Acute exacerbation of unclassifiable idiopathic interstitial pneumonia: comparison with idiopathic pulmonary fibrosis

Noriyuki Enomoto [iD], **Hyogo Naoi, Yuya Aono, Mineo Katsumata, Yasuoki Horiike, Hideki Yasui** [iD], **Masato Karayama, Hironao Hozumi, Yuzo Suzuki, Kazuki Furuhashi** [iD], **Tomoyuki Fujisawa, Naoki Inui, Yutaro Nakamura and Takafumi Suda**

Abstract

Background: Acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) is well known as a life-threatening condition during its clinical course. However, the clinical features and prognosis in AE of unclassifiable idiopathic interstitial pneumonia (AE-UCIIP) remain to be elucidated. The aim of this study was to clarify the clinical features and prognosis of AE-UCIIP compared with those of AE-IPF.
Methods: In 187 patients with UCIIP or IPF, 64 patients with AE-UCIIP or AE-IPF, who were diagnosed and treated at our hospital, were retrospectively evaluated.
Results: A total of 24 patients with AE-UCIIP were significantly older ($p = 0.011$), included more women ($p < 0.001$) and never-smokers ($p < 0.001$), and showed fewer lung lesions on high-resolution computed tomography ($p = 0.006$) than 40 patients with AE-IPF. Incidence of AE-UCIIP was 10.29%/year and was significantly higher than in AE-IPF (Gray's test, $p = 0.008$). Prognosis of AE-UCIIP was as poor as that of AE-IPF (log-rank, $p = 0.681$). Percent-predicted forced vital capacity (%FVC) [hazard ratio (HR) 0.934, $p = 0.045$], and GAP stage within 12 months before AE (HR 3.530, $p = 0.023$), and partial pressure arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio at AE (HR 0.998, $p = 0.016$) were significant prognostic factors. Finally, commencement of long-duration ($\geqslant 12\,h$) direct hemoperfusion with a polymyxin B-immobilised fibre column (PMX-DHP) within 2 days after admission significantly improved survival (log-rank, $p = 0.038$) and was a significant prognostic factor (HR 0.175, $p = 0.0039$) in AE-UCIIP. Long-duration PMX-DHP showed favourable treatment effects even in the combined group of patients with AE-UCIIP or AE-IPF (log-rank $p = 0.002$; HR 0.328, $p = 0.006$).
Conclusions: Patients with AE-UCIIP were older and included more women and never-smokers than those with AE-IPF. Prognosis of AE-UCIIP was as poor as that of AE-IPF.

The reviews of this paper are available via the supplemental material section.

Keywords: acute exacerbation, direct hemoperfusion with a polymyxin B-immobilised fibre column, idiopathic pulmonary fibrosis, idiopathic unclassifiable interstitial pneumonia

Correspondence to:
Noriyuki Enomoto
Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, 1-20-1 Handayama, Hamamatsu 431-3192, Japan

Health Administration Center, Hamamatsu University School of Medicine, Hamamatsu, Japan

norieno@hama-med.ac.jp

Hyogo Naoi
Yuya Aono
Mineo Katsumata
Yasuoki Horiike
Hideki Yasui
Masato Karayama
Hironao Hozumi
Yuzo Suzuki
Kazuki Furuhashi
Tomoyuki Fujisawa
Yutaro Nakamura
Takafumi Suda
Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Japan

Naoki Inui
Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Japan

Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Hamamatsu, Japan

Introduction

Idiopathic interstitial pneumonias (IIPs) are life-threatening diseases that show a variety of inflammation and fibroses on the lung parenchyma, with several pathological and radiological patterns. IIPs are categorized based on their interstitial pneumonia (IP) patterns, and idiopathic pulmonary fibrosis (IPF) is the most frequent IIP with the poorest prognosis.[1,2] Precise classification of IIPs requires a multidisciplinary approach. However, even with a multidisciplinary approach, many patients with IIPs cannot be given a specific IIP diagnosis and are labelled with unclassifiable idiopathic interstitial pneumonia (UCIIP) in
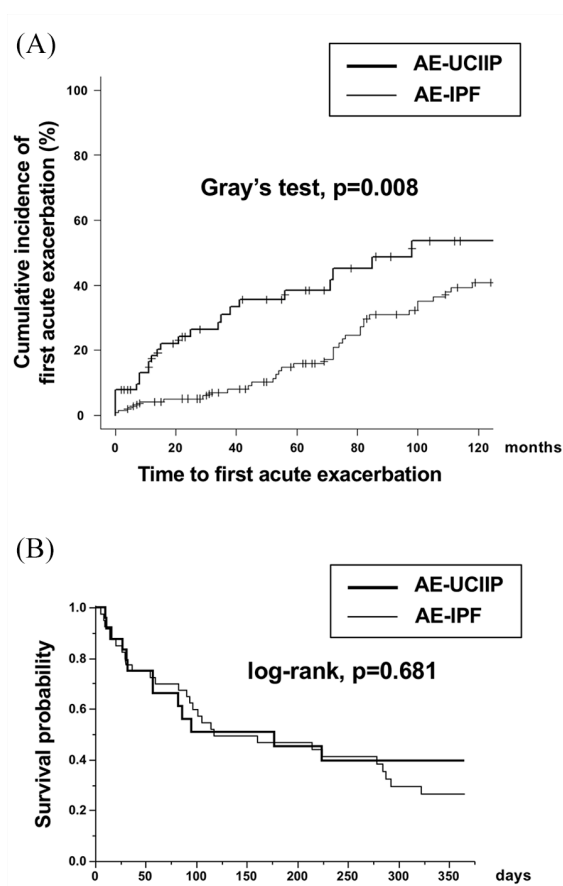
(A)

(B)

Figure 1. Incidence of first acute exacerbation (AE) and Kaplan–Meier survival curves from the first AE onset. Incidence of first AE in patients with unclassifiable idiopathic interstitial pneumonia (AE-UCIIP) was significantly higher than that in AE in patients with idiopathic pulmonary fibrosis (AE-IPF) (A, Gray's test, *p* = 0.008). The 12-month survival rate in patients with AE-UCIIP was as poor as those with AE-IPF (B, log-rank test, *p* = 0.681).

clinical practice.[2–4] The survival of UCIIP is reportedly intermediate between that of IPF and non-IPF,[3,5] and effective treatments for UCIIP have not been established.

Acute exacerbation (AE) of IP is a devastating condition that frequently occurs in the clinical course of IPF,[1,6–8] and AE-IPF accounts for 30–40% of deaths in patients with IPF.[9,10] Furthermore, AE occurs not only in IPF but also in other IIPs such as non-specific interstitial pneumonia or connective tissue disease-associated IP.[11–13] However, little is known about AE in patients with UCIIP, while we sometimes experience AE-UCIIP in clinical practice.

Here, in the present study, we retrospectively evaluated clinical features of AE-UCIIP compared with those of AE-IPF. Furthermore, the prognostic factors including treatments were examined in patient with AE-UCIIP. To our knowledge, this is the first study to provide detailed information about clinical features and prognosis in patients with AE-UCIIP.

Methods

Study design and subjects

Among 187 patients with UCIIP or IPF, 77 patients who were diagnosed and treated for AE-UCIIP or AE-IPF at our hospital between 2002 and 2018 were retrospectively reviewed. The diagnosis of UCIIP was re-evaluated based on the American Thoracic Society (ATS) and European Respiratory Society (ERS) international statement for classification of IIPs in 2013.[2] The diagnosis of IPF was also re-evaluated based on the official clinical practice guideline of the ATS, ERS, Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) in 2018.[14] Patients with AE-IP who had an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality were selected. All patients met the modified diagnostic criteria described by Collard *et al.* in 2016.[15] Briefly, the diagnostic criteria for AE-IP were as follows: (a) previous or concurrent diagnosis of IP; (b) acute worsening or development of dyspnoea typically <1 month in duration; (c) computed tomography (CT) with new bilateral ground-glass opacity and/or consolidation superimposed on background findings of IP; and (d) deterioration not fully explained by cardiac failure or fluid overload. A total of 11 patients with a second recurrence of AE-IP and 1 patient with second and third recurrence of AE-IP were excluded so that the prognosis was evaluated from the first AE-IP in 64 patients with AE-UCIIP or AE-IPF (Supplemental Figure 1). The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine (approval number 18-085). All procedures in this study were performed in accordance with the study protocol and the 1964 Declaration of Helsinki as amended. The need for patient approval and informed consent was waived due to the retrospective nature of the study.

Data collection

Clinical, laboratory, and physiological data were obtained from medical records. Disease severity of IP within 12 months before the AE event was assessed using the gender, age, and physiology (GAP) staging system[16] and the Japanese Respiratory Society (JRS) severity grades for IP.[17] The former considers gender, age, and two lung physiology variables: forced vital capacity (FVC) and diffusion lung capacity for carbon monoxide (DL_{CO}).[16] The latter consists of partial pressure arterial oxygen (PaO_2) at rest and minimum oxygen saturation (SpO_2) during the 6-minute walking test (6MWT).[17] The extent of lung opacity was measured on three high-resolution CT (HRCT) slices as described in our previous report.[18] The pattern of AE-IP on HRCT was classified as (a) peripheral, (b) multifocal, or (c) diffuse, as reported by Akira *et al.*[19] The HRCT findings were reviewed by two observers.

PMX-DHP therapy

Some patients were treated with direct hemoperfusion with a polymyxin B-immobilised fibre column [PMX-DHP (PMX; Toray Medical Co., Ltd, Tokyo, Japan)] starting at the same time as the corticosteroid and immunosuppressant therapy. Patients were treated with PMX-DHP whenever practicable. Inclusion criteria of PMX-DHP for the treatment of AE-IPF were as follows: (a) current diagnosis of AE-IP; (b) able and willing to provide informed consent. Exclusion criteria of PMX-DHP for the treatment of AE-IP were as follows: (a) ≥85 years old; (b) history of hypersensitivity for blood purification or extracorporeal circulation therapy; (c) hemodynamic instability; (d) severe cardiovascular disease; (e) severe hemorrhagic disease; (f) terminal cancer; (g) pregnant or lactating; (h) considered ineligible for PMX-DHP by an attending doctor.[20]

Statistical analysis

Statistical analysis was performed using JMP-13.1.0 (SAS Institute Inc., Cary, NC, USA) and EZR 1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[21] Categorical data were compared using the χ^2 test or Fisher's exact probability test for independence, and continuous data using the Wilcoxon rank sum test. AE-IIPs occurrence was estimated considering the death before AE as a competing event, and analysed using Gray's method. Overall survival of patient groups was estimated using Kaplan–Meier curves. The relationships between variables and mortality were evaluated by Cox proportional hazards regression analysis. All tests were two-sided and statistical significance was set at $p < 0.05$.

Results

Incidence of acute exacerbation in patients with UCIIP or IPF

In 187 patients with UCIIP or IPF (UCIIP: 63; AE-IPF: 124), 64 AE-IP cases (AE-UCIIP: 24 and AE-IPF: 40) occurred during the observation period. Incidences of AE were 10.29%/year in patients with UCIIP and 5.85%/year in those with IPF. Cumulative incidences of the first AE are shown in Figure 1A. Cumulative incidence of AE-UCIIP was 38.1% (24 of 63 patients) and frequency of AE was significantly higher in AE-UCIIP than in AE-IPF (Gray's test, $p = 0.008$). Further, the median period from IP diagnosis to first AE was significantly shorter in patients with UCIIP than in those with IPF (Table 1; 14.5 *versus* 74.5 months, $p < 0.001$).

Clinical characteristics, physiological examination findings, and treatments: comparison between patients with AE-UCIIP and AE-IPF

Clinical characteristics of all patients with AE-UCIIP, including physiological examination findings and treatments, are shown in Table 1 and compared with patients with AE-IPF. In 24 patients with AE-UCIIP, 7 were diagnosed with UCIIP after surgical lung biopsy (SLB). Patients with AE-UCIIP had a median age of 79.5 years at the diagnosis of AE-UCIIP and were significantly older than those with AE-IPF (69.5 years old, $p = 0.011$). More female patients with AE-UCIIP ($p < 0.001$) and more never-smokers ($p < 0.001$) were found in comparison with patients with AE-IPF. The period from first IP diagnosis to first AE in AE-UCIIP was significantly shorter than in AE-IPF (74.5 *versus* 14.5 months, $p < 0.001$). As for lung function within 12 months before AE, %FVC tended to be higher in AE-UCIIP than in AE-IPF (62.0 *versus* 55.7%, $p = 0.051$). %DL_{CO} was not different ($p = 0.414$). The extent score of lung fibrosis within 12 months before AE was significantly lower in AE-UCIIP than in IPF ($p = 0.006$). Severity scores of interstitial pneumonia within 12 months before AE (GAP and JRS scores) were not different ($p = 0.555$ and 0.132, respectively). The proportion

Table 1. Comparison of data between patients with AE-IPF and AE-UCIIP.

	AE-IPF [$n = 40$, median (range)]	AE-UCIIP [$n = 24$, median (range)]	*p* value
Age, years	69.5 (50, 84)	79.5 (64, 85)	0.011
Sex, male/female	37/3	13/11	<0.001
Smoking, never/ex/current	6/29/5	13/11/0	<0.001
Pack-years of smoking	32.9 (0, 81)	0 (0, 100)	0.002
Surgical lung biopsy, +/−	20/20	7/17	0.098
Period from IP diagnosis to first AE, months	74.5 (0, 203)	14.5 (0, 98)	<0.001
Observation period from the onset of AE, days	49 (0, 205)	16 (0, 175)	0.012
Data within 12 months before AE			
FVC, % pred	55.7 (37.5, 89.3)	62.0 (42.1, 95.7)	0.051
DL_{CO}, % pred	54.2 (33.5, 88.2)	65.5 (44.7, 90.2)	0.414
PaO_2 at rest, Torr	72 (49, 91)	75 (53, 88)	0.223
Distance in 6MWT, m	370 (160, 507)	442 (320, 578)	0.192
Minimum SpO_2 in 6MWT, %	82 (60, 95)	85 (79, 94)	0.111
Extent scores on HRCT (full score: 25)	13 (7, 19)	10 (2, 18)	0.006
JRS severity grade, I/II/III/IV/unknown	7/0/12/16/5	7/1/7/4/5	0.132
The GAP staging system, I/II/III/unknown	9/12/14/5	7/6/5/6	0.555
Preceding treatment for IP, +/−	22/18	9/14	0.224
Preceding oxygen therapy, +/−	13/27	5/19	0.308
Data at AE			
Peripheral blood WBC, $\times 10^3/\mu l$	9.9 (1.9, 27.8)	10.7 (5.1, 15.4)	0.793
Peripheral blood Neut, $\times 10^3/\mu l$	7.2 (1.5, 25.8)	8.8 (3.3, 15.1)	0.287
Serum CRP, mg/dl	6.1 (0.9, 23.7)	7.1 (1.2, 19.4)	0.453
Serum LDH, IU/l	347 (183, 603)	376 (220, 936)	0.094
Serum KL-6, U/ml	1520 (481, 6404)	1655 (159, 4190)	0.492
Serum SP-D, ng/ml	368 (23, 1330)	292 (52, 1960)	0.469
P/F ratio	168 (38, 386)	199 (88, 357)	0.179
Extent scores on HRCT (full score: 25)	20 (13, 25)	19.5 (15, 25)	0.853
HRCT pattern, peripheral/multifocal/diffuse/unknown	3/3/31/3	1/2/21/0	0.822
Administration of steroid pulse therapy,* +/−	40/0	24/0	1.000
Administration of immunosuppressants, +/−	26/14	11/13	0.133

(Continued)

Table 1. (Continued)

	AE-IPF [*n* = 40, median (range)]	AE-UCIIP [*n* = 24, median (range)]	*p* value
Treatment with long-duration PMX-DHP, +/–	20/20	14/10	0.517
Intubation, +/–	10/30	3/21	0.216
Δ WBC at 2 days after beginning AE treatment, ×10³/μl	2.3 (–7.2, 15.2)	3.2 (–5.4, 18.1)	0.824
Δ Neut at 2 days after beginning AE treatment, ×10³/μl	5.7 (–3.8, 15.0)	3.1 (–4.5, 18.6)	0.421
Δ LDH at 2 days after beginning AE treatment, IU/l	–44 (–145, 425)	8 (–292, 370)	0.322
Δ P/F ratio at 2 days after beginning AE treatment	31 (–146, 243)	–10 (–89, 428)	0.356

*Methylprednisolone 1000 mg/day for 3 days.
AE, acute exacerbation; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; AE-UCIIP, acute exacerbation of unclassifiable idiopathic interstitial pneumonia; CRP, C-reactive protein; DLCO, diffusion lung capacity for carbon monoxide; FVC, forced vital capacity; GAP, gender, age, and physiology; HRCT, high-resolution computed tomography; JRS, Japanese Respiratory Society; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; Neut, neutrophils; P/F, PaO_2/FiO; PMX-DHP, direct hemoperfusion with a polymyxin B-immobilised fibre column; 6MWT, 6-minute walk test; SP-D, surfactant protein D; WBC, white blood cells.

of patients receiving previous treatments, including steroids, immunosuppressants, and oxygen therapy, was not different between groups. At AE, serum markers were not different between the groups. The partial pressure arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) (P/F) ratio, extent score of all HRCT findings, and HRCT pattern at AE were not different either. All patients were treated with steroid-pulse therapy after hospital admission (methylprednisolone at 1000 mg/day for 3 days) followed by a tapering dose of prednisolone. Treatments with an immunosuppressant (cyclophosphamide or cyclosporine) and/or long-duration (mainly ⩾12h) PMX-DHP[20,22] were added to steroid therapy in more than half of patients. A total of 2 in 24 patients with AE-UCIIP and 2 in 40 patients with AE-IPF had concomitant respiratory infection at the time of admission (triggered AE). Serum endotoxin was undetectable in all patients treated with PMX-DHP. These treatments were commenced concomitantly with the antibiotics as soon as possible after admission. None of these AE treatments were different between groups.

Mortality rate and prognostic factors in patients with AE-UCIIP

Of 24 patients with AE-UCIIP, 4 died within 1 month of onset (mortality rate, 16.7%), 10 died within 3 months (mortality rate, 41.7%), and 13 died within 12 months (mortality rate, 54.2%). Within 12 months of AE-UCIIP onset, 10 patients died of respiratory failure, 1 died of bacterial pneumonia, and 2 died of lethal arrythmia. Figure 1B shows Kaplan–Meier survival curves from the first AE onset. The 12-month survival rate in patients with AE-UCIIP was as poor as those with AE-IPF (log-rank test, *p* = 0.681). The results of univariate Cox proportional hazards models of survival in AE-UCIIP to identify prognostic factors are shown in Table 2. %FVC within 12 months before AE was a significant prognostic factor in patients with AE-UCIIP [hazard ratio (HR) 0.928, *p* = 0.025]. Similarly, the GAP stage within 12 months before AE was also a significant prognostic factor (HR 4.467, *p* = 0.005). At AE, the P/F ratio was significant (HR 0.988, *p* = 0.005), and peripheral blood white blood cells (WBC) and serum lactate dehydrogenase (LDH) tended to be a prognostic factor (HR 1.000, *p* = 0.095 and HR 1.002, *p* = 0.097, respectively). All patients were treated with steroid-pulse therapy. In addition to this, 14 patients with AE-UCIIP were treated with long-duration PMX-DHP, but this could not improve the survival (Figure 2A, *p* = 0.508). However, in AE-UCIIP patients treated within 2 days after admission, commencement of long-duration PMX-DHP improved survival (Figure 2B, *p* = 0.038). Similarly, in Cox proportional hazards models of survival, although treatment with long-duration PMX-DHP itself

Table 2. Univariate Cox proportional hazards models of survival in patients with AE-UCIIP ($n = 24$).

Variable	Hazard ratio	95% CI		*p* value
		Lower	Upper	
Age, years	1.047	0.968	1.133	0.245
Sex, male	0.766	0.254	2.387	0.635
Pack-years of smoking	0.975	0.935	1.004	0.093
Period from IP diagnosis to first AE, months	0.983	0.953	1.005	0.134
Data within 12 months before AE				
Extent score on HRCT	1.103	0.937	1.298	0.237
FVC, % pred	0.928	0.846	0.992	0.025
DL_{CO}, % pred	0.919	0.558	1.072	0.356
Resting PaO_2, mmHg	0.935	0.846	1.031	0.175
Distance in 6MWT, m	0.974	0.840	1.022	0.480
Minimum SpO_2 in 6MWT, %	1.065	0.745	1.572	0.707
JRS severity grade	1.295	0.675	2.714	0.442
The GAP staging system	4.467	1.532	18.59	0.005
Preceding treatments for IP, +	0.829	0.249	2.504	0.743
Preceding oxygen therapy, +	2.923	0.756	9.856	0.113
Data at AE				
Peripheral blood WBC, /μl	1.000	0.999	1.000	0.095
Peripheral blood Neut, /μl	1.000	0.999	1.000	0.174
Serum CRP, mg/dl	1.055	0.960	1.154	0.254
Serum LDH, IU/l	1.002	0.999	1.005	0.097
Serum KL-6, U/ml	0.999	0.999	1.000	0.857
Serum SP-D, ng/ml	1.000	0.998	1.001	0.759
P/F ratio	0.988	0.978	0.996	0.005
Extent score on HRCT	1.126	0.950	1.340	0.169
Treatment with immunosuppressive agents at AE, +	0.801	0.256	2.423	0.691
Treatment with long-duration PMX-DHP, +	0.693	0.229	2.163	0.515
Commencement of treatment with long-duration PMX within 2 days, +	0.109	0.006	0.559	0.005
Intubation at AE, +	3.063	0.656	11.12	0.139
ΔWBC at 2 days after beginning AE treatment, /μl	0.999	0.999	1.000	0.845
ΔNeut at 2 days after beginning AE treatment, /μl	0.999	0.999	1.000	0.472
ΔP/F ratio at 2 days after beginning AE treatment	0.996	0.986	1.002	0.254
ΔLDH at 2 days after beginning AE treatment, IU/l	1.003	0.998	1.007	0.269

AE, acute exacerbation; CRP, C-reactive protein; DLCO, diffusion lung capacity for carbon monoxide; FVC, forced vital capacity; GAP, gender, age, and physiology; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; JRS, Japanese Respiratory Society; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; Neut, neutrophils; P/F, $PaO2/FiO_2$; PMX-DHP, direct hemoperfusion with a polymyxin B-immobilised fibre column; 6MWT, 6-minute walk test; SP-D, surfactant protein D; UCIIP, unclassifiable idiopathic interstitial pneumonia; WBC, white blood cells.
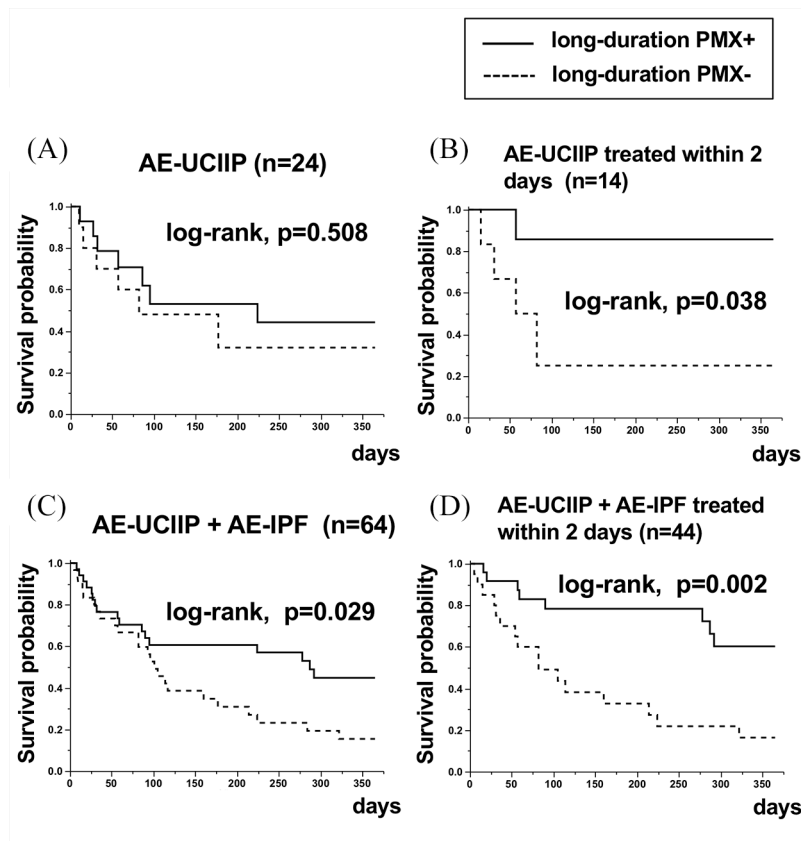
Figure 2. Kaplan–Meier survival curves in patients treated with or without long-duration direct hemoperfusion with a polymyxin B-immobilised fibre column (PMX-DHP). All of the patients were treated with steroid-pulse therapy. In addition to this, 14 out of 24 patients with acute exacerbation of unclassifiable idiopathic interstitial pneumonia (AE-UCIIP) were treated with long-duration PMX-DHP. Long-duration PMX-DHP treatment could not improve the survival (A, log-rank, $p = 0.508$). In AE-UCIIP patients treated within 2 days after admission, long-duration PMX-DHP significantly improved survival (B, log-rank, $p = 0.038$). In all 64 patients with AE-UCIIP or idiopathic pulmonary fibrosis (AE-IPF), treatment with long-duration PMX-DHP improved survival (C, log-rank, $p = 0.029$). In these patients treated within 2 days after admission, long-duration PMX-DHP further improved the survival, especially at 3 months after the onset of AE (D, log-rank, $p = 0.002$).

was not significant, commencement of long-duration PMX-DHP in patients treated within 2 days after admission was a significant prognostic factor (Table 2, HR 0.693, $p = 0.515$ and HR 0.109, $p = 0.005$, respectively).

Mortality rate and prognostic factors in all patients with AE-UCIIP or AE-IPF

The 12-month survival rates of AE-UCIIP and AE-IPF patients were almost the same, as shown in Figure 1B. Therefore, to examine detailed prognostic factors, Cox proportional hazards models of survival were built in for all 64 patients with AE-UCIIP or AE-IPF. Univariate Cox proportional hazards models of survival are shown in Supplemental Table 1. Within 12 months

before AE, extent score on HRCT (HR 1.149, $p = 0.005$), %FVC (HR 0.973, $p = 0.047$), JRS severity grade (HR 1.586, $p = 0.004$), the GAP stage (HR 1.732, $p = 0.021$), and previous oxygen therapy (HR 2.999, $p = 0.002$) were significant prognostic factors. At AE, peripheral blood WBC (HR 1.000, $p = 0.009$), peripheral blood neutrophils (HR 1.000, $p = 0.002$), serum LDH (HR 1.002, $p = 0.038$), P/F ratio (HR 0.994, $p = 0.002$), and extent score on HRCT at AE (HR 1.121, $p = 0.014$) were also significant prognostic factors. Regarding treatments and the later course, intubation at AE (HR 2.564, $p = 0.013$) and ΔP/F ratio and ΔLDH 2 days after beginning AE treatment (HR 0.994, $p = 0.015$ and HR 1.004, $p = 0.008$, respectively) were significant factors. Treatment with long-duration

Table 3. Multivariate Cox proportional hazards models of survival adjusted for GAP stage and PaO_2/FiO_2 ratio in patients with AE-UCIIP or AE-IPF ($n = 64$).

Variable	Hazard ratio	95% CI		p value
		Lower	Upper	
Pack-years of smoking	0.987	0.971	1.001	0.075
Data within 12 months before AE				
Extent score on HRCT	1.176	1.043	1.337	0.007
FVC, % pred	0.990	0.955	1.022	0.561
JRS severity grade	1.244	0.841	1.898	0.278
Preceding oxygen therapy, +	2.293	0.949	5.525	0.065
Data at AE				
Peripheral blood WBC, /μl	1.000	0.999	1.000	0.399
Peripheral blood Neut, /μl	1.000	0.999	1.000	0.141
Serum LDH, IU/l	1.003	0.999	1.005	0.053
Extent score on HRCT	1.116	0.991	1.262	0.071
Treatment with long-duration PMX-DHP, +	0.561	0.264	1.173	0.124
Commencement of treatment with long-duration PMX within 2 days, +	0.328	0.133	0.739	0.006
Intubation at AE, +	1.932	0.787	4.458	0.145
Δ P/F ratio at 2 days after beginning AE treatment	0.994	0.987	0.999	0.048
Δ LDH at 2 days after beginning AE treatment, IU/l	1.004	1.000	1.008	0.024

AE, acute exacerbation; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; AE-UCIIP, acute exacerbation of unclassifiable idiopathic interstitial pneumonia; FVC, forced vital capacity; GAP, gender, age, and physiology; HRCT, high-resolution computed tomography; JRS, Japanese Respiratory Society; LDH, lactate dehydrogenase; Neut, neutrophils; P/F, PaO_2/FiO_2; PMX-DHP, direct hemoperfusion with a polymyxin B-immobilised fibre column; WBC, white blood cells.

PMX-DHP improved survival (Figure 2C, $p = 0.029$) and was a significantly better prognostic factor (Supplemental Table 1, HR 0.505, $p = 0.031$). Further, in patients treated within 2 days after admission, commencement of long-duration PMX-DHP further improved the survival, especially at 3 months after the onset of AE (Figure 2D, $p = 0.002$; Supplemental Table 1, HR 0.249, $p < 0.001$). Supplemental Table 2 compares data between patients treated with long-duration PMX-DHP and those without the treatment. Although patients receiving long-duration PMX-DHP were significantly younger (70 *versus* 80 years old, $p = 0.008$) and receiving less previous oxygen therapy ($p = 0.048$), their %FVC, %DL_{CO}, JRS severity grade, GAP stage within 12 months before AE, and P/F ratio at AE were not different. Next, multivariate Cox proportional hazards models of survival adjusted for GAP stage within 12 months before AE and P/F ratio at AE are shown in Table 3. Extent score on HRCT within 12 months before AE (HR 1.176, $p = 0.007$) and ΔP/F ratio and ΔLDH at 2 days after beginning AE treatment (HR 0.994, $p = 0.048$ and HR 1.004, $p = 0.024$, respectively) were still significant factors. Whereas treatment with long-duration PMX-DHP itself was not significant (HR 0.561, $p = 0.124$), commencement of long-duration PMX-DHP within 2 days after admission was still a significantly better prognostic factor (HR 0.328, $p = 0.006$) in patients with AE-UCIIP or AE-IPF.

Discussion

In this study, we retrospectively evaluated 24 patients with AE-UCIIP and compared their clinical features and prognosis with those of patients with AE-IPF. The incidence of AE-UCIIP was higher and patients with AE-UCIIP were older, included more women and never-smokers, and showed fewer lung lesions on HRCT than those with AE-IPF. Regarding prognostic factors, %FVC and GAP stage within 12 months before AE, and P/F ratio at AE were significant factors. Finally, commencement of long-duration PMX-DHP within 2 days after admission was a significant prognostic factor, not only in AE-UCIIP but also in the combined group of 64 patients with AE-UCIIP or AE-IPF. To our knowledge, this is the first report to provide detailed information about clinical features and prognosis in patients with AE-UCIIP in comparison to those with AE-IPF.

The prevalence of UCIIP has been reported to be as high as 11.9% (0–59.4%).[23] Therefore, a significant number of patients with IIPs are classified as having UCIIPs, and follow-up and treatment of these patients are important in clinical practice. There are three major reasons for UCIIP: (a) incomplete evaluation due to lack of data; (b) presence of overlapping findings that are common to multiple distinct interstitial lung diseases (ILD) subtypes; and (c) non-specific findings that are not characteristic of any single ILD subtype.[5] Among these reasons, incomplete evaluation due to a lack of data is the most frequent, and patients with a high risk of SLB, such as old age and low pulmonary function, accounted for 41–52% of the lack of data.[3,24] Even in the current study, patients with AE-UCIIP were significantly older than those with IPF, and only seven patients among 24 could undergo SLB before AE.

Regarding AE, the occurrence of AE is an apparent poor prognostic factor in IPF. However, the incidence and significance of AE on the prognosis of UCIIPs is poorly known. Nakamura *et al.* reported that AE cumulatively occurred in 30.3% of patients with UCIIP.[25] Similarly, in the current study, the cumulative incidence of AE-UCIIP was 38.1% and the frequency of AE was significantly higher (10.29%/year) in AE-UCIIP than in AE-IPF. Further, the survival of patients with AE-UCIIP was as poor as that of AE-IPF. Therefore, great attention should be paid to prevent AE and to start early treatments against

AE-UCIIP. As for the mechanism of AE-IP, infiltration of activated neutrophils into the lung parenchyma in the early phase of AE plays a pivotal role,[15] and early removal of these neutrophils seems to be important for saving patients with AE-IP, which does not have established treatments. Basically, PMX-DHP was developed to remove endotoxins from patients with sepsis, but it could also remove activated neutrophils in AE-IPF patients.[26] Furthermore, removal of several mediators by PMX-DHP, which can facilitate vascular permeability, may also have a role for the treatment of AE-IP. Treatment with PMX-DHP reportedly decreased the concentrations of serum matrix metalloproteinase-9,[26] vascular endothelial growth factor,[27] and angiopoietin-2.[20,28,29] Regarding the performing time of PMX-DHP, long-duration PMX-DHP significantly improved survival in patients with AE-IPF.[20,22,30,31] In addition, early treatment with long-duration PMX-DHP was effective for improving survival of AE-IPF patients compared with later commencement of PMX-DHP.[32,33] In the current study, commencement of long-duration PMX-DHP within 2 days after admission could also improve survival and was a significant prognostic factor both in patients with AE-UCIIP and all patients with AE-UCIIP or AE-IPF. Aggressive and early treatment with long-duration PMX-DHP may further improve the prognosis especially in patients with AE-UCIIP who had fewer lung lesions on HRCT than those with AE-IPF. As for infection, the current definition of AE-IPF admits 'triggered AE' including infection in addition to 'idiopathic AE'.[15] In this setting, even in the presence of concomitant infection, PMX-DHP may benefit treatment of AE-IP because of its original capacity to remove serum endotoxin by sepsis, although serum endotoxin was undetectable in all patients treated with PMX-DHP in this study.

This study has several limitations. First, only a small number of patients with AE-UCIIP were included. Second, the data were retrospectively collected. Patients with connective tissue disease-related IP were excluded in this study; therefore, those with UCIIP preceding connective tissue diseases may have been missed. Third, in patients with AE-UCIIP, the potential selection bias exists that diagnosis of IPF may have been missed because old UCIIP patients were less likely to be referred for SLB. However, many such old UCIIP patients, who cannot undergo SLB due to a high risk of biopsy, reportedly exist in real-world clinical

practice.[3,24] Fourth, prognostic factors in AE-UCIIP could not have been compared with those in AE-IPF using multivariate analysis due to a small number of patients. Finally, the treatment for AE-UCIIP was not uniform. Therefore, a larger prospective study is needed precisely to assess the clinical features and treatments for AE-UCIIP.

Conclusion

We retrospectively studied 24 patients with AE-UCIIP and 40 patients with AE-IPF. The frequency of AE was higher in AE-UCIIP than in AE-IPF. Patients with AE-UCIIP were older and included more women and never-smokers than those with AE-IPF. %FVC and GAP stage within 12 months before AE, and P/F ratio at AE were significant prognostic factors. Although the prognosis of AE-UCIIP was as poor as that of AE-IPF, commencement of long-duration PMX-DHP therapy within 2 days after admission improved survival not only in AE-UCIIP patients but also in AE-IPF patients. These findings should be useful for the management and treatment of patients with AE-UCIIP in clinical practice. Further evaluation is needed to improve the poor survival of patients with AE-UCIIP.

Author contribution(s)

Noriyuki Enomoto: Conceptualization; Data curation; Formal analysis; Writing-original draft; Writing-review & editing.

Hyogo Naoi: Data curation; Investigation; Resources; Writing-review & editing.

Yuya Aono: Data curation; Investigation; Resources; Writing-review & editing.

Mineo Katsumata: Data curation; Investigation; Resources; Writing-review & editing.

Yasuoki Horiike: Data curation; Investigation; Resources; Writing-review & editing.

Hideki Yasui: Data curation; Investigation; Resources; Writing-review & editing.

Masato Karayama: Data curation; Investigation; Resources; Writing-review & editing.

Hironao Hozumi: Data curation; Investigation; Resources; Writing-review & editing.

Yuzo Suzuki: Data curation; Investigation; Resources; Writing-review & editing.

Kazuki Furuhashi: Data curation; Investigation; Resources; Writing-review & editing.

Tomoyuki Fujisawa: Data curation; Investigation; Resources; Writing-review & editing.

Naoki Inui: Data curation; Investigation; Resources; Writing-review & editing.

Yutaro Nakamura: Data curation; Formal analysis; Resources; Supervision; Writing-review & editing.

Takafumi Suda: Formal analysis; Methodology; Project administration; Supervision; Writing-review & editing.

ORCID iDs

Noriyuki Enomoto https://orcid.org/0000-0003-3187-4264

Hideki Yasui https://orcid.org/0000-0002-7134-3364

Kazuki Furuhashi https://orcid.org/0000-0003-4079-5509

Supplemental material

The reviews of this paper are available via the supplemental material section.

References

1. Raghu G, Collard HR, Egan JJ, *et al.*; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824.

2. Travis WD, Costabel U, Hansell DM, *et al.*; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–748.

3. Ryerson CJ, Urbania TH, Richeldi L, *et al.* Prevalence and prognosis of unclassifiable interstitial lung disease. *Eur Respir J* 2013; 42: 750–757.

4. Patterson KC, Shah RJ, Porteous MK, *et al.* Interstitial lung disease in the elderly. *Chest* 2017; 151: 838–844.

5. Guler SA and Ryerson CJ. Unclassifiable interstitial lung disease: from phenotyping to possible treatments. *Curr Opin Pulm Med* 2018; 24: 461–468.

6. Kim DS, Park JH, Park BK, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006; 27: 143–150.

7. Song JW, Hong SB, Lim CM, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis: incidence, risk factors and outcome. *Eur Respir J* 2011; 37: 356–363.

8. Collard HR, Moore BB, Flaherty KR, *et al.*; Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; 176: 636–643.

9. Ley B, Collard HR and King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; 183: 431–440.

10. Natsuizaka M, Chiba H, Kuronuma K, *et al.* Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. *Am J Respir Crit Care Med* 2014; 190: 773–779.

11. Park IN, Kim DS, Shim TS, *et al.* Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. *Chest* 2007; 132: 214–220.

12. Suda T, Kaida Y, Nakamura Y, *et al.* Acute exacerbation of interstitial pneumonia associated with collagen vascular diseases. *Respir Med* 2009; 103: 846–853.

13. Enomoto N, Oyama Y, Enomoto Y, *et al.* Differences in clinical features of acute exacerbation between connective tissue disease-associated interstitial pneumonia and idiopathic pulmonary fibrosis. *Chron Respir Dis* 2019; 16: 1479972318809476.

14. Raghu G, Remy-Jardin M, Myers JL, *et al.*; American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.

15. Collard HR, Ryerson CJ, Corte TJ, *et al.* Acute exacerbation of idiopathic pulmonary fibrosis. An international working group report. *Am J Respir Crit Care Med* 2016; 194: 265–275.

16. Ley B, Ryerson CJ, Vittinghoff E, *et al.* A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med* 2012; 156: 684–691.

17. Homma S, Sugino K and Sakamoto S. Usefulness of a disease severity staging classification system for IPF in Japan: 20 years of experience from empirical evidence to randomized control trial enrollment. *Respir Investig* 2015; 53: 7–12.

18. Enomoto N, Suda T, Kono M, *et al.* Amount of elastic fibers predicts prognosis of idiopathic pulmonary fibrosis. *Respir Med* 2013; 107: 1608–1616.

19. Akira M, Kozuka T, Yamamoto S, *et al.* Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; 178: 372–378.

20. Enomoto N, Mikamo M, Oyama Y, *et al.* Treatment of acute exacerbation of idiopathic pulmonary fibrosis with direct hemoperfusion using a polymyxin B-immobilized fiber column improves survival. *BMC Pulm Med* 2015; 15: 15.

21. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; 48: 452–458.

22. Enomoto N, Suda T, Uto T, *et al.* Possible therapeutic effect of direct haemoperfusion with a polymyxin B immobilized fibre column (PMX-DHP) on pulmonary oxygenation in acute exacerbations of interstitial pneumonia. *Respirology* 2008; 13: 452–460.

23. Guler SA, Ellison K, Algamdi M, *et al.* Heterogeneity in unclassifiable interstitial lung disease. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2018; 15: 854–863.

24. Hyldgaard C, Bendstrup E, Wells AU, *et al.* Unclassifiable interstitial lung diseases: clinical

characteristics and survival. *Respirology* 2017; 22: 494–500.

25. Nakamura Y, Sugino K, Kitani M, *et al.* Clinico-radio-pathological characteristics of unclassifiable idiopathic interstitial pneumonias. *Respir Investig* 2018; 56: 40–47.

26. Abe S, Seo Y, Hayashi H, *et al.* Neutrophil adsorption by polymyxin B-immobilized fiber column for acute exacerbation in patients with interstitial pneumonia: a pilot study. *Blood Purif* 2010; 29: 321–326.

27. Oishi K, Mimura-Kimura Y, Miyasho T, *et al.* Association between cytokine removal by polymyxin B hemoperfusion and improved pulmonary oxygenation in patients with acute exacerbation of idiopathic pulmonary fibrosis. *Cytokine* 2013; 61: 84–89.

28. Ebihara I, Hirayama K, Nagai K, *et al.* Angiopoietin balance in septic shock patients treated by direct hemoperfusion with polymyxin B-immobilized fiber. *Ther Apher Dial* 2009; 13: 520–527.

29. Ebihara I, Hirayama K, Nagai M, *et al.* Angiopoietin balance in septic shock patients with acute lung injury: effect of direct hemoperfusion with polymyxin B-immobilized fiber. *Ther Apher Dial* 2011; 15: 349–354.

30. Abe S, Azuma A, Mukae H, *et al.* Polymyxin B-immobilized fiber column (PMX) treatment for idiopathic pulmonary fibrosis with acute exacerbation: a multicenter retrospective analysis. *Intern Med* 2012; 51: 1487–1491.

31. Kono M, Suda T, Enomoto N, *et al.* Evaluation of different perfusion durations in direct hemoperfusion with polymyxin B-immobilized fiber column therapy for acute exacerbation of interstitial pneumonias. *Blood Purif* 2011; 32: 75–81.

32. Oishi K, Aoe K, Mimura Y, *et al.* Survival from an acute exacerbation of idiopathic pulmonary fibrosis with or without direct hemoperfusion with a polymyxin B-immobilized fiber column: a retrospective analysis. *Intern Med* 2016; 55: 3551–3559.

33. Furusawa H, Sugiura M, Mitaka C, *et al.* Direct hemoperfusion with polymyxin B-immobilized fibre treatment for acute exacerbation of interstitial pneumonia. *Respirology* 2017; 22: 1357–1362.