Physiology Is a Stronger Predictor of Survival than Pathology in Fibrotic Interstitial Pneumonia

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The histopathologic pattern provides the most important prognostic marker for idiopathic interstitial pneumonia; however, studies have suggested that short-term changes in lung function may be more important. We investigated the prognostic factors for fibrotic interstitial pneumonia. The clinical features and follow-up course of 179 patients (131 with idiopathic pulmonary fibrosis and 48 with nonspecific interstitial pneumonia; 41 fibrotic types and 7 cellular) were analyzed retrospectively. The lung function indices improved or stabilized in most patients with fibrotic nonspecific interstitial pneumonia in contrast to the deterioration or stable condition of most patients with idiopathic pulmonary fibrosis. The 5-year survival of patients with fibrotic nonspecific interstitial pneumonia (76.2%) was better than for those with idiopathic pulmonary fibrosis (43.8%) ($p = 0.007$). Multivariate analysis at the time of presentation revealed that pathologic pattern, age, and diffusion capacity had important prognostic implications. However, after 6 months of follow-up, changes in FVC, initial diffusion capacity, and sex were the only independent prognostic factors, with no additional prognostic information conferred by the histologic diagnosis. Our data confirmed the importance of physiological parameters including short-term change in FVC. However, at the time of diagnosis, histopathology was important for the prediction of prognosis and future change in lung function.

Keywords: fibrotic nonspecific interstitial pneumonia; idiopathic pulmonary fibrosis; prognostic factor; pulmonary function; surgical lung biopsy

In 1994, Katzenstein and Fiorelli proposed the term "nonspecific interstitial pneumonia" (NSIP) to describe a subset of idiopathic interstitial pneumonia (IIP) that could not be classified into any of the other types of interstitial pneumonia. They subcategorized the disease into three subgroups depending on the relative amounts of interstitial fibrosis and inflammation (1). Subsequently a number of other studies showed that an NSIP pattern in a surgical lung biopsy provided important prognostic information compared with other IIPs (2–7). However, there was considerable overlap in outcome, especially between patients with fibrotic NSIP and those with idiopathic pulmonary fibrosis (IPF) (2, 3, 8). Nicholson and coworkers showed that the prognosis of patients with fibrotic NSIP was less favorable than previously thought (3). They reported that the 5-year survival rate of patients with fibrotic NSIP was about 45%, which was worse than that reported by Travis and coworkers (2), although it was better than IPF (3). Therefore, Latsi and coworkers combined the fibrotic type NSIP and usual interstitial pneumonia (UIP) into fibrotic IIP (8). Several reports, including that of Latsi and coworkers, suggested that physiological parameters, especially short-term changes, were important in determining the prognosis for patients with IIP (8–12). These data may raise questions about the necessity for a pathologic diagnosis by surgical lung biopsy in the case of fibrotic IIP. However, accurate clinico–radiologic–pathologic diagnosis is crucial, especially at the time of diagnosis for initial management of patients with IIP. We therefore compared the importance of pathologic patterns in the prognosis for patients with fibrotic IIP (fibrotic NSIP pattern and UIP pattern) with physiological parameters including short-term change of lung function. We also compared the prognosis for those patients with IIP, especially fibrotic NSIP, with those for patients with IPF. Some of the results of this study have been previously reported in the form of an abstract (13).

METHODS

Subjects

Subjects included 179 patients with idiopathic NSIP or IPF diagnosed by surgical lung biopsy from January 1990 to September 2002 at Asan Medical Center, a 2,000-bed university-affiliated tertiary referral center in Seoul, South Korea. Two lung pathologists (M.K. and T.V.C.) reviewed the specimens independently. If the opinions of the two pathologists were different (coefficient of agreement $k = 0.59$), a third opinion was sought and the final diagnosis was made in the context of clinicoradiologic findings. There were 207 patients with IIP who had had surgical lung biopsies. Twenty-eight cases were excluded because of a failure to obtain consensus between the pathologists (9 cases) or because the patients were diagnosed as having other diseases (19 cases). NSIP was subclassified into cellular and fibrotic types, according to the level of fibrosis and inflammation (1).

Methods Used

Clinical data were obtained from medical records and survival status was obtained from telephone interviews and/or medical records. The minimal amount of smoking for a smoker was 1 pack-year, and an ex-smoker was defined as a subject who had not smoked for at least 3 months (3). Patients were excluded if they had taken drugs, experienced occupational or other environmental exposures, or presented evidence of collagen vascular diseases on the basis of a thorough history, physical examination, and serologic tests.

Surgical Lung Biopsy

Surgical lung biopsies were taken from two or more lobes (141 patients) either through open thoracotomy or video-assisted thoracoscopic surgery. The sites of the biopsies were guided by high-resolution computed tomography (HRCT). Until 2000, biopsies were taken from the border between normal-looking and diseased areas including ground glass opacity, but not the area of total honeycombing. Since 2000, the biopsies have been taken from areas showing the full spectrum of HRCT abnormalities.

HRCT Scanning

HRCT scans were performed with a GE 9800 (General Electric Medical Systems, Milwaukee, WI) or Somatom Plus (Siemens, Erlangen,

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Germany). A pulmonary radiologist who was unaware of the clinical and functional findings reviewed the HRCT scans. Honeycombing was defined macroscopically as clustered cystic air spaces with well defined walls and diameters ranging from 0.3 to 1.0 cm, but sometimes up to 2.5 cm.

Pulmonary Function Test

Spirometry (Vmax22; SensorMedics, Yorba Linda, CA), plethysmographic lung volumes (6200 Plethysmograph; SensorMedics), and diffusion capacity for carbon monoxide (D_{LCO}) (Vmax229D; SensorMedics) were used to assess lung function. Improvement and deterioration were defined as more than a 10% change in forced vital capacity (FVC) or total lung capacity (TLC), and more than a 15% change in D_{LCO} (14).

Statistical Methods

Categorical data were compared using a χ^2 statistics test or Fisher exact test. Continuous data were compared using an unpaired Student *t* test. Survival was evaluated using Kaplan–Meier survival curves and the log-rank test. Cox proportional hazards regression analysis was used to identify significant variables predicting survival status. Variables that selected via univariate analysis ($p < 0.05$) were evaluated in the forward selected stepwise multivariate Cox regression analysis. $p < 0.05$ was considered statistically significant (all tests were two-tailed).

RESULTS

Initial Clinical Findings

There were 131 patients with IPF and 48 with NSIP (41 with fibrotic NSIP and seven with cellular NSIP). Table 1 shows the demographic features of the patients at the time of diagnosis. The median follow-up period was 23.7 months (range, 0.3–139.3 months). There were more females and nonsmokers with fibrotic NSIP and more males and smokers with IPF. Compared with patients with IPF, those with fibrotic NSIP were younger ($p = 0.002$) and had a shorter duration of symptoms ($p < 0.001$) before biopsy.

Initial Pulmonary Function Test and Bronchoalveolar Lavage Findings

Table 1 also outlines the pulmonary function data, arterial blood gas analysis, and bronchoalveolar lavage (BAL) fluid findings. The initial FVC and 1-second forced expiratory volume (FEV_1) of patients with IPF were better than those with fibrotic NSIP. However, there were no differences in D_{LCO} or TLC. The resting arterial partial pressure of oxygen (Pa_{O_2}) of patients with fibrotic NSIP was higher than that of patients with IPF. The arterial carbon dioxide levels (Pa_{CO_2}) showed no difference between patients with fibrotic NSIP and those with IPF. Elevated lymphocyte percentage in the BAL fluid was a typical feature of patients with NSIP.

HRCT Findings

In patients with cellular NSIP, ground glass opacity was the main HRCT finding and most patients showed only this feature. Only two patients had some degree of consolidation. For fibrotic NSIP, about half of the patients had ground glass opacity as the dominant pattern and the other half showed a dominant reticular opacity pattern without honeycombing. Among 34 patients with fibrotic NSIP, 7 had some consolidation (less than 5% of diseased area in 5 patients and 15–20% in another 2 patients) in addition to predominant ground glass opacity. In contrast, about two-thirds of the patients with IPF had a dominant honeycombing pattern with or without some degree of ground glass opacity (Table 2).

Treatments

There was no standardized treatment for the patients with IIP before the American Thoracic Society international consensus statement for treating this disease (14). Corticosteroids with or without cytotoxic therapy were given to 95% of our patients with fibrotic NSIP, and a short-term trial of similar medication

TABLE 1. INITIAL CLINICAL CHARACTERISTICS OF PATIENTS WITH NONSPECIFIC INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS

	NSIP				
	Total	Cellular	Fibrotic	IPF	p Value*
Number of patients	48	7	41	131	
Age, yr	54.5 ± 11.3	59.4 ± 10.2	53.7 ± 11.4	59.4 ± 9.9	0.002
Male:female	14:33	3:4	12:29	94:37	< 0.001
Follow-up period, mo†	40.4 (0.40–139.3)	27.2 (14.9–51.6)	41.8 (0.40–139.3)	19.0 (0.30–125.20)	0.004
Smoking					< 0.001
Never-smokers	36	3	33	39	
Ex-smokers	6	3	3	39	
Smokers	5	1	5	53	
Smoking amount, pack-years	6.1 ± 13.6	9.3 ± 8.9	5.34 ± 14.4	24.8 ± 21.5	< 0.001
Duration of symptoms, mo	5.4 ± 6.5	4.0 ± 3.9	5.5 ± 7.0	13.0 ± 14.1	< 0.001
Resting Pa_{O_2}, mm Hg	89.8 ± 15.1	76.6 ± 21.0	92.0 ± 12.9	86.3 ± 14.1	0.022
Initial pulmonary function test‡					
FVC, % predicted	63.7 ± 15.5	67.3 ± 18.9	63.1 ± 15.1	72.5 ± 18.1	0.003
FEV_1, % predicted	71.6 ± 16.7	74.6 ± 16.5	71.1 ± 16.9	83.5 ± 19.1	< 0.001
D_{LCO}, % predicted	56.9 ± 20.1	60.1 ± 15.4	56.3 ± 20.9	60.6 ± 20.1	0.241
TLC, % predicted	80.7 ± 26.5	75.7 ± 14.4	73.9 ± 29.2	73.0 ± 23.4	0.568
Initial BAL finding					
Macrophages, %	49.0 ± 20.4	25.5 ± 11.9	52.4 ± 19.2	69.4 ± 16.8	< 0.001
Lymphocytes, %	38.3 ± 20.8	66.0 ± 13.1	34.2 ± 18.6	18.1 ± 13.8	< 0.001
Neutrophils, %	9.7 ± 9.6	5.1 ± 3.7	10.4 ± 10.1	9.2 ± 8.8	0.486
Eosinophils, %	3.0 ± 4.1	3.4 ± 3.2	2.9 ± 4.2	3.2 ± 6.3	0.824

Definition of abbreviations: BAL = bronchoalveolar lavage; D_{LCO} = diffusion capacity for carbon monoxide; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; TLC = total lung capacity.

*Statistical analysis was performed only between fibrotic NSIP and usual interstitial pneumonia (UIP).

† Median value with ranges in parentheses.

TABLE 2. HIGH-RESOLUTION COMPUTED TOMOGRAPHY FINDINGS OF FIBROTIC NONSPECIFIC INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS*

	Fibrotic NSIP	IPF
Number of patients	34	109
Ground glass opacity	14	5
Ground glass opacity + reticular density	3	27
Ground glass opacity + consolidation	5	3
Reticular opacity	10	4
Consolidation	2	
Honeycombing + ground glass opacity		26
Honeycombing + consolidation		1
Honeycombing + reticular density		17
Honeycombing		26

*$p < 0.001$.

TABLE 4. CHANGES IN LUNG FUNCTION IN FIBROTIC NONSPECIFIC INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS 6 MONTHS AFTER BIOPSY

	Fibrotic NSIP	IPF	p Value
Number of patients	33	103	
FVC change, no. (%)			< 0.001
> 10% increase	15 (45.5%)	7 (6.8%)	
Stable*	16 (48.4%)	75 (72.8%)	
> 10% decrease	2 (6.1%)	21 (20.4%)	
TLC change, no. (%)			0.032
> 10% increase	5 (22.7%)	3 (41.7%)	
Stable*	15 (68.2%)	58 (80.6%)	
> 10% decrease	2 (9.1%)	11 (15.3%)	
D_{LCO} change, no. (%)			0.007
> 15% increase	7 (21.9%)	4 (4.2%)	
Stable*	23 (71.8%)	76 (79.1%)	
> 15% decrease	2 (6.3%)	16 (16.7%)	

*Stable: less than 10% (15% in D_{LCO}) change.

was administered to 76% of our patients with IPF. The typical regimens were shown in Table 3.

Trends in Lung Functions

For fibrotic NSIP, most patients improved or were stable, in contrast to the deterioration or stable condition of most patients with IPF. Changes in lung function among the subgroups of IIP were statistically significant (Table 4).

Survival

There were no deaths among patients with cellular NSIP during the follow-up after surgical lung biopsy. As shown in Figure 1, the survival rate for patients with fibrotic NSIP was better than that for patients with IPF. The 5-year survival rate of patients with fibrotic NSIP was 76.2% in contrast to 43.8% of patients with IPF ($p = 0.007$). At the time of presentation, pathologic pattern, age, and D_{LCO} predicted survival of patients with fibrotic NSIP and IPF as shown in Table 5. After 6 months of follow-up, univariate analysis revealed that older age, male sex, the pathologic pattern of UIP, lower initial lung function (FVC and D_{LCO}), lower initial Pa_{O_2}, and deterioration in FVC were all poor prognostic indicators in patients with fibrotic IIP (Table 6). However, multivariate analysis showed that the 6-month changes in FVC, initial D_{LCO}, and sex were statistically significant predictors of survival (Table 7 and Figure 2). These findings strongly suggested that the change in FVC had prognostic implications and that the pathologic pattern was not a predictive marker in multivariate analysis after considering the short-term change in FVC (Table 7).

DISCUSSION

We confirmed that physiological parameters, especially serial change in FVC, were the most important predictors of survival in patients with fibrotic interstitial pneumonia. However, at the time of initial presentation, the pathologic pattern was a significant prognostic marker not only for survival but also for future changes in lung function.

Many previous studies have shown a favorable prognosis for NSIP (4, 6, 15–17). The prognosis for the cellular pattern of NSIP has been uniformly excellent; however, the reported survival of patients with fibrotic NSIP has varied considerably among studies. Travis and coworkers reported a 5-year survival rate of 90% for fibrotic NSIP (2), whereas Nicholson and coworkers found it to be only a 45% (3). The survival rate of patients with NSIP in our study fell between these extremes. This variability and considerable overlap in the survival of patients on the basis of these two pathologic patterns (2, 3, 18) suggested a need to define other prognostic factors.

Univariate analysis of our data showed that the pathologic pattern of UIP, decreased initial FVC and D_{LCO}, increased age, male sex, a lower resting Pa_{O_2}, and deteriorated FVC at 6 months were all associated with increased mortality among patients with fibrotic IIP. Multivariate analysis confirmed that sex, initial D_{LCO}, and 6-month change in FVC were independent risk factors for the increased mortality of this group of patients. In contrast to previous studies (3, 4, 6, 19, 20), in our study pathologic patterns had no independent prognostic effect when 6-month change of FVC was considered. This finding is supported by other studies showing that clinical, physiological, and radiologic findings were important predictors of survival among patients with fibrotic IIP, providing information beyond that of histopathologic pattern at the time of diagnosis (10–12, 21–26). Latsi and coworkers reported that the distinction between UIP and fibrotic NSIP patterns provided no additional prognostic information, once serial

TABLE 3. TYPICAL REGIMENS FOR IDIOPATHIC INTERSTITIAL PNEUMONIA

	No. of Patients			
	IPF	NSIP	Initial Dose	Maintenance Dose
None	24	1		
PD only	20	12	1 or 0.5 mg/kg/d for 4 wk	15–10 mg/d
PD + azathioprine	45	10	PD (1.0 or 0.5 mg/kg/d) + azathioprine (50 mg/d)	PD (10–15 mg/d) + azathioprine (2 mg/kg/d)
PD + Cytoxan*	35	17	PD (1.0 or 0.5 mg/kg/d) + Cytoxan* (50 mg/d)	PD (10–15 mg/d) + Cytoxan* (2 mg/kg/d)
Colchicine	7	1	600 mg/d	600 mg/d

Definition of abbreviation: PD = prednisolone.
*Cyclophosphamide.

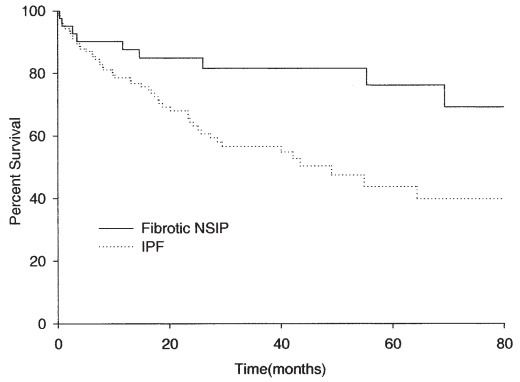

Figure 1. Survival of patients with fibrotic NSIP and IPF. Kaplan–Meier analysis showed that the survival of patients with fibrotic NSIP was better than that of patients with IPF ($p = 0.007$).

pulmonary function trends had been taken into account at 12-month follow-up (8). Furthermore, similar to that report, in our series when the initial D_{LCO} was less than 35% predicted, there was no significant difference in outcome between fibrotic NSIP and IPF, suggesting that the pathologic pattern is less important for the prognosis in the setting of relatively severe impairment in lung function.

The change in D_{LCO} was the most important factor in the series presented by Latsi and coworkers (8). We found that the change in FVC had a more important prognostic value than any other index of lung function. Our findings were similar to those of Flaherty and coworkers (11) and Collard and coworkers (12). The superiority of serial FVC over serial D_{LCO} may be because it is a more reproducible measure. A change in FVC at 6 months was a significant prognostic predictor and remained so after adjusting for pathologic diagnosis, age, sex, and baseline physiological status. That means that if the biopsy cannot be taken, a change in the FVC at 6 months gives sufficient information for prognosis and management in many cases. Histopathologic pattern at the time of diagnosis had a significant prognostic impact independent of the severity of the disease. Therefore, at the time of presentation, accurate diagnosis by surgical lung biopsy is still important for prognosis, not only of the patient's survival but also of future changes in lung function.

Some features of the clinical and physiological status of our patients differed from those of previous studies. Other reports showed no differences in smoking history between patients with NSIP and UIP patterns (4, 16, 19). However, in our study, there were more females and more nonsmokers among patients with NSIP, in contrast to more males and smokers with IPF. Therefore we looked carefully for the possibility of collagen vascular diseases in patients with NSIP by taking a thorough history and performing physical examinations and serological tests, such as for rheumatoid factor, anti-nuclear antibodies, anti-nuclear cytoplasmic antibodies, and Scl-70 antibody. In addition, those patients who developed evidence of such diseases during follow-up were excluded. It is difficult to interpret our finding of sex as an important predictor of survival in multivariate analysis; one possible answer is that more women had fibrotic NSIP whereas more men had UIP. Bivariate analysis restricted to sex and histopathology confirmed that the pathologic diagnosis was an independent factor, not sex.

Our study showed a marked lymphocytosis in BAL fluid for patients with NSIP, especially for the cellular type compared with IPF. This was similar to other reports, some of which did not clearly divide cellular from fibrotic NSIP (15, 17, 18, 27). In contrast, Veeraraghavan and coworkers reported no difference in BAL fluid lymphocyte percentage between patients with IPF and NSIP (28). This difference might reflect the patient population; their patients with NSIP presented a clinical picture similar to that of our group with IPF, with more men and more smokers. However, similar to that report, we found that the BAL fluid lymphocyte percentage was not a prognostic factor for the patients with fibrotic IIP and there was no correlation between BAL fluid lymphocyte level in patients with fibrotic NSIP and

TABLE 6. RESULTS OF UNIVARIATE ANALYSIS OF PROGNOSTIC FACTORS OF PATIENTS WITH FIBROTIC NONSPECIFIC INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS AFTER 6 MONTHS OF FOLLOW-UP

	Hazard Ratio	95% CI	p Value
Age	1.048	1.020–1.076	0.001
Sex*	1.914	1.077–3.401	0.027
NSIP diagnosis	0.389	0.190–0.797	0.010
Macrophages, %	1.013	0.996–1.030	0.130
Lymphocytes, %	0.980	0.960–1.000	0.054
Neutrophils, %	1.000	0.966–1.035	0.985
Smoking amount	1.004	0.993–1.016	0.492
Initial FVC, % predicted†	0.977	0.963–0.992	0.002
Initial FEV_1, % predicted†	0.990	0.977–1.004	0.166
Initial D_{LCO}, % predicted†	0.973	0.960–0.987	< 0.001
Initial TLC, % predicted†	0.985	0.970–1.000	0.056
Six-month change in FVC†	0.946	0.922–0.971	< 0.001
Six-month change in TLC†	0.983	0.966–1.001	0.071
Six-month change in D_{LCO}†	0.989	0.969–1.009	0.286
Resting Pa_{O_2}	0.966	0.949–0.984	< 0.001

*Sex code for male was 1 and code for female was 0.
† Analyzed as continuous variables.

TABLE 5. RESULTS OF MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS OF PATIENTS WITH FIBROTIC NONSPECIFIC INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS AT THE TIME OF PRESENTATION

	Hazard Ratio	95% CI	p Value
Age	1.043	1.012–1.074	0.006
Sex*	0.547	0.291–1.032	0.062
NSIP diagnosis	0.433	0.199–0.943	0.035
FVC, % predicted†	0.984	0.965–1.003	0.094
D_{LCO}, % predicted†	0.977	0.958–0.996	0.016
Resting Pa_{O_2}	0.983	0.963–1.003	0.093

Definition of abbreviation: CI = confidence interval.
*Sex code for male was 1 and code for female was 0.
† Analyzed as continuous variables.

TABLE 7. RESULTS OF MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS OF PATIENTS WITH FIBROTIC NONSPECIFIC INTERSTITIAL PNEUMONIA AND IDIOPATHIC PULMONARY FIBROSIS AFTER 6 MONTHS OF FOLLOW-UP

	Hazard Ratio	95% CI	p Value
Age	1.027	0.992–1.064	0.134
Sex*	2.724	1.277–5.813	0.010
NSIP diagnosis	0.854	0.349–2.093	0.730
Initial FVC, % predicted†	0.987	0.964–1.010	0.262
Initial D_{LCO}, % predicted†	0.972	0.949–0.996	0.022
Six-month change in FVC†	0.925	0.893–0.958	< 0.001
Resting Pa_{O_2}	0.995	0.961–1.031	0.798

*Sex code for male was 1 and code for female was 0.
† Analyzed as continuous variables.

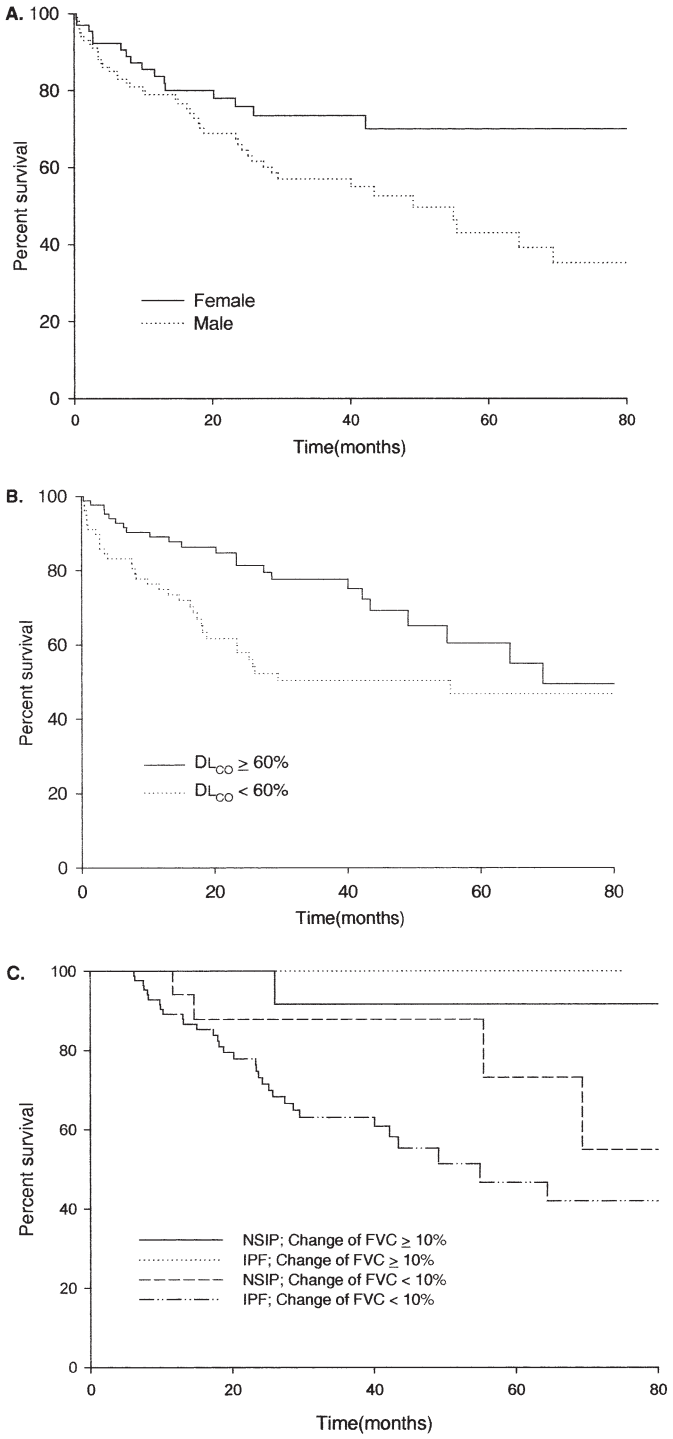

Figure 2. Survival in relation to physiological variables in patients with fibrotic NSIP and patients with IPF. Kaplan–Meier analysis showed that female sex (*A*, p = 0.021), higher initial DL_{CO} (*B*, p = 0.017), and an improved FVC at 6 months (*C*, p = 0.009) were associated with better survival.

disease severity. The BAL fluid lymphocyte count of our patients with IPF seemed to be higher than those reported by others; however, the percentage of BAL lymphocytes of our normal control group was 12.7 ± 9.9% (29). Veeraraghavan and coworkers also reported that 23% of their patients with IPF had elevated lymphocytes.

On HRCT about two-thirds of our patients with IPF had a dominant honeycombing pattern with or without a minimal degree of ground glass opacity, in contrast to patients with fibrotic NSIP, none of whom showed honeycombing. The major HRCT findings of NSIP were patchy areas of ground glass opacity with or without reticular opacity or airspace consolidation, as reported (30–33). However, there was considerable overlap in the HRCT patterns between fibrotic NSIP and IPF groups in previous studies and also in our patients (30, 33, 34–36). Moreover, many patients with IPF in our series did not show any honeycombing, making surgical lung biopsy necessary to differentiate the UIP pattern from the NSIP pattern. There was less consolidation seen on HRCT in our patients with fibrotic NSIP than in previous reports from Japan and Korea (18, 37, 38). Twenty-two percent of our patients had a small area of consolidation (less than 5% of the diseased area in most cases), which is considerably lower than the 74% reported in one Japanese study (38), suggesting that our series does seem to equate to "classic" NSIP as recognized in the United States and Europe, representing an IPF overlap.

This study had some limitations: it was a retrospective study and some parameters, such as TLC, were missing at the time of 6-month follow-up. The median follow-up period for our patients (23.7 months) was relatively short. However, it was enough to reveal the prognostic significance of physiological variables and prognostic differences between fibrotic NSIP and IPF. Our study had a relatively large number of NSIP patients compared with previous reports (2–6, 15–19). The pulmonary function test results of our patients with IPF were better preserved at presentation, and their survival seemed to be better than in some previous series (3, 11, 16, 22, 24). Some selection bias may exist. At present many Koreans have regular medical examinations including chest X-rays, and CT scans are easily available at a lower cost than in any other country, resulting in detection of many interstitial lung diseases at an early stage.

In conclusion, our study confirmed that the outcome of patients with fibrotic NSIP is better than that of patients with IPF and an accurate initial diagnosis based on the histopathologic pattern is a crucial feature in the prediction of response to initial therapy and survival. However, change in physiologic status, particularly FVC over 6 months, becomes a critical predictor of survival once it is declared by the patient.

Conflict of Interest Statement: Y.J. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.S.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; T.S.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.-M.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; S.D.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; Y.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; W.S.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; W.D.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.S.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; W.D.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; T.V.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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