Clinical Features and Outcome of Acute Exacerbation of Interstitial Pneumonia: Collagen Vascular Diseases-Related versus Idiopathic

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For editorial comment see p. 13

Key Words

Acute exacerbation • Collagen vascular diseases • Idiopathic interstitial pneumonia • Idiopathic pulmonary fibrosis • Mortality

Abstract

Background: Relatively little is known about acute exacerbation (AE) of interstitial pneumonia associated with collagen vascular diseases (CVD-IPs). **Objectives:** This study was aimed at clarifying clinical characteristics and outcome in AE of CVD-IPs, compared with those of idiopathic interstitial pneumonias (IIPs). **Methods:** We retrospectively reviewed 112 admission cases with suspected AE of CVD-IPs or IIPs during 2003–2009. IIPs were diagnosed with idiopathic pulmonary fibrosis (IPF) or non-IPF, mostly based on radiologic findings. Of these, 15 AEs of CVD-IPs (6 rheumatoid arthritis, 6 dermatomyositis and 3 systemic sclerosis) and 47 AEs of IIPs (13 IPF and 34 non-IPF) were included. **Results:** The clinical characteristics in AE of CVD-IPs were similar to those of IIPs, except for younger age (63.3 ± 6.8 vs. 73.8 ± 9.1 years; $p = 0.0001$) and higher $\text{PaO}_2/\text{FiO}_2$ at the onset of AE (205 ± 81.2 vs. 145 ± 53.8 mm Hg; $p = 0.002$) in the former. Dermatomyositis-related interstitial pneumonia (IP) showed a relatively indolent onset and was often associated with worsening control of the underlying disease, whereas AE of other CVD-

IPs resembled that of IIPs. 90-day mortality of 33% in AE of CVD-IPs was similar to that of IIPs (44%; $p = 0.44$) or non-IPF (34%; $p = 0.94$), but was significantly better than that of IPF (69%; $p = 0.04$). **Conclusion:** Clinical features and outcome in AE of CVD-IPs were similar, if not identical, to those of IIPs, having a significant impact on the clinical course. AE of advanced IPF with typical radiologic features seems to have higher mortality compared with other forms of IP.

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Introduction

Acute exacerbation (AE) has been increasingly recognized as a major complication of idiopathic pulmonary fibrosis (IPF). AE is characterized by a rapid deterioration in respiratory symptoms and newly developed radiographic opacities, without evidence of any identifiable cause. Histologically, diffuse alveolar damage (DAD) with or without organizing pneumonia is superimposed on an underlying pattern of usual interstitial pneumonia (UIP) [1–4]. AE of IPF is associated with a high mortality rate and is the main cause of death in patients with IPF [5, 6].

More recently, AEs have also been shown to complicate fibrotic interstitial pneumonia (IP) other than IPF,

Fig. 1. Flow chart of the study population.
* Other reasons for exclusion were: transfer after treatment for AE-IP, no newly-developed ground-glass opacities, and unilateral ground-glass opacities. + Other reasons for exclusion were: no underlying IP and chronic deterioration of respiratory symptoms. CHP = Chronic hypersensitivity pneumonitis; DAH = diffuse alveolar hemorrhage; PE = pulmonary embolism.

including nonspecific interstitial pneumonia (NSIP) [7, 8], interstitial pneumonia associated with collagen vascular diseases (CVD-IPs) [8–15] and chronic hypersensitivity pneumonitis [7, 16]. AE of CVD-IPs were mainly associated with rheumatoid arthritis (RA) [8, 10, 12, 14, 15] or systemic sclerosis (SSc) [8, 9, 12], but have been demonstrated in other types of CVDs including polymyositis/dermatomyositis [10, 12], primary Sjögren's syndrome [11, 14] and systemic lupus erythematosus [9]. Although the estimated incidence of AE in CVD-IPs seems to be lower than that in IPF [8, 14], the significance of AE in CVD-IPs rests on its associated high mortality, which is similar to that observed in AE of IPF [8, 12, 14].

To date, relatively little is known about AE of CVD-IPs, and its detailed clinical features and outcomes remain to be fully elucidated. Furthermore, no study to date has compared AEs between CVD-IPs and idiopathic interstitial pneumonias (IIPs). Therefore, we conducted this study to clarify clinical characteristics and mortality in AE of CVD-IPs compared with those of IIPs.

Patients and Methods

Patients

Our hospital is a 900-bed tertiary referral center which plays a central role in treating emergency patients in the surrounding area. We retrospectively reviewed patients with a diagnosis of IP who had been admitted to our department from January 2003

through December 2009. Of 712 cases identified, 112 cases (33 CVD-IP cases, 77 IIP cases and 2 chronic hypersensitivity pneumonitis cases) were treated for suspected acute exacerbation of interstitial pneumonia (AE-IP). According to the criteria of AE-IP described below, 15 cases of CVD-IP and 47 cases of IIP were finally included in the study (fig. 1).

Definition of AE-IP

In the present study, AE-IP was defined based on the criteria for AE of IPF proposed by the Japanese guidelines [17] or the IPF Clinical Research Network [4], with a slight modification for the purpose of adapting for other IPs: (1) previous or concurrent diagnosis of underlying fibrotic IP; (2) unexplained worsening or development of dyspnea within 30 days; (3) high-resolution CT (HRCT) scan with new bilateral ground-glass opacities and/or consolidation superimposed on a background reticular or honeycombing pattern; (4) no evidence of pulmonary infection by bronchoalveolar lavage (BAL) or endotracheal aspiration or sputum culture, in combination with negative blood tests for other potentially infectious pathogens (e.g. *Pneumocystis jiroveci*, *Cytomegalovirus*); and (5) exclusion of left heart failure, pulmonary embolism and alternative causes for acute lung injury.

Patients who presented with rapidly progressing IP as an initial presentation of CVD-IP were distinguished from AE-IP, but they were included in the study if they were clinically stabilized by the initial treatment for at least 30 days and later met the criteria of AE-IP.

Definition of Underlying IP

IPF was diagnosed according to the Japanese diagnostic criteria of IIPs [17], in which a diagnosis of IPF without surgical lung biopsy is allowed when definitive clinical and radiologic features are present. In this study definitive HRCT features of UIP were

defined by basal-predominant subpleural reticulation with honeycombing in the absence of a lot of ground-glass opacities, micronodules, discrete cysts, mosaic attenuation or consolidation [18]. IIPs other than IPF were collectively defined as 'non-IPF' (i.e. NSIP proven by surgical biopsy or IIPs without surgical biopsy not showing definitive HRCT features of UIP).

CVD-IPs were diagnosed without surgical biopsy in an appropriate clinical setting, with the diagnosis of each underlying collagen vascular disease (CVD) in accordance with established criteria. Clinically amyopathic dermatomyositis (CADM) was diagnosed based on the following criteria [19, 20]: (1) characteristic dermatological manifestations of classic dermatomyositis (DM), (2) no muscle weakness and (3) no or only a mild increase in serum muscle enzymes. The definition of undifferentiated connective tissue disease was according to previously published criteria [21].

Data Collection

All clinical and laboratory data were collected from medical records. To assess the impact of AE-IP on outcome, 90-day mortality was calculated. If AE recurred during the same period of hospitalization, the second AE was regarded as a series of events and excluded from the study. BAL was performed as previously recommended [22], usually under noninvasive ventilation (NIV) or endotracheal intubation. HRCT of the lungs were reviewed and interpreted by a radiologist experienced in the evaluation of diffuse lung diseases (H.U.), without knowledge of any relevant clinical information. Surgical lung biopsy or autopsy slides were interpreted by an expert pathologist (Y.I.).

Statistics

Continuous variables are expressed as means $\pm$ SD unless stated otherwise, and were compared using an unpaired Student's *t* test. Categorical variables were compared using a χ^2 test or Fisher's exact test as appropriate. Survival was expressed using the Kaplan-Meier method, and the difference was assessed via a log-rank test. Cox proportional hazards regression analysis was used to identify significant variables predicting survival status. Variables selected via univariate test were evaluated using a multivariate Cox regression analysis. $p < 0.05$ was deemed statistically significant. All statistical analyses were performed using JMP 7.0.2 (SAS Institute Inc., Cary, N.C., USA) software. This study was approved by our institutional review board.

Results

Study Population

Table 1 shows the number of patients and the radiographic or histological patterns according to the IP subtypes. The most common underlying CVD were RA (6 cases) and DM (6 cases), followed by SSc (3 cases). A radiographic UIP pattern as an underlying IP was seen in some cases with RA or SSc, whereas all patients with DM had a non-UIP pattern characterized by mixture of ground-glass, consolidation and linear opacities predominant in the lower and posterior lung zone. IIPs were composed of 13 IPF cases (5 with pathologically proven IPF/

Table 1. Radiographic and histological patterns according to IP subtypes

	Subtype	n	HRCT pattern		Histological pattern		
			UIP	non-UIP	UIP	NSIP	N/A
IIPs	IPF	13	11	2	5	0	8
	Non-IPF	34	0	34	0	6	28
CVD-IPs	RA-IP	6	3	3	1	0	5
	DM-IP	6	0	6	0	0	6
	SSc-IP	3	1	2	0	0	3

HRCT = High-resolution computed tomography; UIP = usual interstitial pneumonia; NSIP = nonspecific interstitial pneumonia; N/A = not available; IIP = idiopathic interstitial pneumonia; CVD-IP = interstitial pneumonia associated with collagen vascular disease; IPF = idiopathic pulmonary fibrosis; RA = rheumatoid arthritis; DM = dermatomyositis; SSc = systemic sclerosis.

UIP) and 34 non-IPF cases (6 with pathologically proven NSIP). Four (12%) of the non-IPF cases met the criteria of UCTD. One patient with RA-IP and 2 with non-IPF experienced AE-IP twice, and each AE episode was separately included. Eight cases (17%) in the IIP group did not have a previous diagnosis of IP and were concurrently diagnosed with underlying IP at the onset of AE.

Comparison of the Clinical Features between the Patients with CVD-IPs and IIPs

The baseline characteristics of patients at the onset of AE are shown in table 2. Patients with CVD-IPs were significantly younger (63.3 ± 6.8 vs. 73.8 ± 9.1 years; $p = 0.0001$) and associated with higher initial partial pressure of arterial O_2 to the fraction of inspired O_2 (PaO_2/FiO_2 ; 205 ± 81.2 vs. 145 ± 53.8 mm Hg; $p = 0.002$). In addition, a higher proportion were receiving immunosuppressive agents (80 vs. 45%; $p = 0.02$) compared with those with IIPs. There were no significant differences between the two groups regarding other parameters. BAL was performed at the onset of AE in 3 CVD-IP patients and 9 IIP patients. Neutrophils in the BAL fluid were similarly elevated in both groups (median: 38 and 35%, respectively). No differences were seen in the other cytological profiles between the two groups.

Comparison of the Clinical Features among the Patients with CVD-IPs

Table 3 shows the characteristics of patients according to the three underlying types of CVD. Although there were no significant differences among them, DM patients

Table 2. Comparison of clinical characteristics between patients with CVD-IPs and IIPs

	CVD-IP	IIP	p value
AE, cases	15	47	
Age, years	63.3 ± 6.8	73.8 ± 9.1	0.0001
Male, %	7 (47)	30 (64)	NS
Smoking status, current/ex/never/unknown	1/7/6/1	1/32/12/2	NS
Duration of worsening symptoms, days	6.8 ± 5.8	5.1 ± 3.0	NS
Long-term oxygen therapy, %	6 (40)	19 (40)	NS
PaO ₂ /FiO ₂ , mm Hg	205 ± 81.2	145 ± 53.8	0.002
Lactate dehydrogenase, IU/l	399 ± 114	406 ± 146	NS
KL-6, U/ml ^a	1,927 ± 861	1,690 ± 1350	NS
C-reactive protein, mg/dl	7.2 ± 5.0	10.4 ± 7.1	NS
Corticosteroids ± immunosuppressants, %	12 (80)	21 (45)	0.02
BAL performed, %	3 (20)	9 (19)	NS
Total cell count, × 10 ⁵ /mm ³	4.5 (2.4–10)	2.6 (0.8–14)	NS
Neutrophils, % ^b	38 (32–66)	35 (11–79)	NS
Lymphocytes, % ^b	6 (0–33)	7 (1–51)	NS
Eosinophils, % ^b	3 (2–7)	3 (0–7)	NS
Macrophages, % ^b	44 (31–49)	27 (2–77)	NS

Values in parentheses represent percentages. PaO₂/FiO₂ = Partial pressure of arterial O₂ to the fraction of inspired O₂.

^a Analysis performed in 15 cases in the CVD-IP group and 44 cases in the IIP group.

^b Data are presented as medians (range).

Table 3. Comparison of clinical characteristics in patients with CVD-IPs

	RA	DM	SSc
AE, cases	6	6	3
Age, years	66.3 ± 2.7	60.3 ± 5.9	63.0 ± 10.9
Male	4 (67)	3 (50)	0
Duration of symptoms, days	6.7 ± 4.1	8.7 ± 8.1	3.3 ± 0.6
Long-term oxygen therapy	2 (33)	3 (50)	1 (33)
PaO ₂ /FiO ₂ , mm Hg	192 ± 96.5	253 ± 48.5	135 ± 47.9
Lactate dehydrogenase, IU/l	433 ± 93.0	378 ± 124	374 ± 161
KL-6, U/ml	2,500 ± 970	1,797 ± 444	1,041 ± 359
C-reactive protein, mg/dl	10.5 ± 3.8	4.4 ± 5.6	5.8 ± 1.5
Distribution of new ground-glass opacity	diffuse	lower zone	diffuse

Figures in parentheses represent percentages. PaO₂/FiO₂ = Partial pressure of arterial O₂ to the fraction of inspired O₂.

had a tendency towards a longer duration of worsening symptoms (8.7 ± 8.1 days) and higher initial PaO₂/FiO₂ (253 ± 48.5 mm Hg). The DM patients were composed of 3 CADM patients and 3 classical DM patients. The former developed AE 3–6 months after the initial diagnosis of IP, while the latter developed AE more than 1 year after the diagnosis of IP. Newly developed ground-glass opaci-

ties were diffusely distributed throughout both lung fields in cases of RA or SSc, as opposed to limited distribution in the lower lung fields in DM cases, in which ground-glass opacities afterwards extended to the upper fields along with the worsening of respiratory status. AEs in RA-IP and SSc-IP were not accompanied by deterioration of extrapulmonary symptoms associated with un-

Fig. 2. Comparison of 90-day mortality in AE-IP between patients with CVD-IPs and those with IIPs.

Fig. 3. Comparison of 90-day mortality in AE-IP between patients with CVD-IPs and those with IPF or non-IPF.

derlying CVDs, whereas 3 cases in DM-IP (1 with CADM and 2 with classical DM) experienced deterioration of rash at the onset of AE.

Precipitating Factors

Corticosteroid tapering within 1 month preceded the development of AE in 4 patients in the CVD-IP group (3 patients with DM, 1 patient with RA) and in 1 patient in the IIP group.

Treatments

There were no significant differences between the two groups with regard to the treatments received (table 4). All patients were treated with high-dose corticosteroids, occasionally combined with intravenous cyclophosphamide. Antibiotics were administered in most cases in both groups. Eight cases (53%) in the CVD-IP group and 29 cases (62%) in the IIP group received mechanical ventilation, which was mostly administered only by NIV. Direct hemoperfusion with a polymyxin B-immobilized fiber column was administered as a treatment for AE-IP in a small number of cases.

Mortality

No significant difference was found in 90-day mortality between the CVD-IP group and the IIP group (33 vs. 44%; $p = 0.44$; fig. 2). Overall 90-day mortality was 40%. When IIPs were subdivided into IPF and non-IPF, the 90-day mortality of CVD-IP was significantly lower than

Table 4. Treatments for AE-IP

	CVD-IP	IIP	p value
AE, cases	15	47	
High-dose corticosteroids	15 (100)	47 (100)	NS
Intravenous cyclophosphamide	9 (60)	25 (53)	NS
Antibiotics	13 (87)	43 (91)	NS
PMX-DHP	1 (7)	3 (6)	NS
Ventilator	8 (53)	29 (62)	NS
Invasive/NIV/both	1/7/0	6/21/2	
Intensive care unit	8 (53)	36 (77)	NS

Figures in parentheses represent percentages. PMX-DHP = Direct hemoperfusion with a polymyxin B-immobilized fiber column.

that of IPF (33 vs. 69%; $p = 0.04$) and was similar to that of non-IPF (33 vs. 34%; $p = 0.94$; fig. 3). According to underlying CVD, 90-day mortality was 17% (1/6) in RA, 50% (3/6) in DM and 33% (1/3) in SSc. All fatal cases in DM were those of CADM. Using univariate Cox analysis, the presence of IPF and initial $\text{PaO}_2/\text{FiO}_2$ were significant predictors for survival (table 5). Multivariate Cox analysis revealed that the presence of IPF was the only significant prognostic factor (HR: 2.485; 95% CI: 1.031–5.660; $p = 0.04$; table 6).

Table 5. Prognostic factors for survival using a univariate Cox model

	n	HR	95% CI	p value
Age	62	0.996	0.957–1.040	0.85
Male sex	62	1.321	0.595–3.123	0.50
Smoking history	58	0.858	0.387–2.030	0.72
LTOT	62	1.216	0.539–2.673	0.63
CVD-IP	62	0.680	0.226–1.680	0.42
IPF	62	2.920	1.231–6.505	0.02
PaO ₂ /FiO ₂	62	0.994	0.986–1.000	0.047
LDH	62	1.003	1.000–1.005	0.06

LTOT = Long-term oxygen therapy; PaO₂/FiO₂ = partial pressure of arterial O₂ to the fraction of inspired O₂; LDH = lactate dehydrogenase.

Table 6. Prognostic factors for survival using a multivariate Cox model

	n	HR	95% CI	p value
IPF	62	2.485	1.031–5.660	0.04
PaO ₂ /FiO ₂	62	0.995	0.988–1.001	0.13

PaO₂/FiO₂ = Partial pressure of arterial O₂ to the fraction of inspired O₂.

Discussion

This study reviewed 15 AE episodes in CVD-IPs and 47 AE episodes in IIPs, with a view to clarifying clinical characteristics and short-term prognoses in AE of CVD-IPs compared with those of IIPs. We found that: (1) clinical features in AE of CVD-IPs were almost similar to those of IIPs, except for some distinctive features in DM patients; (2) the mortality rate in AE of CVD-IPs was similar to that of IIPs, but significantly better than that of IPF; and (3) the mortality rate of AE-IP among all patients in this study was better than previously reported, largely due to favorable outcome in AE of CVD-IPs or non-IPF.

To date, there have been several studies on AE of CVD-IPs [8–15]. Rice et al. [9] reviewed 15 autopsy cases with AE-IP and revealed AE had occurred in 2 patients with SSc and 1 patient with systemic lupus erythematosus. Thereafter, Parambil et al. [11] described 3 cases of AE in 18 patients with biopsy-proven primary Sjögren's syndrome IP and 9 cases with CVD-IPs who had suffered

DAD without an identifiable cause [12]. More recent studies have shown several cases of AE in patients with biopsy-confirmed CVD-IPs, with 1-year frequency of 1.25–3.3% [13, 14]. According to these studies, the frequency of AE in CVD-IPs seems to be lower than in IPF, and RA is the most common underlying CVD in cases of AE-IP [8, 10, 12, 14, 15] followed by SSc [8, 9, 12] and other CVDs. The reported mortality of 56–100% in AE of CVD-IPs [8, 12, 14] is comparable to that observed in AE of IPF [4, 6].

Our findings are in keeping with previous studies in that AE occurred less frequently in CVD-IPs than in IIPs, and that RA-IP and SSc-IP were likely to be complicated by AE. Our data also showed that clinical features of patients with AE of CVD-IPs were similar to those of IIPs, except for younger age, better oxygenation at the onset of AE and a higher proportion receiving immunosuppressive agents. On top of this, AE of DM-IP was as frequently observed as that of RA-IP in this study, showing unique clinical features, i.e. patients with DM-IP experienced a relatively indolent onset of AE as shown by longer duration of worsening symptoms, higher P/F ratio and limited distribution of ground-glass opacities in the lower lung fields. In addition, AE of DM-IP was often preceded by steroid tapering and was accompanied by the characteristic rash of DM, suggesting that AE of DM-IP is more closely related to worsening control of the underlying disease itself. On the other hand, patients with AE of RA-IP or SSc-IP developed diffuse ground-glass opacities as seen in AE of IIPs, and were not accompanied by extrapulmonary symptoms. Prior studies have also reported that AEs of RA-IP and SSc-IP were not associated with deterioration of the underlying disease [8, 14]. Thus, it seems likely that AE of CVD-IPs except DM-IP occurs irrespective of underlying disease activity, bearing a clinical resemblance to AE of IIPs.

The indolent nature of AE in DM-IP might have blurred the distinction between AE-IP and serial worsening of rapidly progressing IP in 3 patients with CADM, in whom fatal respiratory decrement occurred in the early course of the disease. Accordingly, one could argue that the relatively worse prognosis of AE in DM-IP might well reflect the refractoriness of CADM-associated IP, which has a very poor prognosis, especially in the rapidly progressive type [20]. However, patients included in this study were stabilized in respiratory status for at least 30 days, and afterwards developed acute worsening of IP. Thus, by definition, they can be regarded as having AE of preexisting IP rather than serial events of de novo interstitial lung disease.

In the present study, no significant difference in survival existed between cases of AE of CVD-IPs and those of IIPs, indicating that AE of CVD-IPs also carries a high mortality rate and makes the clinical course unpredictable. Moreover, we should note the different survival rates among subgroups: AE of IPF showed a significantly worse 90-day mortality rate of 69% compared with that of 33% in CVD-IPs or 34% in non-IPF. This difference in survival, however, should be viewed in light of the fact that the majority of patients were diagnosed based on radiographic pattern because of limited availability of histological findings. Published series have shown that definite radiographic patterns of UIP are highly specific but not sensitive for predicting a histopathological pattern of UIP [23, 24]. Accordingly, rigorous interpretation of radiographic definitive UIP pattern in this study might have preferentially selected advanced IPF patients with typical radiographic features, resulting in a decrease in the number of IPF patients. In fact, 11 of 13 IPF patients in this study presented a definitive radiologic UIP pattern, and poor prognosis of AE-IPF actually reflected the refractoriness of AE of later stage IPF. Therefore, it seems reasonable to conclude that survival in AE of CVD-IPs was better than that of advanced IPF with typical radiologic features, and similar to that of IIPs without a radiologic UIP pattern.

Viewed from another side, better survival of non-IPF patients could also be confounded because the non-IPF group is recognized as a heterogeneous category in which further diagnostic work-up might have revealed various disease entities including not only NSIP, but also early-stage IPF. Even so, our results demonstrated that there was a group of patients with favorable outcomes in AE of CVD-IP or non-IPF who responded well to conventional treatment. BAL findings in this study were limited and inconclusive, but we presume that different pathological patterns of acute lung injury might be attributed to different responsiveness to treatment among subgroups [7, 9]. For example, Churg et al. [7] examined pathologic features of 12 patients with AE-IP and revealed that all of the 6 patients showing a pattern of organizing pneumonia survived, whereas 2 of 4 patients with DAD died. Although DAD is known for a predominant pathological pattern in AE of IPF, organizing pneumonia might have constituted a larger part of the histological pattern in AE of CVD-IPs or non-IPF in this study, resulting in better survival.

A 90-day mortality rate of 40% among all patients with AE-IP in this study was better than that in published reports on IPF [4, 6] or other fibrotic IPs [8, 12, 14], which

implies that survival of AE-IP is better than previously thought. We have found several possible explanations accounting for this discrepancy. As Churg et al. [25] pointed out, most published data come from retrospective reviews of biopsied cases, intensive care unit admissions or autopsies, and all these types of data are subject to considerable bias. Moreover, as Kim et al. [3] noted, earlier criteria of AE-IPF could be biased toward worse survival because they require a specific level of hypoxemia [1, 26] and might lead to cases being missed that in fact turn out to be AE. In this regard, our findings are strengthened by the relatively large number of patients who were selected from all admission cases during the study period and by the application of the latest criteria of AE-IP. Additionally, our strategy of administering NIV as the primary method of mechanical ventilation could have contributed to better survival by possibly reducing ventilator-associated pneumonia or ventilator-induced lung injury [27, 28].

Many of the limitations of our study were related to its retrospective design. First, we must acknowledge that the lack of histological findings prevented accurate clinicoradiologic-pathologic diagnosis of IIPs, and thus IIPs were merely subclassified into IPF and non-IPF (non-definite IPF). The non-IPF group probably included not only idiopathic NSIP, but also some cases of misclassified IPF or other forms of IP (e.g. chronic hypersensitivity pneumonitis); therefore, discussions on the subgroups are highly speculative. Secondly, lack of a standardized approach to rule-out infection might have overlooked infectious etiologies: although the latest criteria on AE of IPF require exclusion of infection by BAL or endotracheal aspiration [4], it was performed in only one third of our patients, mainly due to the principal use of NIV. However, all patients included in this study had no clinical and radiographic signs of bacterial infection, as well as negative blood tests such as β -D-glucan for *P. jiroveci* or cytomegalovirus antigenemia assay, making involvement of these opportunistic infections less likely [29, 30]. Thirdly, we were unable to provide a separate analysis according to the radiographic patterns of CVD-IPs due to the small number of patients with CVD-IPs. This warrants further investigation because the subgroup of RA-UIP patients, unlike the other CVD-IPs, has been shown to have an equally poor prognosis as IPF patients [13].

In summary, the clinical characteristics and survival of patients with AE of CVD-IPs and IIPs were almost the same, except for some unique features in DM-IP and worse survival in AE of IPF with typical radiologic patterns. Our findings also imply that the mortality rate of AE-IP could be better than previously thought.

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