

Acute exacerbation of idiopathic pulmonary fibrosis: usual interstitial pneumonitis vs. possible usual interstitial pneumonitis pattern

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Abstract

Background: The prognosis of acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is very poor with a high mortality. The aim of this study was to describe the clinical features and survival of patients with AE-IPF with usual pulmonary fibrosis (UIP) and possible UIP (P-UIP) pattern on chest high resolution computed tomography (HRCT).

Methods: This retrospective study included 107 patients with AE-IPF admitted to Nanjing Drum Tower Hospital from January 2010 to December 2016. The subjects were divided into UIP ($n = 86$) and P-UIP group ($n = 21$) based on chest HRCT. Continuous variables were analyzed using Student's t test or Mann-Whitney U test. Categorical variables were analyzed using χ^2 test. Log-rank test was used for the survival analysis. Cox proportional models evaluated the risk factors for AE occurrence and survival.

Results: The male, older patients, previous N-acetylcysteine use, elevated white blood cell (WBC) counts, and microbiology infection were more common in the UIP group than the P-UIP group ($\chi^2 = 13.567, P < 0.001; z = -2.936, P = 0.003; \chi^2 = 5.901, P = 0.015; t = 2.048, P = 0.043; \chi^2 = 10.297, P = 0.036$, respectively). The percentage of AE with UIP pattern in idiopathic interstitial pneumonia (IIP) was significantly higher than P-UIP pattern ($\chi^2 = 40.011, P < 0.001$). Smoking was the risk factor for AE within 6 months after IPF diagnosis in the UIP group. The cumulative proportion survival of 30-days was significantly higher in the UIP group compared with the P-UIP group ($\chi^2 = 5.489, P = 0.019$) despite of the similar overall survival in the two groups. Multivariate Cox regression analysis indicated WBC count, partial pressure of oxygen in artery (PaO₂)/fractional concentration of inspired oxygen (FiO₂), and computed tomography (CT) score were the independent predictors for survival in the UIP group (hazard ratio [HR]: 1.070, 95% confidential interval [CI]: 1.027–1.114, $P = 0.001$; HR: 0.992, 95% CI: 0.986–0.997, $P = 0.002$; and HR: 1.649, 95% CI: 1.253–2.171, $P < 0.001$, respectively).

Conclusions: AE occurrence of UIP patients in IIP was significantly more than P-UIP cases. The short-term survival was better in the UIP group despite of the similar overall survival in the two groups. WBC count, PaO₂/FiO₂, and CT score were the independent predictors for survival in UIP subjects.

Keywords: Idiopathic pulmonary fibrosis; Acute exacerbation; Usual interstitial pneumonitis

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia, occurring primarily in older adults. The median survival is only 2 to 3 years.^[1] Acute exacerbation (AE) of IPF is an acute, clinically significant respiratory deterioration characterized by evidence of newly developed widespread alveolar abnormality.^[2] AE occurs mostly in IPF, but it is also found in other fibrosing interstitial pneumonias, such as idiopathic non-specific interstitial pneumonitis, chronic hypersensitivity pneumonitis, and connective tissue disease-associated fibros-

ing interstitial lung disease (CTD-fILD).^[3-5] Annual incidence of AE in patients with IPF is 4.1% in the United States,^[6] 4.8% in Japan,^[7] and 5.2% in South Korea.^[8] The prognosis of AE-IPF is very poor, with 50.0% in-hospital mortality rate and 90% 6-month mortality.^[2,3,6,9-11] In China, published reports of small series indicated the similar in-hospital mortality.^[12,13] Therefore, AE is the most common cause of death in patients with IPF.^[14,15]

IPF is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonitis (UIP). New algorithm for IPF with UIP patterns is based on high

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resolution computed tomography (HRCT) findings; surgical lung biopsy (SLB) is not an absolute requirement in patients with a classical UIP pattern on HRCT.^[1,16] Patients with possible UIP (P-UIP) pattern on chest imaging appear similar to those with UIP pattern on histopathology.^[1,17,18] P-UIP pattern on HRCT has a high specificity for UIP on SLB, but positive predictive value is highly dependent on underlying prevalence.^[19] Recently, Salisbury *et al*^[18] suggested that IPF patients with P-UIP pattern had a better survival than those with definite UIP pattern and were associated with reduced hazard of death or lung transplant. However, Yunt *et al*^[20] indicated that rheumatoid arthritis is associated with both definite UIP and P-UIP pattern which had equally poor survival. Although the clinical characteristics and survival of patients with fILD with UIP pattern were not completely consistent with P-UIP pattern, the differences of patients with AE-IPF between the two patterns on chest HRCT were not fully described. In this retrospective study, we compared the clinical features and outcomes of AE-IPF patients with UIP and P-UIP pattern on chest HRCT in our single center.

Methods

Ethical approval

This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (No. 2016-160-01) and conducted in accordance with the principles of the *Declaration of Helsinki* (1989). All patients or their relatives signed an informed consent.

Study subjects

We retrospectively reviewed the clinical data of 1606 new-onset patients with idiopathic interstitial pneumonia (IIP) admitted to Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School from January 2010 to December 2016 according to the international criteria.^[1,16] The final study cohort included 107 AE-IPF subjects. The subjects were divided into UIP group and P-UIP group according to chest HRCT as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin America Thoracic Association (LATA) guidelines [Figure 1].^[1,16] The diagnosis of IPF was based on the ATS/ERS/JRS/LATA guidelines and included in (1) exclusion of other known causes of ILD (eg, domestic and occupational environmental exposures, CTDs, and drug toxicity); and (2) the presence of a UIP or P-UIP pattern on HRCT.^[1,16] AE-IPF was defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality with: (1) previous or concurrent diagnosis of IPF, (2) acute worsening or development of dyspnea typically less than 1 month duration; (3) computed tomography (CT) with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP or P-UIP pattern; and (4) deterioration not fully explained by cardiac failure or fluid overload.^[2]

The clinical and imaging data were extracted from the medical records. Vital status was obtained from medical records or telephone interview on follow-up. The time of follow-up was

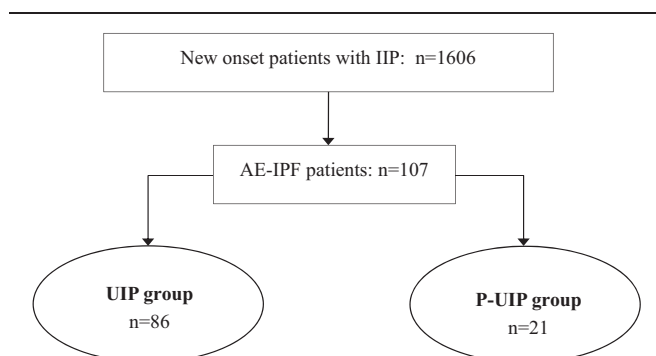


Figure 1: Flow chart of AE-IPF included patients. AE-IPF: Acute exacerbation of idiopathic pulmonary fibrosis; IIP: Idiopathic interstitial pneumonia; P-UIP: Possible UIP; UIP: Usual interstitial pneumonia.

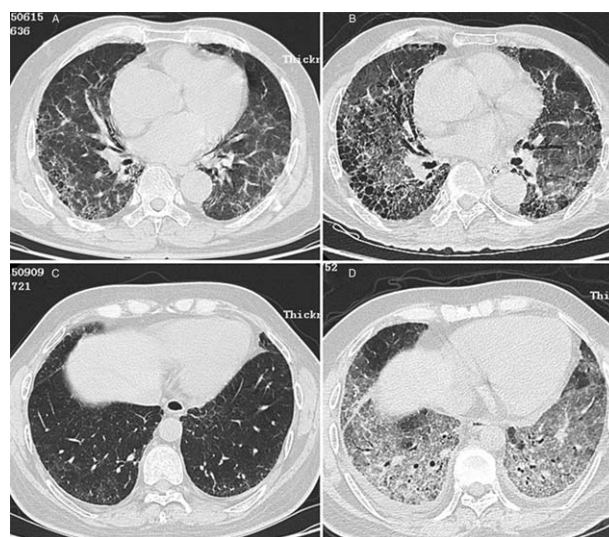


Figure 2: Chest high resolution computed tomography of patients with idiopathic pulmonary fibrosis before and after AE. (A and B) UIP pattern: Sub-pleural and basal predominance, reticular abnormality, honeycombing with or without traction bronchiectasis, and a small amount of GGO (before AE), new bilateral GGO superimposed on a background of UIP pattern (after AE). (C and D) P-UIP pattern: sub-pleural and basal predominance, reticular abnormality (before AE), new bilateral GGO and traction bronchiectasis superimposed on a background of P-UIP pattern (after AE). AE: Acute exacerbation; GGO: Ground glass opacity; P-UIP: Possible UIP; UIP: Usual interstitial pneumonia.

from 6 months to 7 years after AE. The baseline characteristics were obtained upon the admittance to hospital.

Chest imaging

All subjects accepted the examination of chest HRCT with appropriate settings (1.0–1.5 mm thick section, window width: 1600 and window level: –600) within 24 h after diagnosis of respiratory failure due to AEs. Some patients performed HRCT at the time of IPF diagnosis. UIP pattern was defined as: sub-pleural and basal predominance, reticular abnormality, honeycombing with or without traction bronchiectasis, and absence of features inconsistent with UIP pattern [Figure 2A].^[1] P-UIP pattern was described as: sub-pleural and basal predominance, reticular abnormality, and absence of features inconsistent with UIP pattern [Figure 2C].^[1] Each case was evaluated and categorized into UIP pattern or P-UIP pattern according to HRCT.^[1] Those

with inconsistent with UIP pattern were excluded from our study.^[1] When new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with UIP or P-UIP pattern, it was regarded as the AE occurrence [Figure 2B and 2D].^[2] The findings of chest HRCT were reviewed and scored by two senior radiologists blinded to clinical information independently. CT score of the patient with AE-IPF was calculated based on the overall extent of abnormalities (ie, ground glass chioectasis, reticulation, and honeycombing) determined for each entire lung using a four-point scale (0 = no involvement, 1 = 1%–25% involvement, 2 = 26%–50% involvement, 3 = 51%–75% involvement, and 4 = 76%–100% involvement) based on the published reports.^[21,22] The total CT score of each patient was obtained by adding up the scores of both lungs.^[21,22]

Statistical analysis

Continuous variables are presented as mean \pm standard deviation, and analyzed using Student's *t* test or Mann-Whitney *U* test. Categorical variables are presented as percentages and analyzed using χ^2 test. Patient survival was evaluated with Kaplan-Meier method and followed by

the log-rank test. Bivariate correlation analysis was used to identify the relationship between the total survival and clinical variables. The risk factors for recurrence or survival were analyzed using univariate and multivariate Cox proportional models. All statistical analyses were conducted by using SPSS version 23 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined as $P < 0.05$ (two-sides).

Results

Baseline clinical characteristics

There were 107 subjects with AE-IPF (mean age: 68.52 \pm 9.87 years; male/female: 81/26) included in our cohort study [Table 1]. All patients were presented with severe hypoxia (mean partial pressure of oxygen in artery (PaO₂)/fractional concentration of inspired oxygen (FiO₂): 123.71 \pm 48.36 mmHg) and very high CT scores (mean CT score was 7.25 \pm 0.92) [Table 1].

The male gender, older patients, N-acetylcysteine used before AE and white blood cell (WBC) counts at AE

Table 1: Baseline clinical characteristics of patients with AE-IPF.

Clinical variables	All subjects (n = 107)	UIP group (n = 86)	P-UIP group (n = 21)	<i>t</i> / <i>z</i> / χ^2	<i>P</i>
Male/female	81/26	72/14	9/12	13.567	<0.001
Age (years)	70.0 (33.0–86.0)	70.5 (56.0–86.0)	64.0 (33.0–83.0)	–2.936	0.003
Smoking (yes/no)	38/69	33/53	4/17	2.786	0.095
Smoking amount (pack-years)	0 (0–80)	0 (0–80)	0 (0–30)	–1.947	0.052
Previous NAC used (yes/no)	91/16	77/9	14/7	5.901	0.015
Corticosteroid used before AE (yes/no)	68/39	53/33	15/6	0.720	0.403
Anti-reflux therapy	68/39	53/33	15/6	0.720	0.403
Corticosteroid reduction or discontinuation (yes/no)	34/34	24/29	10/5	2.885	0.116
Immunosuppressants used before AE (yes/no)	3/106	3/83	0/21	0.754	0.385
BMI (kg/m ²)	24.25 \pm 2.83	23.86 \pm 2.58	25.47 \pm 3.38	–1.516	0.139
Fever (yes/no)	64/43	54/32	10/11	1.616	0.204
WBC counts ($\times 10^9/L$)	11.26 \pm 4.91	11.73 \pm 5.1	9.32 \pm 3.49	2.048	0.043
ESR (mm/h)	41.48 \pm 27.47	41.65 \pm 26.06	40.76 \pm 33.37	0.132	0.895
CRP (mg/L)	47.00 (0.20–243.50)	47.45 (0.20–243.50)	43.80 (0.20–183.80)	–0.322	0.748
LDH (U/L)	438.28 \pm 158.32	440.42 \pm 166.8	429.52 \pm 120.8	0.281	0.779
ALB (g/L)	32.88 \pm 3.45	32.71 \pm 3.31	33.57 \pm 3.97	–1.018	0.311
BNP (pg/mL)	104.00 (5.00–828.00)	93.10 (5.00–792.00)	137.50 (6.20–828.00)	–0.912	0.362
D-dimer (mg/L)	1.46 (0.02–22.40)	1.68 (0.02–22.40)	1.24 (0.20–6.36)	–0.061	0.951
CT scores	7.25 \pm 0.92	7.24 \pm 0.92	7.29 \pm 0.96	–0.184	0.854
Microbiology (B/F/V/N)	7/18/1/81	6/18/0/62	1/0/1/19	10.297	0.036
PaO ₂ /FiO ₂ (mmHg)	123.71 \pm 48.36	124.98 \pm 46.45	118.52 \pm 56.50	0.548	0.586
Maximal dosage of methylprednisolone (mg/day)	385.6 \pm 300.4	377.9 \pm 303.9	417.1 \pm 290.8	–0.535	0.594
Immunoglobulin (yes/no)	43/64	32/54	11/10	1.616	0.204
Immunosuppressant (yes/no)	14/93	9/77	5/16	2.643	0.144
Caspofungin (yes/no)	16/91	15/71	1/20	2.134	0.187
Co-trimoxazole (yes/no)	57/50	44/42	13/8	0.790	0.467
MV (yes/no)	57/50	47/39	10/11	0.335	0.563

The data are shown as mean \pm standard deviation or *n*, or *n* (range interquartile). AE-IPF: Acute exacerbation of idiopathic pulmonary fibrosis; UIP: Usual interstitial pneumonia; P-UIP: Possible UIP; NAC: N-acetylcysteine; AE: Acute exacerbation; BMI: Body mass index; WBC: White blood cell; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; LDH: Lactic dehydrogenase; ALB: Albumin; BNP: B type natriuretic peptide; CT: Computed tomography; B: Bacteria; F: Fungus; V: Virus; N: Negative; MV: Mechanical ventilation.

occurrences were more common in the UIP group than in the P-UIP group ($P < 0.05$, respectively) [Table 1]. The evidence of microbiology infection was higher in patients with P-UIP pattern than UIP pattern ($\chi^2 = 10.297$, $P = 0.036$). The other clinical variables and treatment after AE, such as maximal dosage of methylprednisolone, immunoglobulin (10–20 g/d for 3–5 days), immunosuppressant, caspofungin, cotrimoxazole, and mechanical ventilation (MV) did not show any difference between the two groups [Table 1].

AE occurrence in patients with IIP

The number of new-onset patients with IIP and AE-IPF was increased gradually from 2010 to 2016 in our single-center [Figure 3A], and the total percentage of AE-IPF was 6.66% in all new-onset IIP cases. The AE occurrence of UIP was higher than P-UIP in patients with IIP in the past few years, and the difference of total AE occurrence was significant between the two groups (5.35% vs. 1.31%, $P < 0.001$) [Figure 3B and 3C]. Univariate and multivariate Cox regression analyses showed that smoking was the significant risk factor for AE within 6 months after IPF diagnosis in UIP group after adjusting other clinical variables (hazard ratio [HR]: 1.974, 95% confidential interval [CI]: 1.140–

3.419, $P = 0.015$). Corticosteroids reduction or discontinuation before AEs had the tendency of being a risk factor for AE (HR: 0.525, 95% CI: 0.274–1.003, $P = 0.051$) [Table 2]. None of these clinical variables could predict AE occurrence in P-UIP group.

Survival

The median survival time of all patients was only 33 days, and the in-hospital mortality was 54.2%. The cumulative proportion survival (CPS) of 30, 60, and 120-day after AE was 56.1%, 30.8%, and 14.0%, respectively. Kaplan-Meier analysis did not reveal any difference in the overall survival between the two groups ($\chi^2 = 0.264$, $P = 0.608$) [Figure 4], but the CPS of 30-day was significantly higher in the UIP group than in the P-UIP group ($\chi^2 = 5.489$, $P = 0.019$) [Table 3].

Risk factors for survival

Bivariate correlation analysis discovered that the survival negatively correlated to WBC count ($r = -0.260$, $P = 0.015$), C-reactive protein (CRP) ($r = -0.296$, $P = 0.006$), lactic dehydrogenase (LDH) ($r = -0.235$, $P = 0.029$), CT score ($r = -0.445$, $P < 0.001$), maximal dosage of

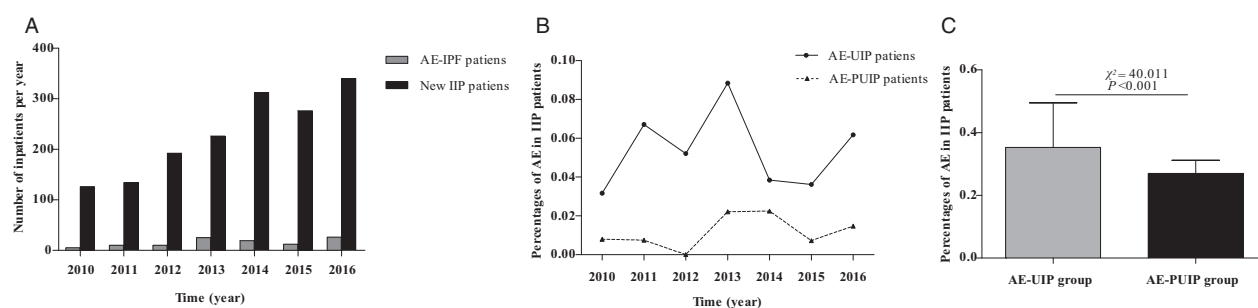


Figure 3: The occurrence of AE-IPF in IIP. (A) The number of new AE-IPF and IIP in patients from 2010 to 2016. (B) AE percentages of UIP and P-UIP in IIP cases from 2010 to 2016. (C) Comparison of the percentages between the AE-UIP and AE-PUIP groups. AE: Acute exacerbation; IIP: Idiopathic interstitial pneumonia; IPF: Idiopathic pulmonary fibrosis; P-UIP: Possible UIP; UIP: Usual interstitial pneumonia.

Table 2: Cox analysis of risk factors for AE within 6 months after IPF diagnosis.

Clinical variables	UIP group			P-UIP group		
	HR	95% CI	P	HR	95% CI	P
Univariate Cox Model						
Gender	1.304	0.6162.763	0.488	0.814	0.295–2.250	0.692
Age	1.018	0.986–1.025	0.276	1.023	0.980–1.068	0.299
Smoking history	1.728	1.011–2.953	0.046	0.931	0.265–3.276	0.912
Smoking amount (pack-years)	1.005	0.991–1.019	0.490	0.970	0.891–1.057	0.491
Corticosteroids used before AE	0.605	0.353–1.036	0.067	0.832	0.289–2.395	0.733
Corticosteroids reduction or discontinuation before AE	0.558	0.293–1.061	0.075	0.639	0.235–1.739	0.381
Immunosuppressants used before AE	0.785	0.191–3.227	0.737	–	–	–
NAC used before AE	1.307	0.472–3.620	1.307	0.639	0.235–1.739	0.381
Multivariate Cox Model						
Age	1.023	0.988–1.059	0.199	1.022	0.975–1.070	0.367
Smoking history	1.974	1.140–3.419	0.015	1.075	0.288–4.018	0.915
Corticosteroids reduction or discontinuation before AE	0.525	0.274–1.003	0.051	0.694	0.251–1.919	0.481

AE: Acute exacerbation; IPF: Idiopathic pulmonary fibrosis; UIP: Usual interstitial pneumonia; P-UIP: Possible UIP; HR: Hazard ratio; CI: Confidential interval; NAC: N-acetylcysteine.

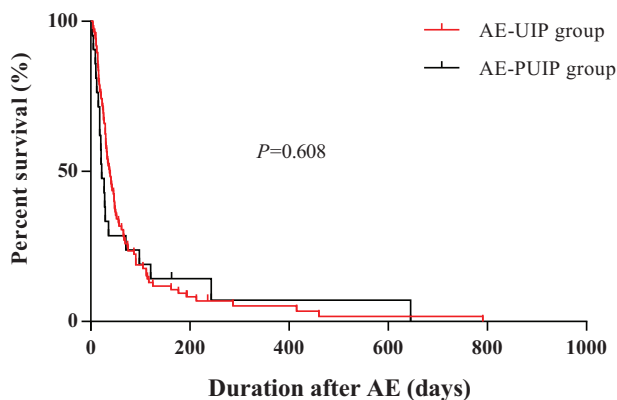


Figure 4: The survival of AE of idiopathic pulmonary fibrosis patients with UIP pattern and P-UIP pattern on chest HRCT. AE: Acute exacerbation; HRCT: High resolution computed tomography; PUIP: Possible UIP; UIP: Usual interstitial pneumonia.

Table 3: Cumulative proportion survival of patients with IPF after AE.

Duration after AE (days)	All subjects (%)	UIP group (%)	P-UIP group (%)	P
30	56.1	61.6	33.3	0.019
60	30.8	31.4	28.6	0.802
120	14.0	12.8	19.0	0.697

IPF: Idiopathic pulmonary fibrosis; AE: Acute exacerbation; UIP: Usual interstitial pneumonia; P-UIP: Possible UIP.

methylprednisolone ($r = -0.024, P = 0.038$) and use of immunoglobulin ($r = -0.231, P = 0.032$), co-trimoxazole ($r = -0.230, P = 0.033$), and MV ($r = -0.407, P < 0.001$) in the UIP group, and positively correlated to PaO₂/FiO₂ ($r = 0.234, P = 0.030$). In the P-UIP group, the survival negatively correlated to D-dimer ($r = -0.519, P = 0.023$) and positively correlated to PaO₂/FiO₂ ($r = 0.457, P = 0.037$) [Table 4].

Univariate cox analysis demonstrated that the survival was associated with WBC count (HR: 1.077, 95% CI: 1.035–1.121, $P < 0.001$), LDH (HR: 1.002, 95% CI: 1.000–1.003, $P = 0.009$), PaO₂/FiO₂ (HR: 0.992, 95% CI: 0.987–0.997, $P = 0.001$), CT score (HR: 1.711, 95% CI: 1.316–2.224, $P < 0.001$), maximal dosage of methylprednisolone (HR: 1.001, 95% CI: 1.000–1.002, $P = 0.012$), use of immunoglobulin (HR: 1.939, 95% CI: 1.212–3.102, $P = 0.006$), caspofungin (HR: 1.992, 95% CI: 1.106–3.590, $P = 0.022$), and MV (HR: 2.497, 95% CI: 1.566–3.980, $P < 0.001$) in the UIP group [Table 5]. Only use of MV was related to the survival of subjects with P-UIP pattern (HR: 3.132, 95% CI: 1.040–9.428, $P = 0.042$) [Table 5]. However, in the multivariate Cox model, WBC count, PaO₂/FiO₂, and CT score were the independent prognostic factors for subjects in the UIP group after adjusting other clinical variables (95% CI: 1.027–1.114, $P = 0.001$; 95% CI: 0.986–0.997, $P = 0.002$; and 95% CI: 1.253–2.171, $P < 0.001$, respectively), none of clinical variables could predict the survival of patients in P-UIP group [Table 5].

Table 4: Bivariate correlation analysis between the clinical variables and survival.

Clinical variables	UIP group		P-UIP group	
	r	P	r	P
WBC counts	-0.260	0.015	-0.424	0.056
CRP	-0.296	0.006	-0.051	0.827
LDH	-0.235	0.029	-0.179	0.438
D-dimer	-0.210	0.070	-0.519	0.023
PaO ₂ /FiO ₂	0.234	0.030	0.459	0.037
CT score	-0.445	<0.001	-0.319	0.158
Maximal dosage of methylprednisolone	-0.024	0.038	-0.156	0.500
Immunoglobulin	-0.231	0.032	-0.299	0.188
Co-trimoxazole	-0.230	0.033	-0.097	0.675
MV	-0.407	<0.001	-0.331	0.143

UIP: Usual interstitial pneumonia; P-UIP: Possible UIP; WBC: White blood cell; CRP: C-reactive protein; LDH: Lactic dehydrogenase; CT: Computed tomography; MV: Mechanical ventilation.

Discussion

The current study showed the clinical features of patients with AE with UIP pattern differed from P-UIP pattern. AE incidence of UIP was significantly higher than P-UIP in IPF patients. Within 6 months after IPF diagnosis, smoking was the risk factor for AE occurrence in UIP group. Although the overall survival was similar in the two groups, the survival of 30-day was much better in UIP group. WBC count, PaO₂/FiO₂, and CT score were the independent risk factors for prognosis in patients with UIP pattern.

The positive predictive value of UIP or P-UIP pattern on chest HRCT for IPF is very high.^[1,23-25] Quite a few of studies suggested that SLB was optional for diagnosis IPF patients with P-UIP pattern. In the study of Sumikawa *et al*,^[26] SLB revealed that 23 subjects were pathological UIP-pattern among 24 patients with radiological P-UIP pattern. Lee *et al*^[27] argued that lung biopsy was not necessary in patients with radiological P-UIP pattern when associated with typical symptoms and excluded other known causes of IPF. Arai *et al*^[28] indicated that AE possibly occurred more often in patients with UIP pattern than those with P-UIP pattern on chest imaging. Population-based epidemiological studies have suggested that IPF tended to occur in male and older people.^[1,29] AE-IPF patients with classical UIP pattern were older than P-UIP subjects.^[28] Consistent with these previous studies, patients with AE in the UIP group had more men and were older than those in the P-UIP group in our study.^[1,28,29] Severe hyoxmia and high CT scores at AEs meant that the conditions of these subjects included in our cohort study were quite serious.

Recent evidences indicated that infection could be an important pathogenic factor and risk factor for mortality for patients with AE-IPF.^[3,30-32] In some patients with AE-IPF, death was attributed to bronchopneumonia and the causes of infection included fungus, virus, and bacteria.^[33] Patients with AE-IPF had higher bacterial burden in

Table 5: Prognostic factors for patients with AE in the UIP and P-UIP groups by multivariate Cox analysis.

Clinical variables	UIP group			P-UIP group		
	HR	95% CI	P	HR	95% CI	P
Univariate Cox Model						
Gender	1.188	0.654–2.159	0.571	0.550	0.206–1.468	0.232
Age	0.982	0.955–1.010	0.209	0.985	0.951–1.021	0.421
Smoking history	0.776	0.495–1.217	0.269	0.518	0.147–1.823	0.305
Smoking amount (pack-years)	0.994	0.982–1.007	0.387	0.930	0.853–1.014	0.099
WBC count	1.077	1.035–1.121	<0.001	1.100	0.966–1.253	0.151
LDH	1.002	1.000–1.003	0.009	1.004	0.999–1.008	0.149
PaO ₂ /FiO ₂	0.992	0.987–0.997	0.001	0.995	0.986–1.003	0.196
CT score	1.711	1.316–2.224	<0.001	1.612	0.911–2.852	0.101
Microbiology	1.129	0.677–1.885	0.641	1.869	0.402–8.686	0.425
Maximal dosage of methylprednisolone	1.001	1.000–1.002	0.012	1.001	0.999–1.002	0.409
Immunoglobulin	1.939	1.212–3.102	0.006	2.951	0.994–8.762	0.051
Immunosuppressants	1.077	0.530–2.185	0.838	0.418	0.135–1.296	0.131
Caspofungin	1.992	1.106–3.590	0.022	1.681	0.212–13.314	0.623
Co-trimoxazole	1.376	0.889–2.131	0.152	1.021	0.408–2.556	0.965
MV	2.497	1.566–3.980	<0.001	3.132	1.040–9.428	0.042
Multivariate Cox Model						
WBC count	1.070	1.027–1.114	0.001	1.155	0.976–1.366	0.093
PaO ₂ /FiO ₂	0.992	0.986–0.997	0.002	0.991	0.981–1.001	0.091
CT score	1.649	1.253–2.171	<0.001	1.187	0.579–2.435	0.640

AE: Acute exacerbation; UIP: Usual interstitial pneumonia; P-UIP: Possible UIP; HR: Hazard ratio; CI: Confidential interval; WBC: White blood cell; LDH: Lactic dehydrogenase; CT: Computed tomography; MV: Mechanical ventilation.

bronchoalveolar lavage fluids than stable cases.^[34] As a result, the updated international diagnostic criteria of AE-IPF no longer excluded respiratory infections, such a broader definition was more inclusive and pragmatic for clinicians who struggled with the historical requirement for exclusion of infection.^[2] In current study, more higher inflammation markers and evidence of microbiology infection were shown in the UIP group when AEs occurred. These findings were consistent with the new definition and diagnostic criteria,^[2] and indicated that infection could be more important in patients with P-UIP than classical UIP cases in AE.

Cohort studies generally reported a higher annual incidence of AE-IPF than clinical trials, 13.0, 14.2, and 8.6 per 100 patients with IPF in the United States, South Korean, and Japan, respectively.^[3,9,35] Low forced vital capacity (FVC), low diffusing capacity for carbon monoxide (DLCO), pulmonary hypertension, poor baseline oxygenation, and increased dyspnea have been proved to be the risk factors for AE-IPF.^[3,6,9,10,35] Now, nationwide epidemiological study in China is lacking. In the current study from our single-center, the incidence of AE-IPF was 6.66% in patients with IIP, and AE incidence of UIP patients was higher than P-UIP subjects per year. The differences of epidemiological data between our center and other countries might be due to the different population of AE-IPF.^[2] Smoking has been identified as a risk factor for AE-IPF by some, but not all studies.^[3,36,37] Results from the current study supported the claim that smoking was a risk factor for AE. A prospective cohort study of the relationship between smoking and AE occurrence should be conducted in the future. Although the international

guideline recommended that patients with IPF should not be treated with corticosteroid mono-therapy or in combination with immunosuppressant therapy,^[1] we included some cases before the guideline published, part of them used corticosteroids in our study. Data analysis showed that there was a tendency of corticosteroids reduction or discontinuation as a risk factor for AE occurrence. We should be cautious with withdrawal of corticosteroids in order to avoiding the fatal events of AE in patients with IPF.

The median survival time of AE-IPF has been estimated at 3 to 4 months approximately.^[3,6] The average survival time and in-hospital mortality of our cases were similar to the published reports.^[3,6,9] In previous small cohort retrospective studies, the survival of patients with AE-IPF between UIP and P-UIP pattern were inconsistent with each other. Arai *et al*^[28] reported that the prognosis of patients with AE-IPF with P-UIP pattern ($n = 12$) might be worse than those with UIP pattern ($n = 29$). However, Usui *et al*^[38] showed a similar survival in patients with AE-IPF with UIP pattern and P-UIP pattern. In our cohort, the short-term survival in patients with UIP was much better, although the overall survival did not show significant difference between the two groups. Such discrepancy was very interesting. We suspected that the better short-term survival might be associated with more microbiology infection in the UIP group. Now, the respiratory infection has been regarded as an important factor for the development of AE-IPF.^[2] We could take the effective targeted treatments once we identified some pathogens. However, it required further clinical studies of multi-center design and larger samples size.

Previous studies revealed that the following prognostic factors were associated with the survival of patients with AE-IPF, such as lower baseline FVC and DLCO,^[3,9] more extensive CT abnormalities,^[39] worse oxygenation,^[3,40] bronchoalveolar lavage neutrophil, and lymphocyte percentages at the time of AE.^[3] Several biomarkers in peripheral blood, including Krebs Von den Lungen-6 (KL-6), heat shock protein 70, LDH, CRP, and leptin have also been proposed.^[37,41-43] In our study, the predictors for survival in patients with AE were also different between the two groups. WBC count, PaO₂/FiO₂, and CT score were the independent prognostic factors in the UIP group, but none in P-UIP group. The findings in the UIP group were generally consistent with results obtained in patients with AE-IPF in previous studies.^[3,40] Fujimoto *et al*^[39] suggested that HRCT CT scores could predict the mortality of patients with AE-IPF. We suspected that the clinical outcomes of patients with AE-UIP were mainly dependent on the degree of inflammation and the injury extents of lung at AEs. The survival of AE patients with P-UIP pattern needs to be further studied.

There is no treatment proven to be effective for AE-IPF. Systemic corticosteroids were often used by clinicians for patients with AE-IPF because the international evidence-based guidelines of the management of IPF made a weak recommendation, but the ILD experts have not reached a consensus on the regimen and dosage of corticosteroids.^[1,2,44] Steroids in combination with immunosuppressant for AE-IPF appeared better than corticosteroid monotherapy.^[1,2,44,45] Supportive cares, such as supplemental oxygen, immunoglobulin, and MV are usually used when AE occurs, although the use of MV is controversial.^[2,46,47] In our analysis, uses of high dose methylprednisolone, immunoglobulin, co-trimoxazole, and MV for AE were associated with a shorter survival in the UIP group. So the current therapies for AE usually could not benefit patients with IPF. Nintedanib, intra-venous thrombomodulin, and polymyxin B-immobilized fiber column perfusion add-on conventional treatment might be the potential treatments for patients with AE-IPF.^[40,48,49] Recently, some experts suggested translating to AE-IPF the lessons learned from the management of patients with ARDS because of the common pathophysiological abnormalities and similar clinical needs.^[50]

The current study had limitations. First, it was retrospectively reviewed for patients from a single center and the sample size was small. Second, the diagnosis of AE-IPF was only based on clinical and radiological findings, without pathological evidences. Third, the definite causes of death were not clear. A prospective, multi-center and nationwide cohort study would be helpful to understand the epidemiological features of patients with AE-IPF in China.

In summary, the clinical features of AE-IPF were different between patients with UIP pattern and P-UIP pattern. AE incidence of cases with UIP pattern was significantly higher than P-UIP pattern in patients with IPF. Within 6 months after IPF diagnosis, smoking was the independent risk factor for AE occurrence in UIP group. The short-term survival of patients with AE-UIP was better despite of the similar overall survival in the two groups. The WBC count,

PaO₂/FiO₂, and CT score were the independent prognostic predictors for patients with UIP pattern, not P-UIP pattern.

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Conflicts of interests

None.

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