Clinical characteristics and prognostic factors of fibrotic nonspecific interstitial pneumonia

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Abstract

Aim: Several studies have reported favorable outcomes of nonspecific interstitial pneumonia (NSIP); however, its prognosis and prognostic factors remain unclear. This study aimed to determine the outcomes of fibrotic NSIP and the prognostic factors for progression, relapse, and survival.

Methods: In this retrospective study, we reviewed the clinical data of 204 patients diagnosed with fibrotic NSIP by surgical lung biopsy at Samsung Medical Center. The factors associated with survival and disease progression or relapse were determined using Cox proportional hazard analysis.

Results: The median age of patients was 54 years and 67 (33%) patients were male. Also, 47 patients (23%) were current or ex-smokers. In all, 141 (69%) patients were diagnosed with idiopathic NSIP, while 63 (31%) patients were associated with connective tissue diseases. Progression or relapse was observed in 100 (49%) patients. The 5-year and 10-year survival rates were 94.6% and 90.4%, respectively. The factors associated with disease progression and relapse were diffusing capacity for carbon monoxide (DLco) <60% [adjusted hazard ratio (HR), 1.739; 95% confidence interval (CI), 1.036–2.921; $p = 0.036$], bronchoalveolar lavage (BAL) lymphocyte >15% (adjusted HR, 0.592; 95% CI, 0.352–0.994; $p = 0.047$), and treatment with corticosteroid and azathioprine (adjusted HR, 0.556; 95% CI, 0.311–0.955; $p = 0.048$). Disease progression or relapse was associated with mortality (adjusted HR, 7.135; 95% CI, 1.499–33.971; $p = 0.014$).

Conclusion: Preserved lung function, BAL lymphocytosis, and treatment with corticosteroids and azathioprine were associated with lower risks of disease progression and relapse, which were risk factors for mortality.

Keywords: fibrotic nonspecific interstitial pneumonia, progression, relapse, survival

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Introduction

Nonspecific interstitial pneumonia (NSIP) is a chronic form of interstitial lung disease (ILD) characterized by a histopathological pattern of uniform interstitial inflammation and fibrosis.[1] NSIP may develop in association with various diseases or conditions such as connective tissue diseases (CTDs), hypersensitivity, environmental or occupational exposures, drugs, or viral infections.[2,3] It may also present as idiopathic, and it is the second most common type of idiopathic interstitial pneumonia.[4] It typically occurs in nonsmoking females during the fifth or sixth decade; this also differentiates it from the most common ILD associated with idiopathic pulmonary fibrosis (IPF).[2]

Another distinct feature of NSIP, compared with IPF, is its favorable prognosis.[2] The reported 5-year and 10-year survival rates of NSIP reach 82.3% and 73.2%, respectively.[2] Nonetheless, a

certain proportion of patients still suffer from progressive fibrosis despite treatment.[5,6] Hence, it is one of the major diseases constituting the recently suggested disease entity of progressive fibrosing ILD (PF-ILD).[7] Considering its impact on survival and potential for treatment with antifibrotic agents, it is important to understand the prognosis of NSIP and identify the subset of patients who will experience progression relapse, and mortality. Several studies have reported factors related to progression and mortality;[6,8,9] however, they are inconsistent. In this study, we aimed to determine the factors that influence the progression, relapse, and mortality of NSIP as well as identify its clinical characteristics and prognosis. As it is well known that cellular NSIP has an excellent response to treatment, we analyzed only patients with fibrotic NSIP.[10]

Methods

Study population and data collection

This cohort study was based on a prospective registry of patients with ILD at Samsung Medical Center (1989-bed, university-affiliated, tertiary referral hospital in Seoul, Republic of Korea). At our hospital, all consecutive ILD patients diagnosed in the ILD clinic have been prospectively registered in the database since January 1998. From the database consisting of 4155 ILD patients, we identified 242 patients diagnosed with fibrotic NSIP after surgical lung biopsy between January 1998 and January 2018. After excluding 38 patients with insufficient data or follow-up of less than 12 months, 204 patients were included in the analysis. Study patients were diagnosed with fibrotic NSIP based on a multidisciplinary discussion by pulmonologists, radiologists, and pathologists, as well as rheumatologists in some cases. Data on patient demographics, serologic tests for CTD, pulmonary function tests, radiologic findings, results of bronchoalveolar lavage (BAL), histopathologic findings, treatment regimen and duration, progression or relapse of the disease, and survival were collected by reviewing the medical records. Chest high-resolution computed tomography (HRCT) scans were reviewed by two authors (KSL and MJC). This study was approved by the Institutional Review Board of Samsung Medical Center for review and publication of information obtained from patient records (IRB No. 2020-04-137). Informed consent was waived owing to the retrospective nature of the study.

Definitions

Progression was defined as meeting at least one of the following criteria within 24 months despite treatment with corticosteroids and immunosuppressants: (1) a relative decline in the forced vital capacity (FVC) of at least 10% of the predicted value, (2) a relative decline in the FVC of 5% to less than 10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on HRCT, or (3) worsening of respiratory symptoms and an increased extent of fibrosis.[11] Relapse was defined as an aggravation of lung function and radiological findings of CT with or without worsening symptoms after complete discontinuation of treatment requiring retreatment with corticosteroids and immunosuppressant agents.[5] CTDs were diagnosed based on the currently proposed diagnostic criteria.[12–16] Undifferentiated CTD (UCTD) was defined as the presence of at least one symptom suggestive of CTD and laboratory or histopathologic evidence of systemic inflammation.[17]

Histopathologic pattern of fibrotic NSIP was defined as spatially and temporally uniform interstitial inflammation with predominant fibrosis.[2,18] Chest HRCT pattern of NSIP was defined as bilateral ground-glass opacity or reticular abnormalities with or without traction bronchiectasis in bilateral and predominantly basal distribution often with subpleural sparing.[1,19,20] HRCT findings of organizing pneumonia (OP) pattern was defined as bilateral patchy consolidative or ground-glass opacities with a predominantly peripheral or peribronchosvascular distribution.[1,19,20] NSIP with OP pattern was diagnosed when radiographic features of both OP and NSIP were coexistent, such as patchy consolidation in the presence of predominantly basal ground-glass opacities with reticular abnormality and traction bronchiectasis.[1,19,20] Finally, subpleural and basal predominant reticular opacities with traction bronchiectasis/bronchiolectasis and honeycombing were regarded as usual interstitial pneumonia (UIP) pattern.[21]

According to the American Thoracic Society/European Respiratory Society guideline, BAL lymphocytosis was defined as a BAL fluid cell differential counts of lymphocytes >15%.[22] Diffusing capacity for carbon monoxide (DLco) <60% was regarded as low DLco in univariate and multivariate analysis for identification of factors associated with poor prognosis.[23]

Statistical analysis

Categorical variables are presented as numbers (percentages), and continuous variables are presented as medians with interquartile ranges (IQR, 25th–75th percentiles). Univariate and multivariate Cox proportional hazard analyses were performed to identify factors associated with progression or relapse and mortality. We estimated the cumulative incidence of disease progression and/or relapse and survival using the Kaplan–Meier method. The factors of progression or relapse and mortality were compared using the log-rank test. All tests were two-sided, and a p value of <0.05 was considered significant. The data were analyzed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of study patients

The baseline characteristics of the 204 patients are summarized in Table 1. The median age of the patients at diagnosis was 54 (48–61) years, and 67 (33%) patients were male. The majority of patients ($n=157$, 77%) were never smokers. The median predicted FVC and DLco were 67% and 62%, respectively. Prevalence of emphysema and pulmonary hypertension in patients with low DLco (<60%) are available in the supplemental material. Antinuclear antibody (ANA) test was performed for 189 patients and was positive for 63 patients (33%). A thorough review of chest HRCT revealed an NSIP pattern in 114 (56%), NSIP combined with OP pattern in 55 (27%), and UIP pattern in 18 (9%). BAL was performed for 159 patients. BAL lymphocytosis (>15%) was observed in 92 patients (58%). The median duration of follow-up for the patients in this study was 70.9 (41.7–122.9) months. Among the 204 study patients, 141 (69%) were diagnosed with idiopathic NSIP and 63 (31%) were diagnosed with CTD-NSIP. Of the 63 patients with CTD, UCTD was the most common subtype in 18 (9%), followed by idiopathic inflammatory myopathy in 17 (8%), Sjogren's syndrome in 11 (5%), and rheumatoid arthritis in 8 (4%) patients (Table 1).

Treatment regimen and outcomes

Treatment was initiated for 197 of the 204 study patients (Table 2). Seven patients with mild disease without symptoms were closely followed without treatment. Of the 197 patients who received treatment, the co-administration of corticosteroid and azathioprine was the most common regimen for 94 (48%) patients, followed by corticosteroid alone for 52 (26%) patients. In all, 20 patients (10%) received azathioprine alone. Disease progression despite treatment occurred in 71 (36%) of 197 patients during follow-up. Of the 171 patients who completed treatment, 47 (27%) experienced relapse requiring re-initiation of treatment. When the duration of initial treatment was analyzed in 171 patients who completed treatment, there was no difference between patients with and without relapse [18.6 months (IQR, 15.2–23.2) *versus* 17.4 months (IQR, 12.0–20.2), $p=0.224$]. Details on the treatment regimen for patients with relapse are described in the supplemental material. In total, both progression and relapse occurred in 18 patients, progression only in 53 patients, and relapse only in 29 patients, collectively resulting in 100 (49%) of the 204 study patients. Mortality was observed in 18 patients (9%). Survival determined by the Kaplan–Meier equation demonstrated that the 1-year, 5-year, and 10-year survival rates were 100%, 94.6%, and 90.4%, respectively.

Prognostic factors of progression/relapse and mortality

To identify the prognostic factors of fibrotic NSIP, univariate and multivariate Cox proportional hazard analyses of the baseline characteristics and treatment regimens for disease progression or relapse and mortality were performed. Low DLco (<60%) was associated with the risk of progression or relapse [adjusted hazard ratio (HR), 1.739; 95% confidence interval (CI), 1.036–2.921; $p=0.036$], whereas BAL lymphocytosis (adjusted HR, 0.592; 95% CI, 0.352–0.994; $p=0.047$) and treatment with corticosteroids and azathioprine (adjusted HR, 0.556; 95% CI, 0.311–0.995; $p=0.048$) were associated with a lower risk (Table 3, Figure 1). Progression and relapse (adjusted HR, 7.135; 95% CI, 1.499–33.971; $p=0.014$) was the only factor associated with the risk of mortality (Table 4). A significant difference in survival was observed between the patients with and without progression or relapse (Figure 2).

Discussion

Our study aimed to determine the prognosis of fibrotic NSIP and identify its prognostic factors.

Table 1. Baseline characteristics of the study patients ($N = 204$).

	No. (%) or median (IQR)
Age, years	54 (48–61)
Sex, male	67 (33)
Smoking	
Current	18 (9)
Ex-smoker	29 (14)
Never smoker	157 (77)
Pulmonary function	
FVC, L ($n = 189$)	2.27 (1.79–2.81)
FVC, % predicted ($n = 189$)	67 (58–80)
FEV_1 ($n = 189$)	1.83 (1.50–2.37)
FEV_1, % predicted ($n = 189$)	72 (63–84)
DL_{CO}, mL/min/mmHg ($n = 153$)	11.8 (10.3–15.2)
DL_{CO}, % predicted ($n = 153$)	62 (50–74)
TLC, L ($n = 138$)	3.71 (3.08–4.39)
TLC, % predicted ($n = 138$)	73 (66–87)
HRCT pattern	
NSIP	114 (56)
NSIP with OP	55 (27)
OP	4 (2)
UIP	18 (9)
Other	13 (6)
Bronchoalveolar lavage ($n = 159$)	
Monocytes (%)	75 (49–87)
Lymphocytes (%)	18 (10–44)
Neutrophils (%)	2 (0–5)
Eosinophils (%)	0 (0–1)
Lymphocytosis (>15%)	92/159 (58)
Serological tests	
Antinuclear antibody (+)	63/189 (33)
Rheumatoid factor	80/191 (42)
Anti-CCP	8/46 (17)
Anti-SSA	27/131 (21)
Anti-SSB	6/130 (5)
Anti-topoisomerase (Scl-70)	3/117 (3)
Anti-RNP	2/122 (2)

(Continued)

Table 1. (Continued)

	No. (%) or median (IQR)
Anti-Jo-1	10/101 (10)
Anti-sm	0/123 (0)
Connective tissue disease	63 (31)
UCTD	18 (9)
Sjogren's syndrome	11 (5)
Idiopathic inflammatory myopathy	17 (8)
Rheumatoid arthritis	8 (4)
Systemic sclerosis	5 (2)
MCTD	2 (1)
SLE	2 (1)
Duration of follow-up, months	70.9 (41.7–122.9)

CCP, cyclic citrullinated peptide; DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HRCT, high resolution computed tomography; IQR, interquartile range; MCTD, mixed connective tissue disease; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; TLC, total lung capacity; UCTD, undifferentiated connective tissue disease; UIP, usual interstitial pneumonia.

Table 2. Treatment outcomes of the study patients ($N = 204$).

	No. (%) or median (IQR)
Initial treatment	
Corticosteroid + azathioprine	94 (46)
Corticosteroids only	52 (25)
Corticosteroid + cyclophosphamide	23 (11)
Azathioprine only	20 (10)
Cyclophosphamide only	6 (3)
No treatment	7 (3)
Other treatments[a]	2 (1)
Duration of treatment, months	17.8 (12.5–19.9)
Treatment outcome ($n = 197$)	
Progression[b]	71 (36)
Relapse[c,d]	47 (24)
Progression or relapse[e]	100 (51)
Mortality	18 (9)

IQR, interquartile range.
[a]Mycophenolate mofetil, N-acetylcysteine.
[b]The numbers include 18 patients who experienced both disease progression and relapse.
[c]The numbers include 18 patients who experienced both disease progression and relapse.
[d]The rate of relapse is 27% (47/171), when calculated only for 171 patients who completed treatment.
[e]The numbers include 18 patients who experienced both disease progression and relapse.

Table 3. Univariate and multivariate Cox regression analysis for factors associated with disease progression and/or relapse ($N = 204$).

	Crude HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Age (⩾65 years)	1.235 (0.603–2.528)	0.564		
Sex, male	1.290 (0.559–2.975)	0.551		
Never smoker	0.945 (0.360–2.478)	0.908		
FVC < 60%	1.187 (0.567–2.484)	0.649		
DLco < 60%	1.739 (1.000–3.023)	0.050	1.739 (1.036–2.921)	0.036
ANA (positive)	1.371 (0.800–2.348)	0.250		
BAL lymphocyte > 15%	0.631 (0.365–1.091)	0.099	0.592 (0.352–0.994)	0.047
Idiopathic NSIP	1.381 (0.744–2.564)	0.307		
UIP pattern on HRCT	0.774 (0.321–1.869)	0.569		
Corticosteroid with azathioprine	0.500 (0.254–0.985)	0.045	0.556 (0.311–0.995)	0.048

ANA, antinuclear antibody; BAL, bronchoalveolar lavage; CI, confidence interval; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio; HRCT, high resolution computed tomography; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

Our results for 204 patients with biopsy-confirmed fibrotic NSIP demonstrated 1-, 5-, and 10-year survival rates of 100%, 94.6%, and 90.4%, respectively. In all, 100 (49%) patients experienced progression or relapse despite treatment during follow-up. The factors associated with progression or relapse were low DLco, low BAL lymphocytes (⩽15%), and treatment regimens other than corticosteroids and azathioprine. Patients with progression or relapse have an increased risk of mortality.

The favorable survival associated with fibrotic NSIP reported in our study is consistent with previous literature. According to the American Thoracic Society report, the 5-year and 10-year survival rates of idiopathic NSIP were 82% and 73%, respectively.[2] Park *et al.*[8] analyzed the impact of CTD on the outcomes of ILD and reported similar 5-year survival rates for CTD-NSIP and idiopathic NSIP, which were 81.5% and 67.4%, respectively. The survival rates in the study by Nunes *et al.*[6] were slightly lower, with a 5-year survival rate of 65.6% and a 10-year survival rate of 49.2%.

Despite the excellent survival, our study demonstrated a relatively high rate of relapse and disease progression in patients with NSIP. Several studies have shown that relapse occurs in NSIP. Park *et al.* analyzed 83 patients with idiopathic NSIP (11 cellular NSIP and 72 fibrotic NSIP) and reported that relapse occurred in 20 of 55 (36%) patients who improved or were stable following treatment. In another Korean study of 35 patients with biopsy-proven NSIP, including 17 (48.6%) patients with cellular NSIP and 9 (25.7%) patients with CTD, 6 of 24 (25%) patients with initial improvement experienced a relapse of the disease. The relapse rate of 27% in our study, as well as previous studies, confirms the relative vulnerability of NSIP to recurrence.

A substantial proportion of patients in our study also experienced disease progression regardless of treatment. Among the 197 patients who received treatment, 71 (36%) experienced progression. Although IPF is the most infamous ILD for its persistent progression, some ILDs other than IPF may demonstrate similar clinical courses.[24] In a single-center observational cohort study, a considerable number (27%, 168/617) of non-IPF ILD patients showed progression despite treatment. A recent study demonstrated that these patients, commonly referred to as PF-ILD patients, experience trajectories of lung function decline comparable with that of IPF.[25] In a phase

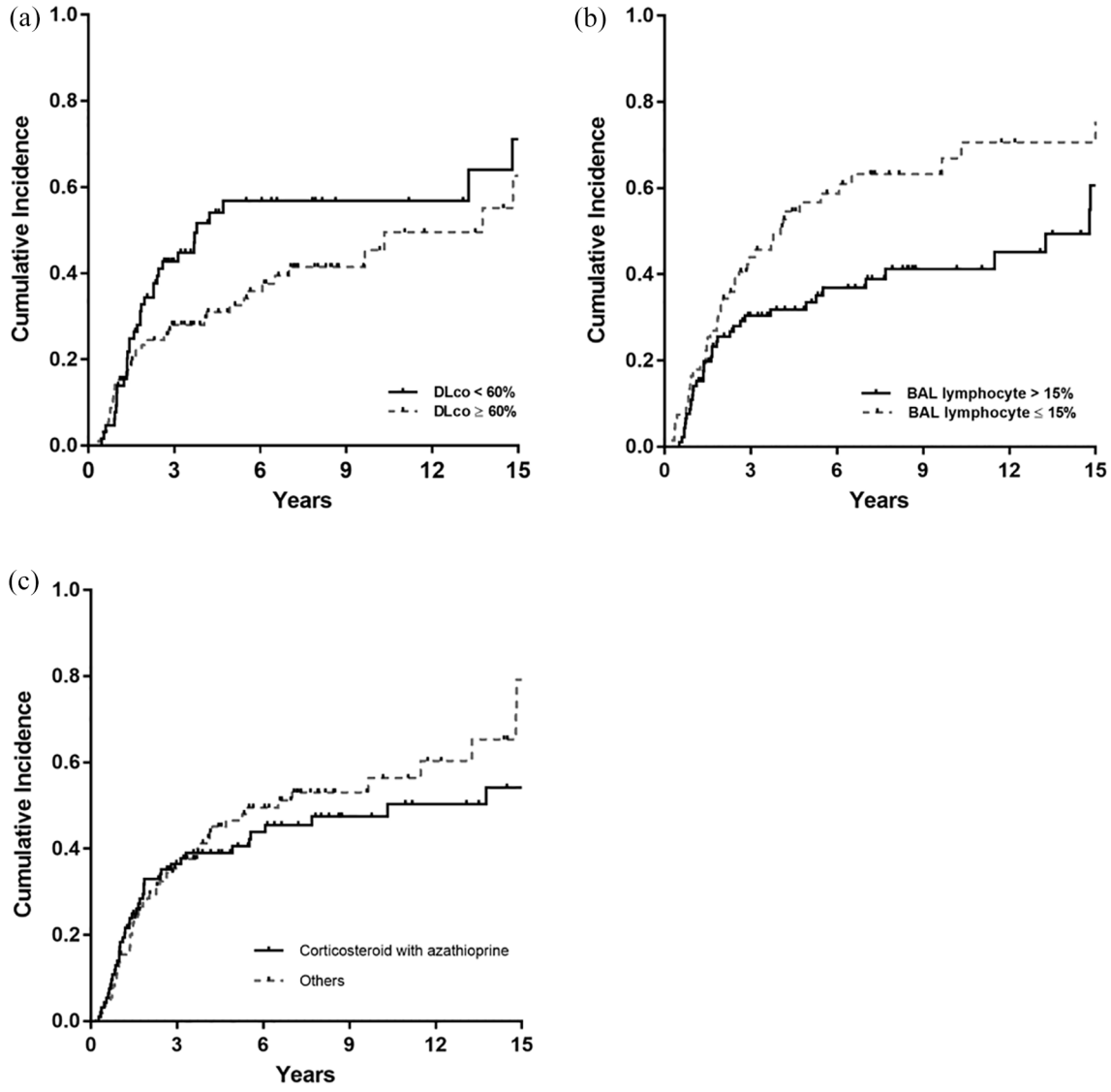

Figure 1. Cumulative incidence of progression and/or relapse according to (a) DLco < 60% (log-rank $p = 0.042$), (b) BAL lymphocyte > 15% (log-rank $p = 0.016$), and (c) combination treatment regimen of corticosteroid and azathioprine (log-rank $p = 0.223$).
BAL, bronchoalveolar lavage; DLco, diffusing capacity for carbon monoxide.

3 trial of the efficacy and safety of nintedanib for non-IPF PF-ILD, almost half of the study patients had CTD-ILD, which commonly presents with an NSIP pattern, or idiopathic NSIP. This indicates that NSIP is a common disease of PF-ILD.[11,26] Only a few studies are available for review regarding the specific rate of progression for NSIP. Lee *et al.* reported that 14% (5/35) of patients with NSIP were unresponsive to corticosteroid treatment.[5] However, 66% (67/101) were unresponsive to first- and second-line treatments in the study by Nunes *et al.*[6] Although the reason for this difference in the progression rate is not clear, a difference in the composition of the study population, including the proportion of cellular NSIP and chronic hypersensitivity pneumonitis, as well as the lack of precise criteria for defining progression, may have affected the results. There are no universally accepted criteria for defining progression; however, the strength of our study is that we incorporated the criteria based on clinical, radiological, and physiological components that were established in a multicenter phase 3 trial for PF-ILD.[11]

Table 4. Univariate and multivariate Cox regression analysis for factors associated with mortality ($N = 204$).

	Crude HR (95% CI)	*p* value	Adjusted HR (95% CI)	*p* value
Age (⩾65 years)	1.485 (0.253–8.704)	0.661		
Sex, male	1.345 (0.133–13.553)	0.801		
Never smoker	0.526 (0.041–6.735)	0.621		
FVC < 60%	0.323 (0.032–3.271)	0.339		
DLco < 60%	1.061 (0.273–4.128)	0.932		
ANA (positive)	0.753 (0.173–3.265)	0.704		
BAL lymphocyte > 15%	1.181 (0.261–5.348)	0.829		
Idiopathic NSIP	1.827 (0.339–9.841)	0.483		
UIP pattern on HRCT	0.730 (0.067–7.954)	0.796		
Corticosteroid with azathioprine	0.650 (0.113–3.734)	0.629		
Progression/relapse	7.977 (1.320–48.215)	0.024	7.135 (1.499–33.971)	0.014

ANA, antinuclear antibody; BAL, bronchoalveolar lavage; CI, confidence interval; DLco, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HR, hazard ratio; HRCT, high resolution computed tomography; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

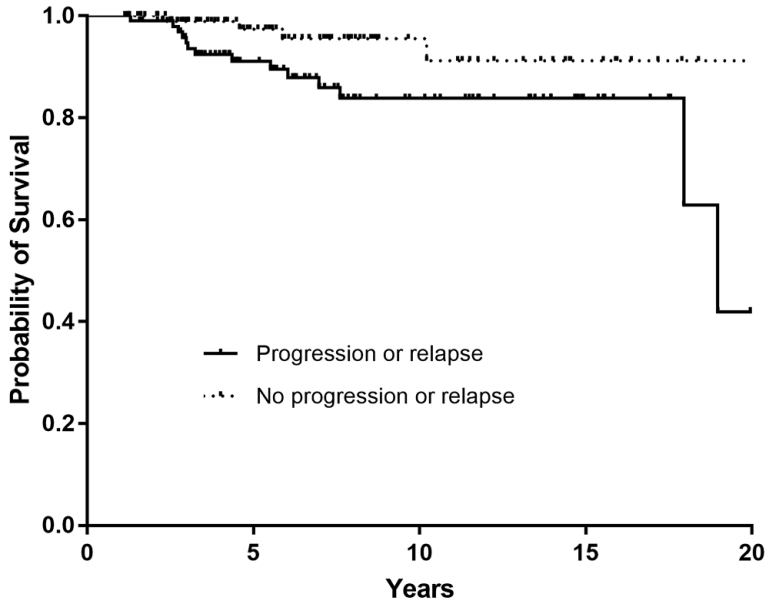

Figure 2. Kaplan–Meier survival analysis comparing patients with and without progression and/or relapse (log-rank $p < 0.001$).

One of the notable findings of our study is that progression or relapse was the sole predictor of mortality, which was associated with low DLco, low BAL lymphocytes (⩽15%), and treatment regimens other than the combination of corticosteroids and azathioprine. Unresponsiveness to treatment has been uniformly reported as a poor prognostic factor for NSIP.[5,6,27] Given that

progression and relapse are associated with grave outcomes, the identification of their predictive factors is important for improving outcomes. Several multicenter survey studies have suggested the presence of ANA, low BAL lymphocyte count (⩽15%), or long duration of symptoms as possible risk factors for unresponsiveness to treatment in fibrotic ILD or idiopathic NSIP;[28,29] however, the predictive factors for progression or relapse in fibrotic NSIP have not been established. To the best of our knowledge, this is the first study to investigate the risk factors for progression or relapse in biopsy-confirmed fibrotic NSIP based on distinct criteria. Several findings about the risk factors for progression or relapse in our study require attention. First, treatment with the combination of corticosteroids and azathioprine was associated with a lower risk of progression or relapse. Corticosteroids and immunosuppressive agents are commonly used as treatments for NSIP.[30] However, the efficacy and safety as well as optimal dose and duration of such treatments have not been validated in randomized controlled trials. The better prognosis of patients treated with a combination of corticosteroids and azathioprine observed in our study and the results of previous studies showing that azathioprine in combination or for maintenance may help stabilize pulmonary function and lower the prednisolone dose for CTD-ILD[31,32] warrant further randomized controlled studies to evaluate the effectiveness of combination regimens. Second, our study may provide insight into the selection criteria of patients who may be candidates for treatment with antifibrotic agents. In the INBUILD trial, nintedanib reduced the decline of pulmonary function in PF-ILD, including CTD-ILD and idiopathic fibrotic NSIP. Given that patients enrolled in the trial were those who had progressed despite standard treatment, and fibrosis may be irreversible in such patients, early initiation of antifibrotic agents or combination with corticosteroid or immunosuppressive agents for newly diagnosed fibrotic NSIP patients with a high risk of progression may improve outcomes. In particular, progression in our study was defined according to the criteria used in the same trial, which demonstrated the significant efficacy of nintedanib in PF-ILD.[11] Nonetheless, additional studies are necessary to evaluate the significance of such treatments for fibrotic NSIP.

Our study has several limitations. First, because of the observational nature, there is always a possibility of confounding which might have influenced the results of our study. Second, there may have been selection bias because we included only patients who were confirmed based on surgical lung biopsy results. This selection bias may be more prominent for cases of CTD-NSIP for which surgical lung biopsy is infrequently performed and patients with advanced ILD or comorbidities who may not have tolerated surgical lung biopsy. Third, relapse occurred in 47 (27%) patients in our study. Although there was no difference in the duration of the initial treatment between patients with and without relapse, sufficient duration of treatment and need for maintenance therapy for fibrotic NSIP are still not known. Further studies are required to determine optimal duration and regimen of treatment to reduce relapse.

Preserved lung function, BAL lymphocytosis, and treatment with corticosteroids and azathioprine were associated with a lower risk of disease progression or relapse, which was a risk factor for mortality.

Author contributions

Hyun Kyu Cho: Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Man Pyo Chung: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Kyung Soo Lee: Data curation; Formal analysis; Investigation; Writing – original draft.

Myung Jin Chung: Data curation; Formal analysis; Methodology; Writing – review & editing.

Joungho Han: Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

O. Jung Kwon: Formal analysis; Investigation; Writing – review & editing.

Hongseok Yoo: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Conflict of interest statement

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

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Human ethics approval declaration

This study was approved by the Institutional Review Board of Samsung Medical Center for review and publication of information obtained from patient records (IRB No. 2020-04-137).

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Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Supplemental material

Supplemental material for this article is available online.

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