organizing pneumonia, IPF, smoking-related interstitial pneumonia
Drug reaction
Sarcoidosis
Infectious disease (e.g., pneumocystis pneumonia)
Chronic eosinophilic pneumonia
Lymphoproliferative lung disease

CTD: connective tissue disease; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis.

Figure 1. High-resolution computed tomography (HRCT) of nonspecific interstitial pneumonia. (A) HRCT axial images (lung window setting) show ill-defined ground-glass opacities with subpleural sparing in periphery of both lower lobes. (B) HRCT axial images (lung window setting) at level of both lower lobes demonstrate reticulation, ill-defined ground-glass opacities, and traction bronchiectasis with subpleural sparing along bronchovascular bundles.



iNSIP cannot be conclusively diagnosed based solely on chest HRCT findings.

2. Bronchoscopy

Analysis of lavage fluid through bronchoalveolar lavage (BAL) often shows an increased fraction of T lymphocytes (>20%). However, this finding is nonspecific. It only serves a supportive role in differential diagnosis. The absence of increased lymphocytes and a high neutrophil fraction in the lavage fluid suggest that IPF is a differential diagnosis[20,21]. Transbronchial lung biopsy is not recommended as a confirmatory test because it is often inconclusive due to an insufficient specimen size.

3. Lung biopsy and histologic features

A surgical lung biopsy is crucial for confirming the diagnosis. Histologically, NSIP is characterized by diffuse interstitial inflammation and fibrosis with an overall uniform appearance while generally preserving the basic alveolar structure, which is distinguishable from the UIP pattern of IPF (Figure 2)[2,3]. The NSIP pattern can be further classified into cellular NSIP and fibrotic NSIP. In cellular NSIP, alveolar walls are infiltrated with chronic inflammatory cells with rare fibrosis, whereas in fibrotic NSIP, alveolar walls are thickened due to fibrosis, regardless of the presence or absence of inflammatory cell infiltration within alveolar walls[5,22,23].

Compared to cellular NSIP, fibrotic NSIP is more prevalent, accounting for 80% to 90% of cases. Organized pneumonia or honeycomb fibrosis should be completely absent or minimally present. When it is observed, it should constitute less than 10% to 20% of the total tissue sample (Table 2).

Treatment

1. Expert recommendation

- Steroids may serve as the primary therapeutic option to mitigate symptoms in iNSIP (Expert consensus recommendation, voting result: unanimous approval, recommendation level - conditional).
- In cases where steroid treatment alone proves ineffective or leads to steroid dependency in iNSIP, a combination therapy involving steroids and immunosuppressants may be employed (Expert consensus recommendation, voting result: unanimous approval, recommendation level – conditional).
- Should pulmonary fibrosis advance to progressive pulmonary fibrosis, antifibrotic drugs can be employed (Expert consensus recommendation, voting result: unanimous approval, recommendation level - strongly).

2. Pharmacological treatment

Steroids and immunosuppressants are commonly utilized to manage iNSIP. However, due to the variable progression of the disease, the potential for side effects, and comorbidities, regular periodic evaluation of symptoms, pulmonary function, and chest radiography is recommended in cases with mild manifestations[24]. Due to the relatively recent classification of iNSIP as a distinct disease and its low prevalence, randomized controlled studies that confirm the natural remission rate in untreated cases or the efficacy of these pharmacological treatments are currently unavailable.

1) Steroids

Retrospective studies indicate that steroids, alone or in combination with other immunosuppressants, can lead to symptomatic and functional improvement or stabilization. Watanabe et al.[25] reported that lung capacity

Figure 2. Pathologic findings of nonspecific interstitial pneumonia (NSIP) pattern. (A) Lung architecture is preserved with uniform appearance (H&E, ×20). (B) Cellular NSIP shows uniform thickening of alveolar septa with cellular infiltration (×200). (C) Fibrotic NSIP shows uniform thickening of alveolar septa by collagen (×200).

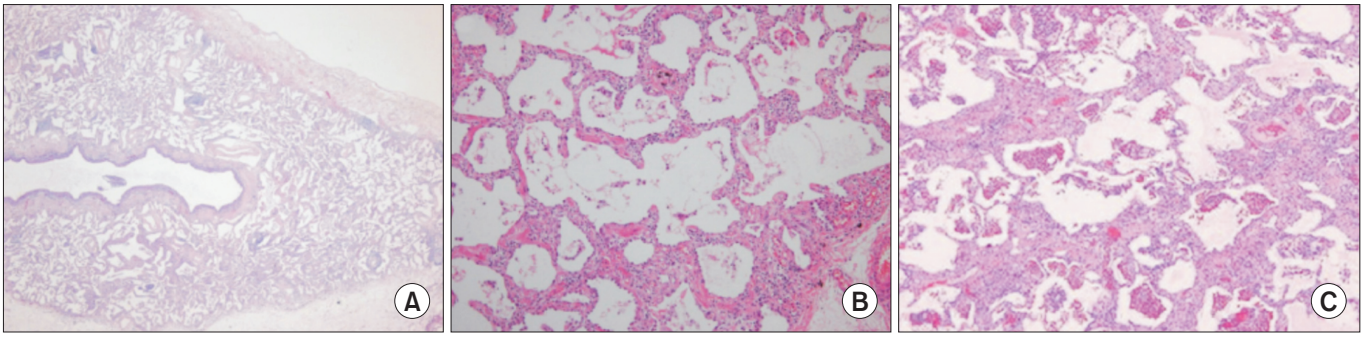


Table 2. Histological diagnostic criteria for nonspecific interstitial pneumonia

Essential findings for diagnosis
Cellular pattern
Mild to moderate interstitial chronic inflammation
Type II pneumocyte hyperplasia in areas of inflammation
Fibrosing pattern
Dense or loose interstitial fibrosis with uniform appearance
Lung architecture is frequently preserved
Interstitial chronic inflammation: mild or moderate
Findings that should not be seen, that is, other diagnoses should be considered
Cellular pattern
Dense interstitial fibrosis: absent
Organizing pneumonia is not the prominent feature (<20% of biopsy specimen)
Lack of diffuse severe alveolar septal inflammation
Fibrosing pattern
Temporal heterogeneity pattern: fibroblastic foci with dense fibrosis are inconspicuous or absent: this is especially important in cases with patchy involvement and subpleural or paraseptal distribution
Honeycombing: inconspicuous or absent
Enlarged fibrotic airspaces may be present
Both patterns
Acute lung injury pattern, especially hyaline membranes: absent
Eosinophils: inconspicuous or absent
Granulomas: absent
Lack of viral inclusions and organisms on special stains for organisms
Dominant airway disease such as extensive peribronchiolar metaplasia

and oxygenation levels were improved in all 10 patients after 1 year of steroid therapy, although one patient died after 4.3 years. This treatment can be effective in cases characterized by an inflammatory mechanism, such as cellular NSIP or NSIP concurrent with OP. However, it may be less effective in progressive fibrotic NSIP[26]. Xu et al.[27] observed that among 74 iNSIP patients treated with steroids, 17 (22.9%) died over a follow-up period averaging 54 months and 34 (45.9%) experienced a relapse upon cessation of steroid treatment, underscoring the efficacy of this approach. Park et al.[12] found that lung function remained stable in approximately 80% of 68 iNSIP patients treated with steroids alone or in combination for an average of 17.4 months, although 36% experienced a relapse. Lee et al.[28] noted that among 35 histologically confirmed iNSIP patients treated with steroids, 32 survived, 24 showed improved pulmonary function tests, and six remained stable. However, of the 30 patients who initially responded to steroid treatment, six (20%) relapsed over an average follow-up of 55 months. The relapse might be associated with initial low dosages of steroids (0.5 mg/kg) and short treatment durations.

There are no definitive guidelines for the optimal dosage or duration of steroids in iNSIP treatment. Typically, an initial dose of 0.5–1.0 mg/kg or 40–60 mg of prednisone is administered and maintained until a response is observed, usually about 1 month, followed by a gradual tapering approach[12,26].

In severe, fulminant cases, pulse therapy may be initiated with high-dose methylprednisolone (750 to 1,000 mg/day intravenously for 3 days, followed by an oral taper starting at 1 mg/kg)[24,25]. Treatment response is monitored over 4 to 6 weeks. Maintenance often continues at a low dose (5 to 10 mg/day).

2) Immunosuppressants

Immunosuppressants considered for treating iNSIP include azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil (MMF). These are often used in conjunction with steroids to mitigate complications associated with long-term steroid use and to

stabilize lung function while reducing steroid dosage. Although it is unclear whether these drugs should be initiated at diagnosis or upon disease progression or steroid dependency, they are generally employed in cases unresponsive to steroids or to maintain disease remission or prevent recurrence[26,29]. Expectations and predictions regarding the efficacy of these pharmaceuticals in treating iNSIP primarily derive from clinical experiences with CTD-ILD, which imposes certain limitations.

Among drugs mentioned above, cyclophosphamide has the highest number of reports. Kondoh et al.[30] treated 12 patients with histologically confirmed fibrotic NSIP, initially with high-dose intravenous methylprednisolone (1,000 mg/day for 3 days), followed by a combination of steroid (20 mg prednisone every other day) and cyclophosphamide (1 to 2 mg/kg/day) over a year. This regimen achieved improvement in 33% of patients and stabilization in 67%, although 21% experienced significant side effects such as hemorrhagic cystitis and leukopenia[30]. Corte et al.[31] reported favorable outcomes in rapidly progressing iNSIP patients treated with cyclophosphamide, with 46% maintaining their condition and 41% showing improvement after 6 months. Schupp et al.[32] found that NSIP patients had better progression-free survival when treated with cyclophosphamide pulse therapy (500 to 1,000 mg in conjunction with urometian monthly) than other types of ILDs. However, Fujita et al.[14] analyzed the outcomes of 22 iNSIP patients treated with steroids alone or in combination with cyclophosphamide, reporting a 1.5 times higher mortality rate in the immunosuppressant group compared to the steroid group, although their study's retrospective design and small size necessitated further research. Other drugs such as azathioprine, cyclosporine, and MMF have also shown effectiveness in a small number of case reports[4].

In a Korean national multicenter cohort, treatment responses were documented for 95 out of 261 patients with iNSIP who were followed for over a year[33]. Within the treatment cohort of 86 patients, 81 received either prednisolone alone or in combination with azathioprine, five were treated with azathioprine alone, and nine underwent conservative treatment only. The group receiving treatment exhibited significant improvements in lung function, with a noted correlation between shorter symptom duration at diagnosis and enhanced treatment response. Furthermore, a separate study at a single-center analyzed factors influencing disease progression in 20 patients with fibrotic NSIP confirmed by surgical biopsy[34]. Of these, 141 (69%) patients were diagnosed with iNSIP, while 63 (31%) had CTD-related NSIP. The average duration of treatment was 17.8 months, during which the disease progressed or recurred in 51% of patients. Good prognostic indicators included a diffusing capacity of the lungs for carbon monoxide (DL_{CO}) ≥60%, BAL fluid lymphocytes >15%, and the use of combined corticosteroid and azathioprine therapy.

Keir et al.[35] reported that rituximab treatment (1,000 mg administered on days 0 and 14) improved lung function in 50 patients with severe ILD other than IPF who were unresponsive to existing immunosuppressants. However, patients with iNSIP were excluded from their study. More recently, a phase 3 trial using rituximab with or without MMF in NSIP pattern of ILD investigated effects of adding rituximab to MMF on prognosis and pulmonary function of refractory NSIP patients, including those with CTD-ILD and iNSIP who had not responded to initial immunosuppressant therapy[36]. Of a total of 122 NSIP patients, 63 patients received a combination of rituximab and MMF (2 g daily) for 6 months, while 59 patients were treated with only MMF. The rituximab combination group showed a 1.60% increase in forced vital capacity (FVC), whereas the MMF-alone group experienced a 2.01% decrease. Furthermore, progression-free survival significantly improved in the rituximab combination group. However, among the 43 iNSIP patients assigned (21 to the rituximab combination and 22 to the MMF-alone group), subgroup analysis did not demonstrate a significant difference in FVC change after 6 months of treatment[36].

3) Antifibrotic agents

Pirfenidone and nintedanib are antifibrotic medications demonstrated to be effective in treating IPF. There is a growing interest in their application in fibrotic processes in ILDs other than IPF. While there are no randomized studies exclusively focusing on NSIP, positive outcomes in their roles in fibrotic NSIP have been observed through subgroup analyses[37,38].

A randomised controlled trial involved 663 patients with progressive fibrosing ILD (PF-ILD) comparing nintedanib 150 mg twice daily to a placebo over 52 weeks[37]. This trial evidenced a slower decline in FVC in the nintedanib group. Specifically, a subgroup analysis of 125 iNSIP patients indicated effectiveness, with a significant volume difference in FVC decline of 141.7 mL. Despite more frequent occurrences of diarrhea, nausea, vomiting, weight loss, and elevated liver enzymes in the nintedanib group, no significant increase in severe adverse effects such as death or disability was reported. Conversely, the trial using pirfenidone in 127 patients with PF-ILD compared pirfenidone with a

placebo included 27 patients with fibrotic NSIP[38]. Although the pirfenidone group exhibited a significantly reduced rate of FVC decline, the trial was terminated early. A cautious interpretation of these results is warranted. However, a detailed subgroup analysis was not feasible.

In contrast, a retrospective study evaluating pirfenidone response in 67 IPF patients and 24 fibrotic NSIP patients over 6 to 24 months highlighted a significant delay in lung function decline in the IPF group compared to an untreated control[39]. However, this delay was not statistically significant in the fibrotic NSIP subgroup. While progression-free survival differed significantly in the IPF group, no such difference was noted in the fibrotic NSIP group. Given the small number of fibrotic NSIP patients (n=9) who were administered pirfenidone, these findings should be interpreted with caution.

Presently, the absence of randomized studies and large-scale cohort research focused solely on fibrotic NSIP means that the efficacy of antifibrotic drugs in altering disease progression and prognosis remains uncertain, underscoring the need for further investigation.

3. Non-pharmacological treatment

Beyond pharmacological interventions, managing concomitant conditions such as reflux esophagitis and pulmonary hypertension and providing symptomatic relief for symptoms such as shortness of breath and cough are essential[40]. Oxygen therapy is beneficial in preventing nocturnal or exertional hypoxia, enhancing exercise capacity, and reducing the risk of hypoxia-induced pulmonary hypertension[41,42].

A study involving 51 patients with fibrotic NSIP undergoing home rehabilitation for up to 12 months revealed improvements in exercise capacity, quality of life, and depression indices, regardless of disease severity classified by pulmonary function[43]. These findings suggest that educating and managing home rehabilitation may positively influence long-term outcomes.

Although the relationship between smoking and iNSIP is not well defined, some case reports have suggested that cessation of smoking may benefit the clinical course[44]. Smoking cessation should be recommended to patients with NSIP who smoke.

4. Follow-up

There is no standardized method for evaluating treatment response in iNSIP. However, as with IPF, response is typically assessed based on a combination of chest imaging, symptoms such as dyspnea or cough, pulmonary function tests (FVC, DL_{CO}), and 6-minute walk distance. This assessment is usually conducted between 3 and 6 months after treatment initiation[45].

Longitudinal changes in lung function are recognized as valuable indicators of survival. Notably, a reduction in DL_{CO} greater than 15% after 12 months or a decline in FVC greater than 10% between 6 and 12 months is independently linked to increased mortality[12,46,47]. Consequently, if there is a decrease in DL_{CO} greater than 15% or a reduction in FVC greater than 10% without an apparent cause such as infection, adjustments or changes in medication dosage might be needed. In terminal stages, other interventions such as lung transplantation can be considered[48].

Natural Course and Prognosis

The survival rate for iNSIP is more favorable than that for IPF, with studies reporting a 5-year survival rate exceeding 70%[49]. Particularly in cases of cellular NSIP, disease-related mortality is rare[2,8,12]. Treatment typically involves steroids, azathioprine, cyclophosphamide, cyclosporine, and MMF, with these immunosuppressants often yielding a positive clinical response after initial treatment. Over two-thirds of patients show improvement or stabilization. However, there is a considerable rate of recurrence after treatment discontinuation, with Lee et al.[28] reporting a 20% recurrence rate and Park et al.[50] noting a rate of 36%[12]. Recurrence is associated with poorer prognosis. Similar to IPF, acute exacerbations may occur during the course of iNSIP, with Park et al.[50] reporting an incidence of acute exacerbation at 4.2% over 1 year.

Patients with CTD-related NSIP generally have a better prognosis than those with iNSIP. Patients experiencing rapid declines in FVC or DL_{CO} by more than 5% or 7.5% per year respectively, face a worse prognosis[51,52]. In BAL fluid, concentrations of Calgranulin B and Krebs von den Lungen-6 (KL-6) correlate with the severity of the disease[53]. Additionally, blood concentrations of KL-6 and surfactant protein-D (SP-D) in patients with fibrotic NSIP have been reported to be inversely related to DL_{CO}. Rising levels of these biomarkers in subsequent follow-up tests are associated with disease worsening unresponsive to treatment[52]. Despite these indicators, a definitive biomarker does not exist currently to predict the prognosis of iNSIP, underscoring the necessity for further research.

Authors' Contributions

Conceptualization: all authors. Methodology: all au-

thors. Formal analysis: all authors. Software: all authors. Validation: all authors; Investigation: all authors. Writing - original draft preparation: Jo YS. Writing - review and editing: all authors. Approval of final manuscript: all authors.

Conflicts of Interest

Yong Suk Jo is an editor and Hye Jin Jang is an early career editorial board member of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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