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

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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% per 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 (PaO2/FiO2) ratio at AE (HR 0.998, p = 0.016) were significant prognostic factors. Finally, commencement of long-duration (≥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

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Introduction
Idiopathic interstitial pneumonias (IIPs) are life-threatening diseases that show a variety of inflammation and fibrosis 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
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,\(^1\,^6\,^7\,^8\) 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.\(^11\,^12\,^13\) 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 patients 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 IP, 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.

![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, \(p=0.681\)).](image)
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\textsuperscript{16} and the Japanese Respiratory Society (JRS) severity grades for IP.\textsuperscript{17} The former considers gender, age, and two lung physiology variables: forced vital capacity (FVC) and diffusion lung capacity for carbon monoxide (DL\textsubscript{CO}).\textsuperscript{16} The latter consists of partial pressure arterial oxygen (PaO\textsubscript{2}) at rest and minimum oxygen saturation (SpO\textsubscript{2}) during the 6-minute walking test (6MWT).\textsuperscript{17} The extent of lung opacity was measured on three high-resolution CT (HRCT) slices as described in our previous report.\textsuperscript{18} The pattern of AE-IP on HRCT was classified as (a) peripheral, (b) multifocal, or (c) diffuse, as reported by Akira et al.\textsuperscript{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.\textsuperscript{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).\textsuperscript{21} Categorical data were compared using the χ\textsuperscript{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 \textit{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 \textit{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 \textit{versus} 55.7%, \( p = 0.051 \)). %DL\textsubscript{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   |
| DLCO, % pred           | 54.2 (33.5, 88.2)               | 65.5 (44.7, 90.2)                 | 0.414   |
| PaO2 at rest, Torr     | 72 (49, 91)                     | 75 (53, 88)                       | 0.223   |
| Distance in 6MWT, m    | 370 (160, 507)                  | 442 (320, 578)                    | 0.192   |
| Minimum SpO2 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, ×10^3/μl | 9.9 [1.9, 27.8]               | 10.7 [5.1, 15.4]                  | 0.793   |
| Peripheral blood Neut, ×10^3/μl | 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)
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 (PaO2/FiO2) (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 ≥12 h) PMX-DHP 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.

**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, ×10⁹/μl | 2.3 (−7.2, 15.2)              | 3.2 (−5.4, 18.1)                | 0.824   |
| Δ Neut at 2 days after beginning AE treatment, ×10⁹/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, PaO2/FiO2; 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.

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 arrhythmia. 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 |
|----------|--------------|----------------|---------|
| 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**

| Variable | Hazard ratio | 95% CI         | p value |
|----------|--------------|----------------|---------|
| Extent score on HRCT | 1.103 | 0.937 - 1.298 | 0.237   |
| FVC, % pred | 0.928 | 0.846 - 0.992 | 0.025   |
| DLCO, % pred | 0.919 | 0.558 - 1.072 | 0.356   |
| Resting PaO₂, mmHg | 0.935 | 0.846 - 1.031 | 0.175   |
| Distance in 6MWT, m | 0.974 | 0.840 - 1.022 | 0.480   |
| Minimum SpO₂ 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**

| Variable | Hazard ratio | 95% CI         | p value |
|----------|--------------|----------------|---------|
| 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   |
| ALDH 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/FiO₂; 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.
was not significant, commencement of long-dura-
tion 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 pro-
portional 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 oxy-
gen therapy (HR 2.999, \(p = 0.002\)) were signifi-
cant 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 prog-
nostic factors. Regarding treatments and the
later course, intubation at AE (HR 2.564, \(p = 0.013\)) and \(\Delta P/F\) ratio and \(\Delta LDH\) 2 days after
beginning AE treatment (HR 0.994, \(p = 0.015\)
and HR 1.004, \(p = 0.008\), respectively) were sig-
ificant factors. Treatment with long-duration

![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, \(p = 0.002\)).]
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 and PaO2/FiO2 ratio in patients with AE-UCIIP or AE-IPF (\( n = 64 \)) are shown in Table 3. Extent score on HRCT within 12 months before AE (HR 1.176, \( p = 0.007 \)) and \( \Delta P/F \) ratio and \( \Delta LDH \) 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.

Table 3. Multivariate Cox proportional hazards models of survival adjusted for GAP stage and PaO2/FiO2 ratio in patients with AE-UCIIP or AE-IPF (\( n = 64 \)).

| Variable                                           | Hazard ratio | 95% CI       | \( p \) value |
|----------------------------------------------------|--------------|--------------|--------------|
| 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| 0.053        |
| Treatment with long-duration PMX-DHP, +             | 0.561        | 0.264 - 1.173| 0.124        |
| Commencement of treatment with long-duration PMX   | 0.328        | 0.133 - 0.739| 0.006        |
| within 2 days, +                                   |              |              |              |
| Intubation at AE, +                                 | 1.932        | 0.787 - 4.458| 0.145        |
| \( \Delta P/F \) ratio at 2 days after beginning AE| 0.994        | 0.987 - 0.999| 0.048        |
| \( \Delta LDH \) at 2 days after beginning AE      | 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, PaO2/FiO2; PMX-DHP, direct hemoperfusion with a polymyxin B-immobilised fibre column; WBC, white blood cells.
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%). 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. 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. 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. 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, 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. 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, vascular endothelial growth factor, and angiopoietin-2. Regarding the performing time of PMX-DHP, long-duration PMX-DHP significantly improved survival in patients with AE-IPF. 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. 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’. 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. 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.

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

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