Prognosis of Fibrotic Interstitial Pneumonia
Idiopathic versus Collagen Vascular Disease–related Subtypes

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***Background*: To investigate whether the better prognosis of interstitial pneumonias associated with collagen vascular disease (CVD) compared with idiopathic interstitial pneumonia (IIP) is due to higher frequency of the nonspecific interstitial pneumonia (NSIP) pattern in CVD, we compared the outcomes of patients from these two groups with the same histopathologic pattern.**

***Subjects*: The clinical features and survival of 362 patients (269 with IIP and 93 with CVD) diagnosed using surgical lung biopsy were analyzed.**

***Results*: The mean survival of the CVD group (131.0 mo) was longer than that of the IIP group (80.5 mo) ($p < 0.0001$). The patients with usual interstitial pneumonia pattern among the CVD group ($n = 36$) was younger, female, and predominantly nonsmoking compared with the IIP group ($n = 203$). Although baseline lung functions were not significantly different, the CVD group survived longer (mean, 177.0 mo) than the IIP group (mean, 66.9 ± 6.5 mo; $p = 0.001$). By multivariate analysis, younger age, better pulmonary function, and the presence of a CVD were independent prognostic factors. In NSIP pattern, no significant differences in survival, clinical features, or lung function were found between the two groups.**

***Conclusion*: Our data suggest that the better prognosis of patients in the CVD group is not solely due to the predominance of the NSIP pattern. The prognosis of patients with the usual interstitial pneumonia pattern in CVD is better than in those with idiopathic pulmonary fibrosis, despite the same pathologic pattern. In contrast, in those with an NSIP pattern, the prognosis is similar in both groups.**

Keywords: prognosis; collagen vascular disease–interstitial pneumonia; idiopathic interstitial pneumonia; usual interstitial pneumonia; nonspecific interstitial pneumonia

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Even though interstitial pneumonia associated with collagen vascular disease has a better prognosis than idiopathic pulmonary fibrosis, it is not certain whether this is due to the predominance of a nonspecific interstitial pneumonia pattern or to a genuine difference in the same pathologic pattern.

What This Study Adds to the Field

Patients with collagen disease–usual interstitial pneumonia had significantly better survival than those with idiopathic usual interstitial pneumonia–idiopathic pulmonary fibrosis. In patients with a nonspecific interstitial pneumonia pattern, no significant difference was noted between the two groups.

It has been reported that patients with interstitial pneumonia associated with collagen vascular disease (CVD-IP) have a better prognosis than patients with idiopathic interstitial pneumonia (IIP) (1–5). IIP is currently classified into seven clinico-radiologic-pathologic entities, which differ not only in pathology but also in clinical features, especially in relation to prognosis (6, 7). Of these, the two most common histologic patterns are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP) (8), with UIP being the predominant pattern in idiopathic pulmonary fibrosis (IPF) and NSIP being seen in a more heterogeneous group of clinical settings, one of which is an idiopathic presentation (6–15). Because the differential diagnosis between these subtypes of IIP requires surgical lung biopsy and biopsy is rarely performed in patients with CVD-IP, most patients with CVDs were classified as having UIP up until the 1990s. Since then, the major histopathologic pattern in many CVDs (scleroderma, dermatomyositis, and Sjögren syndrome) has been shown to be NSIP (2, 5, 16–19). These findings suggest that the better prognosis of CVD-IP may be primarily related to a higher frequency of NSIP. However, there is evidence of differences in relation to the same histologic pattern between IIPs and CVD-IPs, in that myofibroblasts have different appearances in patients with IPF-UIP compared with UIP in association with rheumatoid arthritis (RA-UIP) (16), and there are fewer fibroblastic foci in CVD-UIP compared with IPF-UIP (2). The main purpose of this study is therefore to investigate whether there is a difference in prognosis of patients with CVD-IP compared with those with IIPs in relation to individual histopathologic patterns. The data were presented at the American Thoracic Society (ATS) meeting in 2004 in abstract form (20).

METHODS

Subjects

The subjects included 362 patients (269 with IIP and 93 with CVD-IP) diagnosed using surgical lung biopsy as UIP pattern (203 with IPF

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and 36 with CVD-UIP) or fibrotic NSIP pattern (66 with idiopathic [I]-NSIP and 57 with CVD-NSIP) from 1990 to April 2006 at Asan Medical Center in South Korea. Most of the patients with IIP were included in a previous physiologic study (12); some patients in an ATS/European Respiratory Society (ERS)–sponsored NSIP workshop (not published), and some patients with scleroderma, primary Sjögren syndrome, and RA were also included in other reports (18, 21, 22). The mean follow-up period was 36.8 ± 2.1 months for IIP (0.2–186.3 mo) and 56.0 ± 4.2 months for CVD-IP (1.0–177.0 mo).

Diagnostic Criteria

IPF was diagnosed according to the ATS/ERS consensus classification (6) and UIP pattern was determined at the biopsy. Patients with a history of drug toxicity or environmental exposures were excluded. Because the prognosis of cellular NSIP has been reported to be clearly different (much better) from that of IPF-UIP or fibrotic NSIP (9, 10, 12), only patients with fibrotic NSIP were included. Individual CVDs were diagnosed according to the criteria of corresponding societies (*see* References 23–30 and Table 1).

Method

The biopsy slides were reviewed independently by two pairs of pathologists (T.V.C. and M.K.: 164 cases; κ, 0.590; or T.V.C. and S.J.J.: 138 cases; κ, 0.429) and, for most patients, consensus was achieved after a third opinion by A.G.N. For the remaining controversial cases, consensus opinion was achieved by a final face-to-face meeting. The pathologic diagnoses of the subjects included in previous studies were reviewed separately by different pathologists listed in each study as coauthors (12, 18, 21, 22). However, one pathologist (T.V.C.) was involved in all studies, except for the study on Sjögren disease (21). Pathologists were blinded to the clinical information except in three studies of CVDs.

All data were obtained from the medical records and survival status was obtained from telephone interview and/or medical records. All the clinical parameters were obtained within 1 month before surgical lung biopsy. The Medical Research Council system was used for dyspnea scoring (31).

Pulmonary Function Test

Spirometry (Vmax 22; Sensormedics, Yorba Linda, CA), plethysmographic lung volumes (6200 Plethysmograph; Sensormedics), and diffusion capacity of carbon monoxide (D_{LCO}) (Vmax 229D; Sensormedics) were measured and the results were expressed as a percentage of normal predicted values (32).

Bronchoalveolar lavage (BAL) was performed as previously described (33).

Statistical Analysis

All values were described as mean ± standard deviation and survival period was expressed as mean ± standard error. A chi-square statistics test or Fisher's exact test was used for categorical data and an unpaired Student's *t* test or a Mann-Whitney test for continuous data. 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 selected via univariate test ($p < 0.05$) were evaluated in a multivariate Cox regression analysis. A p value less than 0.05 was considered statistically significant (two-tailed). All data were analyzed using SPSS version 11.0 (SPSS, Inc., Chicago, IL).

This study was approved by the institutional review board of Asan Medical Center.

RESULTS

Comparison of Survival of Patients with IIP and Those with CVD-IP

The IIP group was older, male, and predominantly smokers compared with the CVD-IP group. However, there was no significant difference in lung function or BAL fluid findings (data not shown) between the two groups (Table 2). Patients in the CVD-IP group survived longer (mean, 131.0 ± 9.1 mo) than those in the IIP group (mean, 80.5 ± 6.3 mo; $p < 0.001$) (Figure 1). Multivariate analysis revealed that age, FVC, D_{LCO}, and the presence of CVD are independent marker for prognosis (Tables E1 and Table E2 of the online supplement).

Comparison of Survival between Patients with IPF-UIP and Those with CVD-UIP

The CVD-UIP group was younger, female, and predominantly nonsmoking compared with the IPF-UIP group (Table 3). However, there was no significant difference in baseline pulmonary function and BAL fluid findings between the two groups (Table E3). Patients in the CVD-UIP group survived longer (mean, 125.5 ± 16.0 mo) than those in the IPF-UIP group (mean, 66.9 ± 6.5 mo) ($p = 0.001$; Figure 2). In addition, 3-year survival rates (81.6 vs. 57.4%) and 5-year survival rates (81.6 vs. 44.8%) were better in the CVD-UIP group than in the IPF-UIP group, respectively ($p = 0.001$; Figure 2). Using univariate Cox analysis, age, dyspnea score, presence of CVD, FVC, D_{LCO}, total lung capacity (TLC), and Pa_{O_2}/FI_{O_2} ratio (mm Hg) were significant predictors of survival (Table 4). Multivariate analysis by Cox regression model revealed that only age (hazard ratio [HR], 1.042; 95% confidence interval [CI], 1.019–1.066; $p < 0.001$), better pulmonary function (FVC; HR, 0.982; 95% CI, 0.967–0.997; $p = 0.020$) and D_{LCO}, HR, 0.975; 95% CI, 0.961–0.989; $p = 0.001$), and presence of CVD (HR, 2.861; 95% CI, 1.327–6.171; $p = 0.007$) were independent

TABLE 1. PATHOLOGIC PATTERNS OF LUNG FIBROSIS IN THE CLINICAL SETTINGS OF IDIOPATHIC AND COLLAGEN VASCULAR DISEASES: RELATIVE FREQUENCY OF FIBROTIC NONSPECIFIC INTERSTITIAL PNEUMONIA

	Number of Subjects	NSIP, n (%)
Idiopathic	269	66 (24.5)
Rheumatoid arthritis	28	10 (35.7)
Scleroderma	35	23 (65.7)
Dermatomyositis–polymyositis	8	7 (87.5)
Sjögren syndrome	11	7 (63.6)
Systemic lupus erythematosus	1	1 (100)
Mixed connective tissue disease	5	5 (100)
Polymyalgia rheumatica	2	2 (100)
CREST syndrome	2	2 (100)
Undifferentiated	1	0

Definition of abbreviations: CREST = calcinosis, Reynaud syndrome, esophageal reflux, sclerodactyly, and telangiectasia; NSIP = nonspecific interstitial pneumonia.

TABLE 2. BASELINE CLINICAL AND DEMOGRAPHIC FEATURES OF ALL PATIENTS

	IIP	CVD-IP	p Value
Total number	269	93	
Age, yr	58.1 ± 9.5	50.7 ± 11.7	0.001
Male sex, n	166 (61.7%)	22 (23.7%)	0.001
Smoking, current/ex/never	80/78/111	13/9/71	0.001
Smoking history, pack-years	22.6 ± 21.3	8.8 ± 16.9	0.001
Pathologic pattern of UIP, n	203 (75.5%)	36 (38.7%)	0.001
Duration of dyspnea, mo	11.7 ± 15.6	12.2 ± 19.3	NS
Dyspnea score	3.1 ± 1.3	2.8 ± 1.2	NS
Pulmonary function	n = 257	n = 93	
FVC, % predicted	70.1 ± 17.2	66.6 ± 16.1	NS
TLC, % predicted	75.8 ± 17.7	73.4 ± 14.4	NS
D_{LCO}, % predicted	61.5 ± 20.5	59.0 ± 16.8	NS
Pa_{O_2}/FI_{O_2} ratio, mm Hg	435.4 ± 69.9	455.4 ± 57.9	0.018

Definition of abbreviations: CVD-IP = interstitial pneumonia associated with collagen vascular disease; D_{LCO} = diffusion capacity of carbon monoxide; ex = ex-smoker; IIP = idiopathic interstitial pneumonia; NS = nonsignificant; TLC = total lung capacity; UIP = usual interstitial pneumonia.

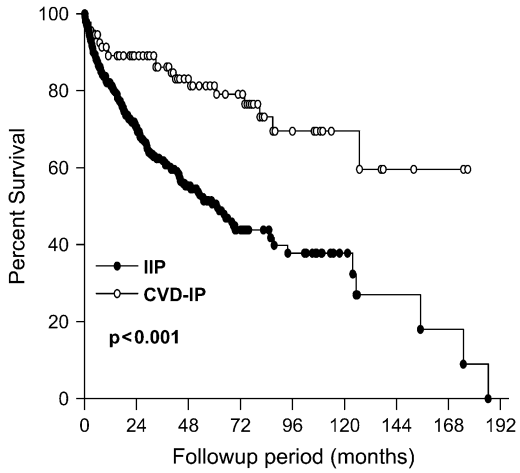

Figure 1. Survival of total subjects with idiopathic interstitial pneumonia (IIP) and interstitial pneumonia associated with collagen vascular disease (CVD-IP).

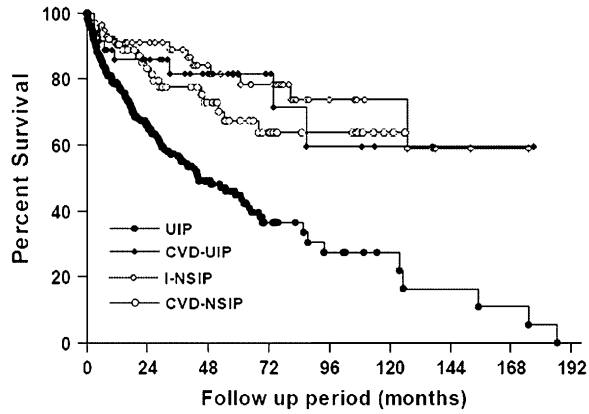

Figure 2. Comparison of the survival curves of all subject groups. CVD-UIP = usual interstitial pneumonia associated with collagen vascular disease; CVD-NSIP = nonspecific interstitial pneumonia associated with collagen vascular disease; I-NSIP = idiopathic nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

predictors of better survival in patients with UIP pattern disease (Table E4).

Comparison of Survival between Patients with I-NSIP and CVD-NSIP

The CVD-NSIP group was younger and predominantly female compared with the I-NSIP group (Table 5). There were no differences in lung function and BAL fluid findings between these two groups (Table 5 and Table E3). The 3-year survival rates were 88.9% in the CVD-NSIP group and 77.6% in the I-NSIP group, whereas the 5-year survival rates were 81.5 and 67.4%, respectively. Using the log-rank test, no significant difference in survival was found between CVD-NSIP and I-NSIP ($p = 0.2$) (Figure 2). According to a univariate Cox model, age, FVC, TLC, and dyspnea score were significant predictors of survival (Table 6). Multivariate analysis revealed that age (HR, 1.076; 95% CI, 1.037–1.116; $p < 0.001$) and FVC (HR, 0.946; 95% CI, 0.916–0.977, $p = 0.001$) were independent risk factors for survival of patients with the NSIP pattern (Table E5). Unlike in those with the UIP pattern, D_{LCO} was not an independent risk factor in those with the NSIP pattern. In contrast to patients with the UIP pattern, the presence of CVD in patients with the NSIP pattern was not associated with a better prognosis.

Comparison of Survival between Patients with CVD-UIP and Those with CVD-NSIP

In contrast to IIP, in which the survival of patients with the UIP pattern was much worse than in patients with the NSIP pattern (Figure 2), there was no difference between patients with CVD-UIP and CVD-NSIP (Table 7 and Table E6).

RA. The survival of the patients with IP related to RA (RA-IP) was better than that in those with IPF ($p = 0.019$); however, there was no significant difference in the survival between patients with RA-IP and those with other types of CVD (non–RA-CVD-IP) or I-NSIP (Table 8 and Table E7; Figure E1). Even though the Kaplan-Meier analysis showed that the survival of those with RA-UIP was significantly worse than that in those with non–RA-CVD-UIP ($p = 0.015$) or CVD-NSIP ($p = 0.043$) (Figure 3), after the adjustment for age, sex, and FVC, the difference became statistically insignificant by multivariate Cox

TABLE 3. BASELINE CLINICAL AND DEMOGRAPHIC FEATURES OF PATIENTS WITH A USUAL INTERSTITIAL PNEUMONIA PATTERN

	IPF-UIP	CVD-UIP	p Value
Number of patients	203	36	
Age, yr	59.2 ± 9.2	53.0 ± 12.1	0.006
Male sex, n	144 (70.9%)	12 (33.3%)	< 0.001
Smoking, current/ex/never	69/68/66	7/4/25	0.001
Smoking history, pack-years	25.8 ± 21.1	15.4 ± 22.3	0.018
Duration of dyspnea, mo	13.4 ± 17.1	8.8 ± 9.7	0.030
Dyspnea score	3.0 ± 1.3	2.7 ± 1.2	NS
Pulmonary function	n = 191	n = 36	
FVC, % predicted	72.2 ± 17.4	67.7 ± 15.7	NS
TLC, % predicted	76.6 ± 16.6	74.9 ± 13.0	NS
D_{LCO}, % predicted	62.9 ± 20.6	59.6 ± 16.3	NS
Pa_{O_2}/FI_{O_2} ratio, mm Hg	435.1 ± 69.4	447.6 ± 51.8	NS

Definition of abbreviations: ex = ex-smoker; CVD-UIP = usual interstitial pneumonia associated with collagen vascular disease; D_{LCO} = diffusion capacity of carbon monoxide; IPF-UIP = usual interstitial pneumonia associated with idiopathic pulmonary fibrosis; NS = nonsignificant; TLC = total lung capacity.

TABLE 4. PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS WITH A USUAL INTERSTITIAL PNEUMONIA PATTERN USING A UNIVARIATE COX MODEL

	n	Hazard Ratio	95% CI	p Value
Age	239	1.044	1.023–1.067	< 0.001
Male sex	239	1.352	0.891–2.049	NS
Smoker vs. nonsmoker	239	0.857	0.575–1.277	NS
Dyspnea score	201	1.486	1.266–1.745	< 0.001
IPF vs. CVD-UIP	239	3.158	1.534–6.501	0.002
FVC, %, predicted	227	0.978	0.968–0.989	< 0.001
D_{LCO}, %, predicted	219	0.974	0.964–0.985	< 0.001
TLC, %, predicted	206	0.986	0.974–0.999	0.030
Pa_{O_2}/FI_{O_2} ratio, mm Hg	206	0.996	0.993–0.999	0.008
BAL total cells	151	1.003	0.999–1.008	NS
BAL neutrophils, %	154	1.006	0.985–1.028	NS
BAL lymphocytes, %	155	0.998	0.980–1.016	NS

Definition of abbreviations: BAL = bronchoalveolar lavage; CI = confidence interval; CVD-UIP = usual interstitial pneumonia associated with collagen vascular disease; D_{LCO} = diffusion capacity of carbon monoxide; IPF = idiopathic pulmonary fibrosis; n = number of patients; NS = nonsignificant; TLC = total lung capacity.

TABLE 5. BASELINE CLINICAL AND DEMOGRAPHIC FEATURES OF PATIENTS WITH A NONSPECIFIC INTERSTITIAL PNEUMONIA PATTERN

	I-NSIP	CVD-NSIP	p Value
Number of patients	66	57	
Age, yr	54.9 ± 10.0	49.3 ± 11.2	0.004
Male sex, n	22 (33.3%)	10 (17.5%)	0.047
Smoking, current/ex/never	11/10/45	6/4/50	NS
Smoking history, pack-years	11.7 ± 18.4	5.0 ± 11.7	0.031
Duration of dyspnea, mo	6.4 ± 8.3	14.3 ± 23.3	0.022
Dyspnea score	3.1 ± 1.3	2.8 ± 1.3	NS
Pulmonary function	n = 66	n = 57	
FVC, % predicted	64.1 ± 15.1	65.9 ± 16.5	NS
TLC, % predicted	73.2 ± 20.7	72.4 ± 15.2	NS
D_{LCO}, % predicted	57.2 ± 19.7	58.6 ± 17.2	NS
Pa_{O_2}/FI_{O_2} ratio, mm Hg	436.3 ± 72.0	460.2 ± 61.4	NS

Definition of abbreviations: CVD-NSIP = nonspecific interstitial pneumonia associated with collagen vascular disease; D_{LCO} = diffusion capacity of carbon monoxide; I-NSIP = idiopathic nonspecific interstitial pneumonia; NS = nonsignificant; TLC = total lung capacity.

TABLE 7. PROGNOSTIC FACTORS FOR THE SURVIVAL OF PATIENTS WITH INTERSTITIAL PNEUMONIA ASSOCIATED WITH COLLAGEN VASCULAR DISEASE USING A UNIVARIATE COX MODEL

	n	Hazard Ratio	95% CI	p Value
Age, yr	93	1.059	1.015–1.105	0.008
Male sex	93	1.250	0.477–3.273	NS
Smokers vs. nonsmokers	93	1.066	0.386–2.941	NS
Dyspnea score	83	1.578	1.099–2.265	0.013
CVD-UIP vs. CVD-NSIP	93	1.288	0.524–3.164	NS
RA vs. other CVDs	93	1.840	0.750–4.515	NS
Scleroderma vs. other CVDs	93	0.457	0.166–1.262	NS
FVC, %, predicted	93	0.964	0.935–0.993	0.017
D_{LCO}, %, predicted	89	0.982	0.954–1.011	NS
TLC, %, predicted	80	0.983	0.945–1.022	NS
Pa_{O_2}/FI_{O_2} ratio, mm Hg	87	0.999	0.991–1.007	NS

Definition of abbreviations: CI = confidence interval; CVD-NSIP = nonspecific interstitial pneumonia associated with collagen vascular disease; CVD-UIP = usual interstitial pneumonia associated with collagen vascular disease; D_{LCO} = diffusion capacity of carbon monoxide; n = number of patients; NS = nonsignificant; RA = rheumatoid arthritis; TLC = total lung capacity.

regression analysis (RA-UIP vs. non–RA-CVD-UIP: p = 0.1; RA-UIP vs. CVD-NSIP: p = 0.07) (Table E8). We could not find any significant difference in the survival between patients with RA-UIP and those with IPF-UIP by either method.

Scleroderma. The survival of patients with scleroderma-IP was much better than that in those with IPF and not significantly different from those with other types of CVD or I-NSIP (Table E8 and Figure E2).

Treatment

Among the IPF group, 153 patients (75.4%) were treated with corticosteroid alone or with cytotoxic drugs (azathioprine, 95 patients; cyclophosphamide, 50 patients), 7 patients (3.4%) received colchicine, and 43 patients (21.2%) did not have any treatment. The majority of the CVD-UIP group (32 patients, 88.9%) received corticosteroid and azathioprine (10 patients) or cyclophosphamide (15 patients), and 2 patients received colchicine. Similarly, most of the patients in the NSIP group (I-NSIP, 93.9%; CVD-NSIP, 96.5%) were treated with steroid alone or with cytotoxic drugs.

TABLE 6. PROGNOSTIC FACTORS FOR SURVIVAL OF PATIENTS WITH A NONSPECIFIC INTERSTITIAL PNEUMONIA PATTERN USING A UNIVARIATE COX MODEL

	n	Hazard Ratio	95% CI	p Value
Age, yr	123	1.058	1.023–1.094	0.001
Male sex	123	1.657	0.774–3.544	NS
Smoker vs. nonsmoker	123	0.730	0.334–1.595	NS
Dyspnea score	108	1.346	1.018–1.779	0.037
I-NSIP vs. CVD-NSIP	123	1.634	0.771–3.466	NS
FVC, % predicted	123	0.964	0.940–0.989	0.005
D_{LCO}, % predicted	117	0.983	0.962–1.004	NS
TLC, % predicted	104	0.966	0.937–0.995	0.024
Pa_{O_2}/FI_{O_2} ratio, mm Hg	115	0.995	0.990–1.000	0.06
BAL total cells	71	0.983	0.959–1.007	NS
BAL neutrophils, %	76	1.001	0.962–1.043	NS
BAL lymphocytes, %	76	0.992	0.965–1.019	NS

Definition of abbreviations: BAL = bronchoalveolar lavage; CI = confidence interval; CVD-NSIP = nonspecific interstitial pneumonia associated with collagen vascular disease; D_{LCO} = diffusion capacity of carbon monoxide; I-NSIP = idiopathic nonspecific interstitial pneumonia; n = number of patients; NS = nonsignificant; TLC = total lung capacity.

Cause of Death

The most common cause of death in patients with IPF, CVD-UIP, or I-NSIP was disease progression, with or without infection, including acute exacerbation (Table 8).

DISCUSSION

The aim of this study was to investigate whether the better prognosis of CVD-IP compared with IIP was solely due to a predominance of an NSIP pattern in CVD-IP. We confirmed that the patients with CVD-IP survived longer than those with IIP, but the was mainly because the survival of patients with CVD-UIP was longer than those with IPF-UIP, and not just due to a higher prevalence of an NSIP pattern in patients with CVDs. In patients with an NSIP pattern as an overall group, there was no survival benefit in the CVD-NSIP group compared with the I-NSIP group.

UIP is the most common pattern of IIP, being seen in 47 to 62% of recent series compared with 14 to 36% for NSIP (10, 11, 14, 15), with similar results seen at our own institution (63.3 vs. 23.2%) (12). All of these series reported that the prognosis of I-NSIP was better than that of IPF-UIP. In contrast, most series of CVD-IP that studied histologic patterns show NSIP is more common than UIP. In scleroderma, Fujita and colleagues (17) first reported that five of nine patients showed a pattern of NSIP, which was confirmed by others in larger series (67 and 78%) (18). Similarly, in polymyositis–dermatomyositis (PM-DM), an NSIP pattern was the most common type with a prevalence of up to 82% (5, 34, 35), with only a 5 to 12% prevalence of UIP; furthermore, Ito and colleagues evaluated 33 patients with primary Sjögren's syndrome and found NSIP to be more common than UIP (21). However, data are more conflicting with regard to patients with RA, with data from our institution showing prevalence of UIP and NSIP (62.1 and 37.9%, respectively), whereas others have shown NSIP to be more prevalent (12 vs. 41%, respectively) (35). The reasons for this are uncertain, but to exclude the possibility of selection bias in this series, we searched for all patients with RA-IP in our hospital medical records and compared the clinical and high-resolution computed tomography (HRCT) features between the biopsy group and the nonbiopsy group. There was no significant difference in the clinical features and lung function data, and we found that more than 80% of the nonbiopsy group had typical HRCT features

TABLE 8. CAUSES OF DEATH IN PATIENTS WITH INTERSTITIAL PNEUMONIA

	Number of Patients (%)			
Cause of Death	IPF-UIP	I-NSIP	CVD-UIP	CVD-NSIP
Total deaths	103	18	8	12
Disease progression	31 (30.1)	7 (38.9)	2 (25.0)	1 (8.3)
Disease progression with combined infection	4 (2.9)	4 (22.2)	0	1 (8.3)
Disease progression with renal failure	0	1 (5.6)	0	2* (16.7)
Disease progression with pulmonary embolism	0	0	1 (12.5)	0
Acute exacerbation	18 (18.4)	2 (11.1)	3 (37.5)	1 (8.3)
Pneumonia	10 (9.7)	0	1 (12.5)	1 (8.3)
Lung cancer	5 (4.9)	0	0	1 (8.3)
Cardiovascular disease	1 (1.0)	0	0	1 (8.3)
Nonpulmonary infection	1 (1.0)	0	0	1 (8.3)
Nonpulmonary cancer	1 (1.0)	2 (11.1)	0	1 (8.3)
Other	2 (1.9)	0	0	0
Unknown	30 (29.1)	2 (11.1)	1 (12.5)	2 (16.7)

Definition of abbreviations: CVD-NSIP = nonspecific interstitial pneumonia associated with collagen vascular disease; CVD-UIP = usual interstitial pneumonia associated with collagen vascular disease; I-NSIP = idiopathic nonspecific interstitial pneumonia; IPF-UIP = usual interstitial pneumonia associated with idiopathic pulmonary fibrosis.

* Renal failure associated with underlying CVD.

of UIP (subpleural reticulation and honeycombing without much ground-glass opacity), supporting the result of a UIP pattern predominance in pathologic study. These data suggest a need for further clinical and histologic assessment of patients with IPs in association with RA (RA-IP), particularly as RA is the most common type of pattern is the most commonly seen CVD, and especially as there are several studies of survival in patients with RA-IP with variable results, which will be discussed later more in detail.

Although clinical and radiologic features of CVD-IP are similar to IIP, many studies have reported better prognosis in patients with CVD-IP (1–5). Agusti and colleagues found that all the lung function parameters and Pa_{O_2} were reduced in the patients with IPF (9 patients) in contrast to no change in those with CVD-IP (11 patients) 2 years after the diagnosis (1). In the study

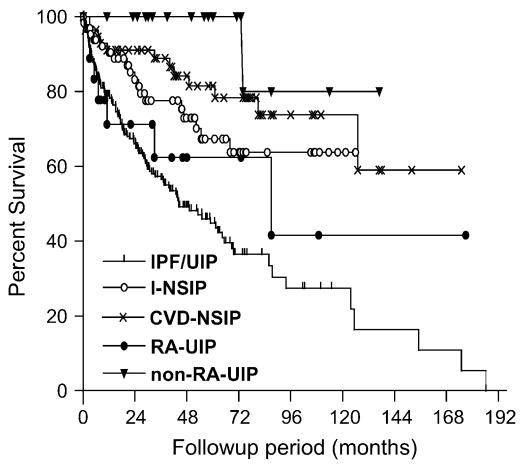

Figure 3. Comparison of the Kaplan-Meier survival curves between the subject groups and the usual interstitial pneumonia associated with rheumatoid arthritis (RA-UIP). CVD-NSIP = nonspecific interstitial pneumonia associated with collagen vascular diseases; I-NSIP = idiopathic nonspecific interstitial pneumonia, IPF/UIP = idiopathic pulmonary fibrosis/usual interstitial pneumonia; non-RA-UIP = usual interstitial pneumonia in the patients with non–rheumatoid arthritis-collagen vascular diseases. The statistical significance between groups were as follows: RA-UIP versus non–RA-UIP, $p = 0.015$; RA-UIP versus CVD-NSIP, $p = 0.043$; RA-UIP versus I-NSIP, not significant; RA-UIP versus IPF/UIP, not significant.

by Papiris and coworkers on the survival of 43 patients (18 with IPF and 25 with scleroderma-IP), two-thirds of patients with IPF died in 2.7 years in contrast to no deaths in the CVD-IP group during 5.6 years of follow-up (3). Wells and colleagues reported that 142 of 205 patients with IPF (70%) died, whereas only 11 of 68 patients with scleroderma-IP (16%) died (4). However, in these earlier studies, the pathologic pattern was not defined. Later, Bouros and colleagues, in the largest series of surgical lung biopsy-proven CVD-IP (80 patients), reported higher survival in patients with scleroderma-IP (5-yr survival of 91% in NSIP pattern and 82% in UIP pattern; 10-yr survival of 69% in NSIP pattern and 29% in UIP pattern) (19). There was no significant difference in survival between patient with NSIP pattern and those with UIP pattern disease. In PM-DM, Douglas and colleagues compared the survival of 58 patients with PM-DM–IP with that of historical controls (i.e., 63 patients with biopsy-proven IPF-UIP and 14 patients with I-NSIP) (5). One-year survival for patients with PM-DM–IP was 85.8%, 3-year survival was 74.7%, and 5-year survival was 60.4%. Survival was better ($p < 0.001$) for the PM-DM–IP group when compared with the group with IPF, and was not different from the group with I-NSIP ($p = 0.247$). However, in this study, the majority of pathologic patterns of PM-DM were NSIP (81.8%) and only 1 (4.5%) of 22 patients had a UIP pattern.

In contrast to all of those studies, Hubbard and associates recently reported a different result (40). They analyzed a longitudinal dataset containing 979 patients with IP (872 patients with IPF, 107 patients with CVD-IP) diagnosed (without biopsy) between April 1989 and October 1997. Patient data were drawn from the U.K. General Practice Research Database, which is the largest primary care population database in the United Kingdom. Using a univariate Cox regression model, survival was similar for patients with CVD-IP compared with patients with IPF. Even though there was some criticism about this study (39, 41), it raised an important question about the uniformly better prognosis of CVD-IP. In this study, the majority (80%) of the patients with CVD-IP had RA. All these findings may suggest that the better survival of patients with CVD-IP may be due to the higher prevalence of an NSIP pattern between IIP and CVD-IP in the CVD group rather than the genuine difference between IIP and CVD-IP. Furthermore, Kocheril and colleagues recently conducted a case-control study of patients with CVD-IP ($n = 46$) and IIP ($n = 51$), and found that CVD-IP was associated with a worse prognosis compared with IIP when adjusted for

age (43). Therefore, we analyzed the survival of our large cohort of patients with IIP and CVD-IP and confirmed that the survival of patients in the CVD-IP group as a whole was significantly better than that in those with IIP. To test that the possibility of this better survival was due to the early diagnosis of interstitial lung diseases in those who undergo frequent check-up for rheumatologic diseases, we compared the baseline parameters between two groups. Even though the patients with CVD-IP were younger and predominantly female nonsmokers, lung functions were similar. To investigate the cause of better prognosis of CVD-IP, the survival was analyzed further in relation to histologic pattern. For UIP pattern, the mean survival in patients with CVD-UIP was longer compared with those with IPF-UIP. Furthermore, the presence of a CVD was an independent parameter for better prognosis together with younger age and better pulmonary function (FVC and D_{LCO}). This is supported by other studies. Flaherty and colleagues, who reviewed 108 patients with a UIP pattern on surgical lung biopsies, reported that patients with CVD-UIP had fewer fibroblastic foci and better survival than those with IPF even after adjustment for age, TLC, and onset of symptoms (2). However, the number of their CVD-UIP group was only nine patients and these patients were younger with shorter duration of symptoms (0.5 vs. 2 yr) and higher TLC compared with the patients with IPF-UIP. In contrast, our study was performed on a much larger number of patients with CVD-UIP. Our patients with CVD-UIP were also younger, predominantly female, and with a slightly shorter duration of symptoms (8.8 vs. 13.4 mo); however, lung function tended to be lower than in the IPF group (Table 3). The average lung function of our IPF group was better and the duration of symptoms was shorter (13.4 mo) than the patients with IPF in Flaherty and colleagues' report (2 yr). In contrast, Flaherty and coworkers' patients with CVD-UIP had better lung function, especially TLC, with shorter duration of symptoms (0.5 yr) compared with our patients with CVD-UIP (8.8 mo) (2). These findings suggested that patients with CVD-UIP in Flaherty and colleagues' study might have been diagnosed at an earlier stage than their patients with IPF-UIP (lead-time bias). However, our study showed that the prognosis of CVD-UIP was better than that of IPF/UIP without lead-time bias.

Nakamura and colleagues specifically compared the prognosis of a UIP pattern (76 patients with IPF-UIP and 17 patients with CVD-UIP) and an NSIP pattern (22 patients with I-NSIP and 26 with CVD-NSIP). Similar to our data, patients with CVD-UIP had significantly better survival than those with IPF-UIP, whereas no survival difference was found between patients with I-NSIP and those with CVD-NSIP (42). Our study verified that patients with CVD-UIP survived longer than those with IPF-UIP not only using simple Kaplan-Meier survival curves but also using multivariate analysis with Cox proportional hazards regression analysis in a larger number of patients.

In contrast to other types of CVD, the reported prognosis of RA-IP was variable. Turner-Warwick and coworkers reported on a series of patients with RA and lung disease and found no difference in mortality rate from that found in cryptogenic fibrosing alveolitis, although this result may be biased because of inclusion of patients with diseases other than IPF, using recent criteria (36). Hakala evaluated the course of 57 patients with RA admitted to the hospital with interstitial lung fibrosis, and found a poor prognosis, with a median survival of 3.5 years and a 5-year survival rate of 39%, which is similar to that of IPF-UIP (37). Later, Akira and colleagues (38) reported that the mean survival of 29 patients with RA-IP diagnosed by HRCT was 3 years. Among 19 patients who had features of IP, 10 patients died of respiratory failure, and 1 died of small cell lung carcinoma. In contrast, Saravanan and associates reported a better prognosis for RA-IP (n = 18) compared with IPF (n = 18) (39), with a 5-year survival of 44% in patients with RA-IP compared with 11% in patients with IPF. In our previous series of RA, even though the numbers were small, all deaths occurred in the UIP group. In the present study, with larger number of the subjects, we found that the survival of patients with RA-IP was similar to that in patients with other non–RA-CVD-IP or I-NSIP (Table E8, Figure 3). However, the survival of patients with RA-UIP seems to be similar to that in those with IPF/UIP and worse than that in patients with CVD-NSIP or other non–RA-CVD-UIP using Kaplan-Meier survival analysis, even though the difference became insignificant after the adjustment of age, sex, and FVC using multivariate Cox proportional hazards regression analysis, suggesting the similarity of RA-UIP to other non–RA-CVD-IPs. More study with larger numbers of subjects is required to confirm our results. To exclude the possibility that only the more severe cases were selected for surgical lung biopsy, we compared the survival of patients with RA-UIP and RA-IP who did not undergo biopsy but who had typical HRCT patterns of IPF. There was no significant difference in the survival between the two groups (data not shown). On the contrary, scleroderma-IP seems to be a more uniform group with a similar prognosis to I-NSIP or other non–scleroderma-CVD-IP, regardless of the pathologic pattern (Figure E2).

Our study has several limitations. Because of the diversity of CVDs themselves, it is very difficult to accrue enough numbers of biopsy-proven cases to analyze data separately for individual CVDs. Even though the number of our subjects was relatively large, it might not be enough to clearly show the differences in the prognosis among different types of CVD-IPs (Table E8). The other limitation is there might be a selection bias, especially for CVD-IP, because this is a retrospective study and the subjects were restricted to the patients who had undergone surgical lung biopsy. Although we have had a policy to perform surgical lung biopsy on all patients with CVDs with clinically significant interstitial lung disease, we still cannot exclude this selection bias. However, the lung function parameters and radiologic features of the patients with CVD-IP were comparable to those of patients with IIP, suggesting that our subjects may not be a markedly biased sample for our purpose of comparison of prognosis of two diseases with the same histologic pattern. Further studies of larger numbers, perhaps through multicenter cooperation, will be required to overcome this limitation.

In conclusion, our data suggest that the better prognosis of the CVD group is not solely due to the prevalence of NSIP, but also due to better prognosis in patients with a CVD and a histologic pattern of UIP compared with patients with UIP-IPF.

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