Pathologic and Radiologic Differences Between Idiopathic and Collagen Vascular Disease-Related Usual Interstitial Pneumonia

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Background: **Patients with usual interstitial pneumonia (UIP) associated with collagen vascular disease (CVD) have been reported to have a better prognosis than those with idiopathic pulmonary fibrosis with a UIP pattern (IPF/UIP) seen on histology. The aim of this study was to evaluate the pathologic and radiologic differences between the two conditions and their relationship with clinical outcome.**

Methods: **A retrospective review of 100 patients (CVD-UIP, 39 patients; IPF/UIP, 61 patients) with UIP pattern diagnosed by surgical lung biopsy at one tertiary referral center.**

Results: **The median follow-up period was 34.4 months. The CVD-UIP group was younger, included more women and nonsmokers, and showed better survival than the IPF/UIP group. Pathologically, CVD-UIP patients had fewer fibroblastic foci and smaller honeycombing (HC) spaces with higher germinal centers and total inflammation scores than IPF/UIP patients. Radiologically, CVD-UIP patients had a lower emphysema score and more likely a nontypical UIP pattern without HC. The germinal centers score was the best distinguishing feature between CVD-UIP and IPF/UIP patients (odds ratio, 2.948; $p = 0.001$) and was marginally related to survival ($p = 0.076$). The HC score (hazard ratio [HR], 1.134; $p < 0.001$), total lung capacity (TLC) [HR, 0.932; $p = 0.004$], and age (HR, 1.052; $p = 0.017$) were significant predictors of survival in all patients with UIP histology, regardless of the presence of CVD. Among IPF/UIP patients, those with positive autoantibodies were pathologically more similar to CVD-UIP than to IPF/UIP without autoantibodies, despite no difference in survival between them.**

Conclusions: **The germinal centers score was the best discriminative between CVD-UIP and IPF/UIP patients; it was of marginal prognostic significance. Age, TLC, and HC score were independent prognostic factors in all patients with UIP histology.**

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Abbreviations: Ab− = negative for autoantibodies; Ab+ = positive for autoantibodies; CI = confidence interval; CVD = collagen vascular disease; DLCO = diffusing capacity of the lung for carbon monoxide; GGO = ground-glass opacity; HC = honeycombing; HR = hazard ratio; IPF/UIP = idiopathic pulmonary fibrosis with a usual interstitial pneumonia pattern; κw = weighted κ coefficient of agreement; NSIP = nonspecific interstitial pneumonia; TLC = total lung capacity; UIP = usual interstitial pneumonia

Patients with interstitial pneumonia associated with collagen vascular disease (CVD) have a better prognosis than those with idiopathic interstitial pneumonia.[1–5] We have reported that this better prognosis is due not only to an increased prevalence of the nonspecific interstitial pneumonia (NSIP) pattern,[6–10] but also to a better prognosis for patients with usual interstitial pneumonia (UIP) associated with CVD (termed CVD-UIP from this point) than for those with idiopathic pulmonary fibrosis with a UIP pattern (IPF/UIP).[11] Other investigators[3,12] have also reported similar results. Therefore, the aim of this study was to investigate the pathologic and radiologic differences accounting for the difference in prognosis between CVD-UIP and IPF/UIP patients. We also compared subjects with IPF/UIP who were positive for autoantibodies (Ab+) to those negative for autoantibodies (Ab−).

Materials and Methods

Study Populations

UIP was diagnosed in a total of 320 patients (IPF/UIP, 272 patients; CVD-UIP, 48 patients) by surgical lung biopsy at the Asan Medical Center in South Korea from August 1991 to December 2007. Idiopathic pulmonary fibrosis was diagnosed according to the American Thoracic Society/European Respiratory Society consensus classification,[13] and individual CVDs were diagnosed in patients according to the criteria of the corresponding societies.[14–20] All patients with IPF/UIP lacked symptoms or signs of CVDs, including undifferentiated connected tissue diseases, not only at the time of diagnosis but also during follow-up. Because the total cohort included fewer patients with CVD-UIP than with IPF/UIP, we restricted the numbers of patients with IPF/UIP to 1.5 times the total number of CVD-UIP patients. The selection and enrollment of patients with IPF/UIP to the present study was largely random, only matched with the baseline lung function and the time of diagnosis to avoid a possibility of the early diagnosis of CVD-UIP by frequent assessment during rheumatologic follow-up. A total of 100 patients were enrolled into the study; most of the CVD patients in the present study had been included in a previous study[11]; however, only 21.7% of the IPF/UIP patients in the previous study were included in this study. This study was approved by the Institutional Review Board of the Asan Medical Center.

Methods

Clinical data were obtained from medical records, and survival status was obtained from medical records and/or telephone interviews. All clinical parameters were assessed no more than 1 month before biopsies were performed.

Pathologic Evaluation

The biopsy slides were randomized and reviewed independently by two pathologists (T.V.C. and S.J.J.), who were blinded to the clinical information. The following histologic features were semiquantitatively graded: fibroblastic foci, 1 to 4; germinal centers, 0 to 3; plasma cells, 0 to 3; organizing pneumonia, 0 to 3; intraalveolar macrophages, 0 to 3; overall extent of mononuclear interstitial inflammation (total inflammation), 0 to 3; honeycombing (HC) and pleural changes. HC was scored as follows, according to the measured size of the largest HC spaces in the biopsy specimen: 0, none; 1, $<$ 1 mm; 2, 1 to 3 mm; 3, 3 to 5 mm; and 4, $>$ 5 mm. Pleural changes were tallied as follows: 1, normal; 2, pleural fibrosis; 3, fibrinous pleuritis; and 4, fibrosis and fibrinous pleuritis. The criteria for the scoring are presented in the online supplemental material with pictures (see Fig 1 in the online supplement). After the initial slide review, cases with a difference of more than two grades were reassessed by the two observers after they had shared the images used for grading between them.

Physiologic Assessments

Spirometry, total lung capacity (TLC) by plethysmography, and diffusing capacity of the lung for carbon monoxide (DLCO) were measured according to American Thoracic Society recommendation,[21–23] and the results were expressed as percentages of normal predicted values. BAL was performed as previously described.[24]

High-Resolution CT Scanning

High-resolution CT scans were also randomized and reviewed independently by two thoracic radiologists (M.Y.K. and K.H.D.) who were blinded to clinical information or histologic diagnosis. The extent of emphysema, ground-glass opacity (GGO), reticulation, consolidation, and HC were scored on a scale of 5% for all lobes. HC was defined as clustered cystic airspaces of 3 to 10 mm in diameter with shared well-defined walls and layering in the subpleural areas of the lungs.[25] Overall, the radiologic pattern was categorized as a typical UIP pattern, a nontypical UIP pattern with HC, or a nontypical UIP pattern without HC. A typical UIP pattern was defined as predominant reticulation and HC with rare or no GGOs, found predominantly in the lower lobe and with subpleural distribution. On the second trial of radiologic assessment, the consensus scores were made.

Statistical Analysis

All values were described as the mean $\pm$ SD or median (range). The χ^2 test or Fisher exact test was used for categorical data, and an unpaired Student *t* test or the Mann-Whitney *U* test was used for continuous data. The relationships among the three disease groups was analyzed using the Kruskal-Wallis test. When significant differences were indicated by the Kruskal-Wallis test, a Mann-Whitney *U* test was used to determine which pair-wise differences were significant at the 5% level. Interobserver variation was quantified using a weighted κ coefficient of agreement (κ_W; using quadratic weighting) to account for the degree of disagreement on a semiquantitative categorical scale (poor, $<$ 0.2; fair, 0.2 to 0.4; moderate, 0.4 to 0.6; good, 0.6 to 0.8; excellent, $>$ 0.8).[26] Logistic regression analysis was used to identify significant variables predicting the presence of CVD-UIP. Variables selected by univariate analysis ($p < 0.1$) were evaluated in a multivariate analysis. Survival was evaluated using a Kaplan-Meier approach and the log-rank test. Cox regression analysis was used to identify significant variables predicting survival. A p value $<$ 0.05 was considered statistically significant (two-tailed). All data were analyzed using a statistical software package (SPSS, version 12.0; SPSS, Inc; Chicago, IL).

Results

Comparison of Clinical Findings Between CVD-UIP and IPF/UIP Patients

The mean age of the study population was 56.6 years, and 56.0% were men. The median follow-up period for all patients was 33.4 months. The under-

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lying types of CVD were rheumatoid arthritis (n = 19), systemic sclerosis (n = 13), Sjögren syndrome (n = 3), undifferentiated connective tissue disease (n = 2), polymyositis (n = 1), and mixed connective tissue disease (n = 1). The CVD-UIP group was younger, and it included more women and nonsmokers compared with the IPF/UIP group (Table 1). However, there were no significant differences in lung function, resting PaO_2, and BAL fluid findings between the two groups. Patients with CVD-UIP had a longer survival time (median, 143.8 months) than those with IPF/UIP (40.1 months; p = 0.001) and showed reduced mortality rates (1-year mortality rate, 7.9% vs 17.3%, respectively; 3-year mortality rate, 13.9% vs 43.2%, respectively; p = 0.001) [Fig 1].

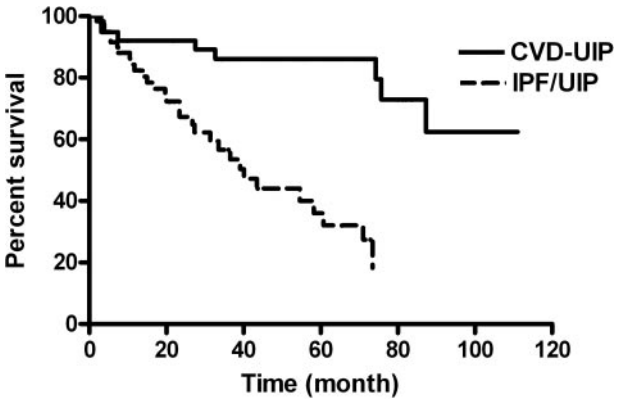

FIGURE 1. Comparison of the survival curves for CVD-UIP and IPF/UIP patients.

Comparison of Pathologic Findings Between CVD-UIP and IPF/UIP Patients

The initial interobserver agreement in histologic scores assessed by κw coefficients was moderate for fibroblastic foci (κw = 0.442) and total inflammation (κw = 0.588), and good for germinal centers (κw = 0.793). After the second review of the cases, the interobserver agreement improved (fibroblastic foci; κw = 0.664), although the intraobserver agreements were still better than interobserver agreement (κw = 0.894 and 0.935, respectively, for S.J.J. and T.V.C.). Intraobserver agreements represent the consistency of the scores of the same pathologic specimens performed by one pathologist on two different evaluations.

Patients with CVD-UIP had lower fibroblastic foci and microscopic HC scores (*ie*, smaller HC spaces), and higher germinal centers and total inflammation scores compared with those with IPF/UIP (Table 2). However, there were no differences in other parameters between the two groups. None of the patients showed fibrinous pleuritis; 11 of the 100 patients showed pleural fibrosis (CVD group, 4 patients; IPF group, 7 patients).

Comparison of Radiologic Findings Between CVD-UIP and IPF/UIP Patients

The initial interobserver agreement in radiologic scores was good for emphysema (κw = 0.747) and HC (κ = 0.733), but only fair to moderate for GGO (κw = 0.416), reticulation (κw = 0.299), and consolidation (κw = 0.462). Patients with CVD-UIP had

Table 1—*Comparison of the Baseline Characteristics Between Patients With CVD-UIP and Those With IPF/UIP*

Characteristics	CVD-UIP Patients	IPF/UIP Patients	p Value
Patients	39 (39)	61 (61)	
Age, yr	52.4 ± 11.2	59.2 ± 8.3	0.002
Male gender	10 (25.6)	46 (75.4)	< 0.001
Smoking			0.004
Never-smokers	28 (71.8)	19 (31.1)	
Ex-smokers	6 (15.4)	34 (55.7)	
Current-smokers	5 (12.8)	8 (13.1)	
Smoking amount, pack-yr	8.5 ± 16.9	23.8 ± 25.1	< 0.001
Pulmonary function, % predicted			
FVC	65.7 ± 15.7	65.6 ± 15.7	NS
DLCO	60.2 ± 17.9	63.9 ± 17.9	NS
TLC	73.1 ± 13.0	68.2 ± 14.8	NS
PaO_2 at rest, mm Hg	87.2 ± 13.1	84.2 ± 11.5	NS
BAL fluid, %			
Macrophages	65.4 ± 22.6	65.8 ± 18.2	NS
Lymphocytes	19.5 ± 14.8	16.0 ± 10.7	NS
Neutrophils	12.2 ± 16.6	14.4 ± 20.1	NS
Eosinophils	1.8 ± 5.1	3.0 ± 4.6	NS
Follow-up, mo	56.1 (3.0–200.8)	22.0 (1.9–138.5)	< 0.001

Data are presented as No. (%), mean ± SD, or median (range), unless otherwise indicated. NS = not significant.

Table 2—*Comparison of Pathologic Scores Between CVD-UIP and IPF/UIP*

Category	CVD-UIP Patients	IPF/UIP Patients	p Value
Fibroblastic foci	1.56 ± 0.74	2.01 ± 0.81	0.007
Germinal centers	1.04 ± 1.07	0.33 ± 0.61	< 0.001
Total inflammation	2.10 ± 0.69	1.74 ± 0.66	0.010
HC (size)*	1.71 ± 1.09	2.20 ± 1.09	0.034
Plasma cells	1.72 ± 0.68	1.43 ± 0.71	0.044
Organizing pneumonia	0.33 ± 0.53	0.38 ± 0.60	NS
Intraalveolar macrophages	0.76 ± 0.54	0.85 ± 0.45	NS
Pleural fibrosis, % of affected cases	4 (10.5)	7 (11.5)	NS

Data are presented as the mean ± SD or No. (%), unless otherwise indicated. See Table 1 for abbreviation not used in the text.
*See "Materials and Methods" section.

Table 3—*Comparison of Radiologic Scores Between CVD-UIP and IPF/UIP*

Category	CVD-UIP Patients	IPF/UIP Patients	p Value
Emphysema	0.43 ± 0.76	1.65 ± 3.27	0.007
HC	4.00 ± 6.77	7.04 ± 8.34	0.064
GGO	4.10 ± 5.26	2.81 ± 4.65	NS
Reticulation	9.55 ± 4.89	10.83 ± 6.92	NS
Consolidation	0.66 ± 1.59	0.46 ± 1.50	NS
Total extent	18.74 ± 10.33	22.79 ± 12.89	NS
CT scan pattern			0.043
Typical UIP	3 (8.6)	9 (15.0)	
Nontypical UIP pattern with HC	11 (31.4)	29 (48.3)	
Nontypical UIP pattern without HC	21 (60.0)	22 (36.7)	

Data are presented as the mean ± SD or No. (%), unless otherwise indicated. See Table 1 for abbreviation not used in the text.

lower scores of emphysema, and they were more likely to have a nontypical UIP pattern without HC compared with IPF/UIP patients (Table 3). They also had marginally significant lower scores for HC ($p = 0.064$). However, there were no differences in other parameters between the two groups.

Discriminating Features Between CVD-UIP and IPF/UIP Patients

Among the parameters with significant differences on univariate analysis, germinal centers score was the most discriminating factor for CVD-UIP by multivariate analysis in addition to age and gender (Table 4).

Prognostic Factors Predicting Clinical Outcome in Patients With UIP

Among the parameters with $p < 0.1$ by univariate analysis (Table 5), multivariate analysis by Cox regression model revealed that the HC score, TLC, and age were independent predictors of survival in all patients with UIP histology, regardless of the presence of CVD. The germinal centers score had a marginal significance ($p = 0.076$) by multivariate analysis (Table 6).

In pure IPF/UIP patients, among the factors shown to be significant by univariate analysis (see Table 1 in the online supplemental material), multivariate analysis revealed that DLCO and the HC score on the CT scan were independent predictors of survival (see Table 2 in the online supplemental material). In CVD-UIP patients, the presence of rheumatoid arthritis was the only independent predictor of survival by multivariate analysis (hazard

Table 4—*Discriminating Factors for CVD-UIP Assessed Using a Multivariate Logistic Model*

Predictors	Odds Ratio	95% CI	p Value
Age	0.925	0.871–0.983	0.011
Male gender	0.192	0.068–0.543	0.002
Germinal centers	2.948	1.578–5.505	0.001

Table 5—*Prognostic Factors for the Survival in Patients With UIP Pattern Assessed Using a Univariate Cox Model*

Predictors	HR	95% CI	p Value
Age	1.045	1.010–1.081	0.012
Male gender	2.343	1.201–4.573	0.013
Ever-smokers	1.651	0.874–3.120	NS
Presence of CVD	0.193	0.086–0.436	< 0.001
FVC % predicted	0.980	0.961–1.000	0.055
DLCO % predicted	0.985	0.967–1.003	0.099
TLC % predicted	0.975	0.951–0.999	0.045
PaO_2 at rest	0.959	0.928–0.991	0.013
BAL fluid			
Macrophages	0.988	0.966–1.012	NS
Lymphocytes	0.998	0.972–1.026	NS
Neutrophils	1.043	1.001–1.086	0.047
Eosinophils	1.049	0.966–1.140	NS
Pathologic features			
Fibroblastic foci	1.360	0.952–1.942	0.091
Germinal centers	0.600	0.353–1.021	0.060
Plasma cells	1.058	0.665–1.683	NS
Organizing pneumonia	1.185	0.705–1.993	NS
Intraalveolar macrophages	0.908	0.518–1.594	NS
Total inflammation	0.821	0.517–1.303	NS
HC, size	0.996	0.751–1.320	NS
Pleural change	1.523	0.591–3.925	NS
Radiologic findings			
Emphysema	1.002	0.883–1.137	NS
GGO	1.008	0.945–1.075	NS
Reticulation	1.032	0.987–1.079	NS
Consolidation	0.868	0.677–1.115	NS
HC	1.070	1.035–1.106	< 0.001
Total extent	1.043	1.017–1.069	0.001
Nontypical UIP without HC	0.392	0.188–0.817	0.012

See Table 1 for abbreviation not used in the text.

Table 6—*Prognostic Factors for the Survival in Patients With UIP Pattern Assessed Using a Multivariate Cox Model*

Predictors	HR	95% CI	p Value
HC (on CT scan)	1.134	1.059–1.214	< 0.001
TLC % predicted	0.932	0.889–0.978	0.004
Age	1.052	1.009–1.098	0.017
Germinal centers	0.485	0.219–1.078	0.076
Nontypical UIP without HC	2.797	0.888–8.804	0.079
FVC % predicted	1.040	0.994–1.089	0.092

ratio [HR], 16.382; p = 0.011) [see Table 3 in the online supplemental material].

Comparison Between IPF/UIP(Ab+) and IPF/UIP(Ab−)

Clinical Features: About a third of patients with IPF/UIP were Ab+; 19 had antinuclear antibodies, and 8 had rheumatoid factor. No patients with autoantibodies showed signs or symptoms of CVD (including undifferentiated connected tissue disease) before or after the biopsies. There were no differences in clinical features between IPF/UIP(Ab+) and IPF/UIP(Ab−) patients (data not shown).

Pathologic Findings: IPF/UIP(Ab+) patients had a higher germinal centers score and more plasma cells compared with IPF/UIP(Ab−) patients (Table 7), and multivariate analysis showed that germinal centers score was the best feature for distinguishing IPF/UIP(Ab+) from IPF/UIP(Ab−) patients (odds ratio, 6.430; 95% confidence interval [CI], 1.447 to 28.565; p = 0.014). Interestingly, no pathologic variables differed significantly between the IPF/UIP(Ab+) and CVD-UIP groups, whereas the IPF/UIP(Ab−) group had lower germinal centers and plasma cells scores and more fibroblastic foci compared with the CVD-UIP group, indicating that IPF/UIP(Ab+) is pathologically similar to CVD-UIP rather than IPF/UIP(Ab−).

Radiologic Findings: IPF/UIP(Ab+) patients had higher GGO and HC scores and larger extent of the lesions compared with IPF/UIP(Ab−) or CVD-UIP patients. Patients with IPF/UIP(Ab−) had lower GGO and higher HC scores compared with those with CVD-UIP (Table 8).

Survival: The survival time for the IPF/UIP(Ab+) group (median, 43.4 months) was similar to that of the IPF/UIP(Ab−) group (39.1 months) [Fig 2].

Discussion

In this study, we found that CVD-UIP and IPF/UIP patients show different pathologic features, despite having the same basic UIP pattern; CVD-UIP patients had more germinal centers and total inflammation with plasma cells and fewer fibroblastic foci and smaller HC spaces histologically compared with IPF/UIP patients. Radiologically, CVD-UIP patients showed a lesser extent of emphysema, higher prevalence of nontypical UIP pattern without HC, and a tendency for less HC, at the same degree of lung function derangement. Smaller HC spaces histologically appear to have a radiologic correlate because an absence of HC was more common radiologically in the CVD-UIP group (see Fig 2 in online supplement). The germinal centers score was the best discriminator between IPF/UIP and CVD-UIP patients in addition to age and gender, and it had a marginal prognostic significance. On multivariate analysis, radiologic HC score, TLC, and age are independent prognostic factors for survival. Interestingly, among IPF/UIP patients, the pathologic features of patients with positive autoantibodies were more similar to those of CVD-UIP patients than those of IPF/UIP(Ab−) patients, although no difference in survival was found.

Several studies have reported that CVD-UIP patients have a better prognosis than IPF/UIP patients. Flaherty et al[3] and Nakamura et al[12] reported significantly better survival for the CVD-UIP group compared with the IPF/UIP group, a finding that was confirmed in the larger cohorts of our previous study.[11] Several studies have also reported a difference in histopathologic features between CVD-UIP and IPF/UIP patients. Yoshinouchi et al[27] reported high numbers of both vimentin-positive and α-smooth muscle actin-positive myofibroblasts in UIP patients with rheumatoid arthritis (n = 12), in contrast to the dominance of vimentin-positive but α-smooth mus-

Table 7—*Comparison of Pathologic Scores Between IPF/UIP With Autoantibodies and Without Autoantibodies*

Category	CVD-UIP Patients	IPF/UIP(Ab+) Patients	IPF/UIP(Ab−) Patients	p Value*
Germinal centers	1.04 ± 1.07†	0.71 ± 0.92†	0.15 ± 0.28	< 0.001
Plasma cells	1.72 ± 0.68†	1.76 ± 0.81†	1.27 ± 0.62	0.003
Fibroblastic foci	1.56 ± 0.74†	1.89 ± 0.77	2.06 ± 0.84	0.009
Total inflammation	2.10 ± 0.69†	1.92 ± 0.67	1.65 ± 0.65	0.017
HC size	1.71 ± 1.09†	1.95 ± 1.03	2.31 ± 1.12	0.069
Intraalveolar macrophages	0.76 ± 0.54	0.82 ± 0.42	0.87 ± 0.47	NS
Pleural change	1.11 ± 0.31	1.05 ± 0.23	1.14 ± 0.35	NS
Organizing pneumonia	0.33 ± 0.53	0.47 ± 0.75	0.33 ± 0.53	NS

Data are presented as the mean ± SD, unless otherwise indicated. See Table 1 for abbreviation not used in the text.
*Kruskal-Wallis test.
†p < 0.05 (significant compared to IPF/UIP[Ab−] patients).

Table 8—*Comparison of Radiologic Scores Between IPF/UIP With Autoantibodies and Without Autoantibodies*

Category	IPF/UIP(Ab−) Patients	IPF/UIP(Ab+) Patients	CVD-UIP Patients	p Value*
GGO	1.73 ± 3.70†	5.17 ± 5.67‡	4.10 ± 5.26	0.004
HC	5.95 ± 6.79†	9.46 ± 10.85†	4.00 ± 6.77	0.021
Total extent	20.17 ± 10.62	28.60 ± 15.64†‡	18.74 ± 10.33	0.032
Emphysema	1.81 ± 3.64	1.29 ± 2.30	0.43 ± 0.76	NS
Reticulation	10.34 ± 6.76	11.93 ± 7.32	9.55 ± 4.89	NS
Consolidation	0.33 ± 1.20	0.75 ± 2.01	0.66 ± 1.59	NS

Data are presented as the mean ± SD, unless otherwise indicated. See Table 1 for abbreviation not used in the text.
*Kruskal-Wallis test.
†$p < 0.05$ (significant compared to CVD-UIP patients).
‡$p < 0.05$ (significant compared to IPF/UIP[Ab−]).

cle actin-negative fibroblasts in IPF/UIP patients (n = 7). Flaherty et al[3] reported that fibroblastic foci profusion was the best feature for distinguishing IPF/UIP from CVD-UIP and was associated with better survival in CVD-UIP patients; however, there were only nine CVD-UIP patients. Enomoto et al[28] also confirmed significantly higher fibroblastic foci scores for the IPF/UIP group than the CVD-UIP group using a quantitative scoring method; whereas, Nagao et al[29] reported different results; their semiquantitative analysis showed no difference in fibroblastic foci profusion between IPF/UIP patients (n = 16) and CVD-UIP patients, although the number of patients with CVD-UIP was relatively small (n = 15).

Our present study with larger patient cohorts found fewer fibroblastic foci, smaller HC spaces, more germinal centers, and more total inflammation in CVD-UIP patients compared with IPF/UIP patients. Multivariate analysis showed that germinal centers score was the best discriminating feature. Germinal centers are sites of Ig class switching,[30,31] Ig gene variable-region somatic hypermutation,[32–36] and B-cell tolerization.[37–39] They are most likely to be the sites at which mutated IgG autoantibodies are generated; hence, they may be important sites for immune dysregulation in autoimmune diseases.[40] Therefore, our finding that germinal centers score is the best feature for discrimination between CVD-UIP and IPF/UIP correlates with the postulated autoimmune mechanisms in CVD-UIP compared to IPF/UIP.

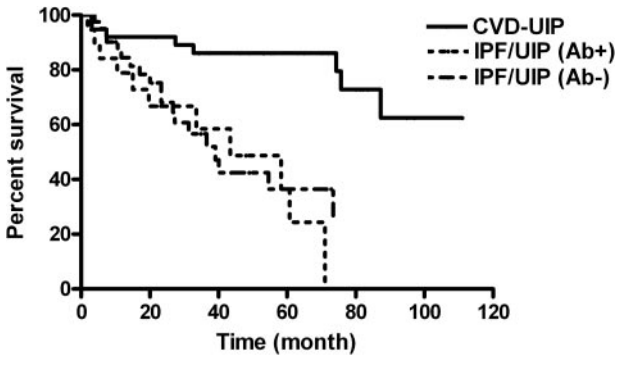

FIGURE 2. Comparison of the survival curves for IPF/UIP(Ab+) and IPF/UIP(Ab−) patients.

Regarding the radiologic differences between CVD-UIP and IPF/UIP, CVD-UIP was reported to more likely show a NSIP pattern,[3] and IPF/UIP patients were more likely to show more advanced radiologic involvement.[4,29,41] Our study confirmed those results, showing that a nontypical UIP pattern (which may be interpreted as a NSIP pattern on a high-resolution CT scan) is more common in CVD-UIP patients than in IPF/UIP patients and higher HC scores are more common in IPF/UIP, despite stratification of similar lung function in both groups. The radiologic HC score was the most significant prognostic factor, together with TLC and age in all patients with UIP histology by multivariate analysis. In addition, the present study showed that the IPF/UIP group had a higher score for emphysema; however, this may be related to the higher proportion of male smokers in this group.

Among pure IPF/UIP patients, the degree of lung function derangement (DLCO) and radiologic HC extent are independent prognostic factors (see Table 2 in the online supplemental material). By contrast, among CVD-UIP patients, only the presence of rheumatoid arthritis was a significant prognostic factor for survival (see Table 3 in the online supplemental material).

One unexpected finding was the pathologic difference between the IPF/UIP(Ab+) and IPF/UIP(Ab−) groups. The histopathologic features of the IPF/UIP(Ab+) group were more similar to the CVD-UIP group rather than to the IPF/UIP(Ab−) group. Multivariate analysis showed that germinal centers score was the best feature for distinguishing IPF/UIP(Ab+) from IPF/UIP(Ab−) patients, whereas there were no differences in all pathologic variables between the IPF/UIP(Ab+) and CVD-UIP groups.

Despite the differences in pathology, there was no significant difference in survival between IPF/UIP(Ab+) and IPF/UIP(Ab−) patients; this might to be due to the small numbers of patients in each group.

Our study had several limitations. Although the interobserver agreement for histopathologic findings was moderate to good, there was a difficulty in reaching consensus diagnoses, perhaps owing to an inability to hold face-to-face meetings. The other limitation is that this was a retrospective study performed in a single center. Owing to the much larger number of IPF/UIP patients compared with CVD-UIP patients, we had to restrict the number of IPF/UIP patients enrolled (21.7% of previous study subjects) by random selection but with stratification for lung function and time (year) of biopsy, which might have introduced some selection bias. However, the prognostic factor results for patients with pure IPF/UIP were similar to those of previous reports, indicating that the selected subjects are unlikely to be a biased sample. In addition, although the number of patients in the present study was larger than in previous studies, it might not be sufficiently large to clearly show differences in prognosis between IPF/UIP(Ab+) and IPF/UIP(Ab−) patients. Further studies including greater numbers of patients are needed to overcome this limitation.

In conclusion, our data indicate that higher germinal centers score is the best feature for distinguishing between CVD-UIP and IPF/UIP, and that this is a marginal prognostic factor for survival. Radiologic HC score, TLC, and age were independent prognostic factors in all patients with UIP regardless of the presence of CVD. The IPF/UIP(Ab+) patients were pathologically more similar to CVD-UIP patients than IPF/UIP(Ab−) patients; however, further investigations are needed to confirm this observation.

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