INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Beneficial Effect of Polymyxin B-immobilized Fiber Column (PMX) Hemoperfusion Treatment on Acute Exacerbation of Idiopathic Pulmonary Fibrosis

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Abstract

Objective This study was aimed to investigate the effect of polymyxin B-immobilized fiber column (PMX) hemoperfusion treatment on the acute exacerbation of idiopathic pulmonary fibrosis (IPF).

Patients and Methods Six patients with a clinical diagnosis of idiopathic pulmonary fibrosis (IPF) who developed acute exacerbation were included in this study. Although five of six patients were treated with high-dose corticosteroid therapy, mechanical ventilation was necessary for all six patients due to severe respiratory failure. Blood endotoxin levels were undetectable in all patients. PMX treatment was performed on these six patients.

Results In four of six patients, alveolar-arterial difference of oxygen ($AaDO_2$), serum KL-6 and lactate dehydrogenase (LDH) were improved after PMX treatment. These four patients were successfully weaned from mechanical ventilation and survived more than 30 days after the initial PMX treatment.

Conclusion These data suggest a potential beneficial effect of PMX treatment on acute exacerbation of IPF.

Key words: acute exacerbation of idiopathic pulmonary fibrosis, polymyxin B-immobilized fiber column (PMX) treatment, alveolar-arterial difference of oxygen ($AaDO_2$), KL-6, lactate dehydrogenase (LDH)

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Introduction

Idiopathic interstitial pneumonias (IIPs) represent a heterogenous group of diffuse parenchymal lung disorders of unknown etiology. Idiopathic pulmonary fibrosis (IPF) is among the most common IIP and is characterized by clinically progressive dyspnea and worsening of pulmonary function (1, 2). Some IPF patients have acute exacerbations generally characterized by severe respiratory failure and pathological lesions of diffuse alveolar damage (DAD) (3-7). Mortality of these patients with acute exacerbation has been reported to be high during their hospitalization (4-6).

Polymyxin B-immobilized fiber (PMX) treatment has been reported to be effective in both gram-negative and gram-positive sepsis (8). Recent reports have suggested that PMX treatment may improve oxygenation in patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) (9-11). In this study, we investigated whether direct hemoperfusion with PMX could be effective in acute exacerbation of clinical IPF patients. Analyses of alveolar-arterial difference of oxygen ($AaDO_2$), serum KL-6, serum lactate dehydrogenase (LDH) and survival for more than 30 days after PMX treatment were performed to evaluate its effectiveness in acute exacerbation of IPF.

Patients and Methods

Six patients with acute exacerbation of IPF were enrolled in an open-label pilot trial of hemoperfusion treatment with

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the PMX column. IPF was defined clinically according to the criteria of the American Thoracic Society/European Respiratory Society (ATS/ERS) international consensus statement (1, 2): 1) exclusion of other known causes of diffuse lung diseases, such as environmental exposure, drug toxicities and collagen vascular diseases (CVD). The presence of CVD was excluded by means of detailed history, clinical examination and the following serum test: anti-neutrophil cytoplasmic antibody (MPO-, and PR3-ANCA), anti-nuclear and anti-DNA antibodies, rheumatoid factor and angiotensin-converting enzyme; 2) abnormal pulmonary function studies, including evidence of restriction, impaired gas exchange, decreased diffusing capacity of the lung for CO (DL_{CO}); 3) High resolution computed tomography (HRCT) scan showing reticular opacities, honeycombing and traction bronchiectasis with basal and peripheral predominance in the absence of atypical features for IPF, such as peribronchovascular nodules, micronodules, isolated cysts and consolidation; 4) age >50 years; 5) insidious onset of otherwise unexplained dyspnea on exertion; 6) duration illness of >3 months; 7) persistent bibasilar, inspiratory crackles; 8) transbronchial biopsy specimens in all cases showing no features incompatible with a diagnosis of IPF. Based on these clinical criteria, the diagnosis of IPF has been reported to be correct in more than 90% (12).

Acute exacerbation of IPF was defined as follows (3, 4): exacerbation of dyspnea within one month, newly developing diffuse pulmonary opacities on chest radiographs, decrease in arterial oxygen tension (PaO_2) of more than 10 mmHg under similar conditions, and absence of heart failure or an identified infectious agent. All of the above criteria were satisfied in all cases. To rule out congestive heart failure, ultrasound cardiography was performed. None of the patients had evidence of left ventricular dysfunction. Cultures of sputum, blood and urine to detect bacteria, fungus and mycobacterium were negative in all patients. Serological test for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, Legionella, and various viruses (cytomegalovirus, herpes simplex, adenovirus, influenza virus, parainfluenza virus, and respiratory syncytial virus) were negative. Blood endotoxin levels were determined by the Endospecy test using the new perchloric acid method described previously (8, 9). The upper normal limit was 1.0 pg/ml. High resolution computed tomography (HRCT) of the thorax was carried out on all six patients just before PMX treatment. The difference between alveolar and arterial oxygen tension ($AaDO_2$) was calculated with the use of a simplified form of the alveolar gas equation: partial pressure of alveolar oxygen=partial pressure of inspired oxygen (partial pressure of arterial carbon dioxide÷R), where R, the respiratory quotient, was assumed to be 0.8. The arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) (P/F) ratio was also calculated. Serum KL-6 and LDH were assessed by enzyme-linked immunoadsorbent assay (ELISA) to evaluate PMX treatment. For venous access, a double-lumen catheter (Arrow International Inc., Reading, PA) was inserted into the femoral vein using Seldinger's method as described previously (8-10). Direct hemoperfusion with PMX (Toraymyxin 20R, Toray Medical Co., Tokyo, Japan) was carried out at a flow rate of 80-100 ml/min 1-5 times for 2-6 hours. There have been varied reports on the length of the treatment and how many times PMX treatment should be performed (8, 9, 13). In this study, patients were started on PMX therapy at different time points. Therefore the period of PMX treatment varied, depending on the patient's condition. Nafamostat mesilate (Torii Pharma Co., Tokyo, Japan) was used as an anticoagulant during the PMX treatment. It has been reported that the half-life of nafamostat is 8 minutes and anticoagulant effects are observed only in the extra-corporeal circuit (8, 9). PMX treatment was initiated when respiratory failure progressed even though the patients were treated with high-dose corticosteroid therapy (1 g of methylprednisolone given IV for three days). To evaluate the effect of PMX treatment, conventional therapies were not changed pre- and post-PMX treatment. A PaO_2 of greater than 60 mmHg with $\leq$35% oxygen was considered to be an indication for weaning from mechanical ventilation. PMX treatment was stopped only if the patient died, or was successfully weaned from ventilation. Previous reports have used 30-day mortality after an episode of ARDS (9, 14). We evaluated the 30-day survival rate after the initiation of PMX treatment. The survivors were followed by primary physicians for at least 90 days after PMX treatment. Written informed consent was obtained from each patient or guardian. The study was approved by the Ethics Committee of Nippon Medical School.

Results

The clinical characteristics before PMX treatment and patient outcomes are listed in Table 1. There were four males and two females, aged 57-79 (average 67) years. Four patients (cases 1, 4, 5 and 6) were ex-smokers. The duration of symptoms before acute exacerbation averaged 29 months (range, 3-72 months). Four patients (cases 1, 3, 4 and 5) were receiving corticosteroid (prednisolone; PSL) therapy (40 mg/day, 10 mg, 10 mg and 30 mg, respectively). Case 3 underwent immunosuppressive therapy with cyclophosphamide (CPA). Two patients (cases 2 and 4) were receiving inhalation of *N*-acethylcystein (NAC). Serum KL-6, a marker of lung injury and fibrosis (15) was elevated to 1030-3700 IU/ml (normal range <500 IU/ml) before PMX therapy. Serum LDH was elevated to 439-746 (normal range <250 IU/ml). $AaDO_2$ was elevated to 392-550 mmHg and P/F (PaO_2/FiO_2) ratio was decreased to 50-246 (normal range >300) (mmHg). We assessed the sputum, urine, and blood cultures and serum beta-D-glucan in order to exclude bacterial and fungal infection. Although case 3 was positive for serum beta-D-glucan (24.0) before PMX treatment, no organisms were detected in any patient. Blood endotoxin levels and D-dimer were within normal limits in all six patients. HRCT of the thorax before PMX treatment showed diffuse parenchymal opacifications consistent with acute ex-

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Table 1. Characteristics and Outcome of the Patients

case	sex/age	duration (months)	P/F	$AaDO_2$ (mmHg)	LDH (U/ml)	KL-6 (U/ml)	ES/β-DG (pg/ml)	previous therapy	outcome*
1	M/61	3	93	443	498	3700	<0.8/<5.0	PSL 40mg	alive
2	F/73	72	180	392	439	1690	<0.8/<5.0	NAC	alive
3	F/67	36	109	515	652	1030	<0.8/ 24.0	PSL 10mg+CPA 50mg	died at day 18
4	M/64	48	50	550	518	2420	<0.8/<5.0	PSL 10mg+NAC	died at day 7
5	M/57	14	180	359	413	2610	<0.8/<5.0	PSL 30mg	alive
6	M/79	3	246	397	746	1488	<0.8/<5.0	none	alive

β-DG=β-D-glucan, CPA=cyclophosphamide, ES=endotoxin, NAC=inhalation of N-acethylcystein, PSL=prednisolone

*survival more than thirty days after the initial PMX treatment

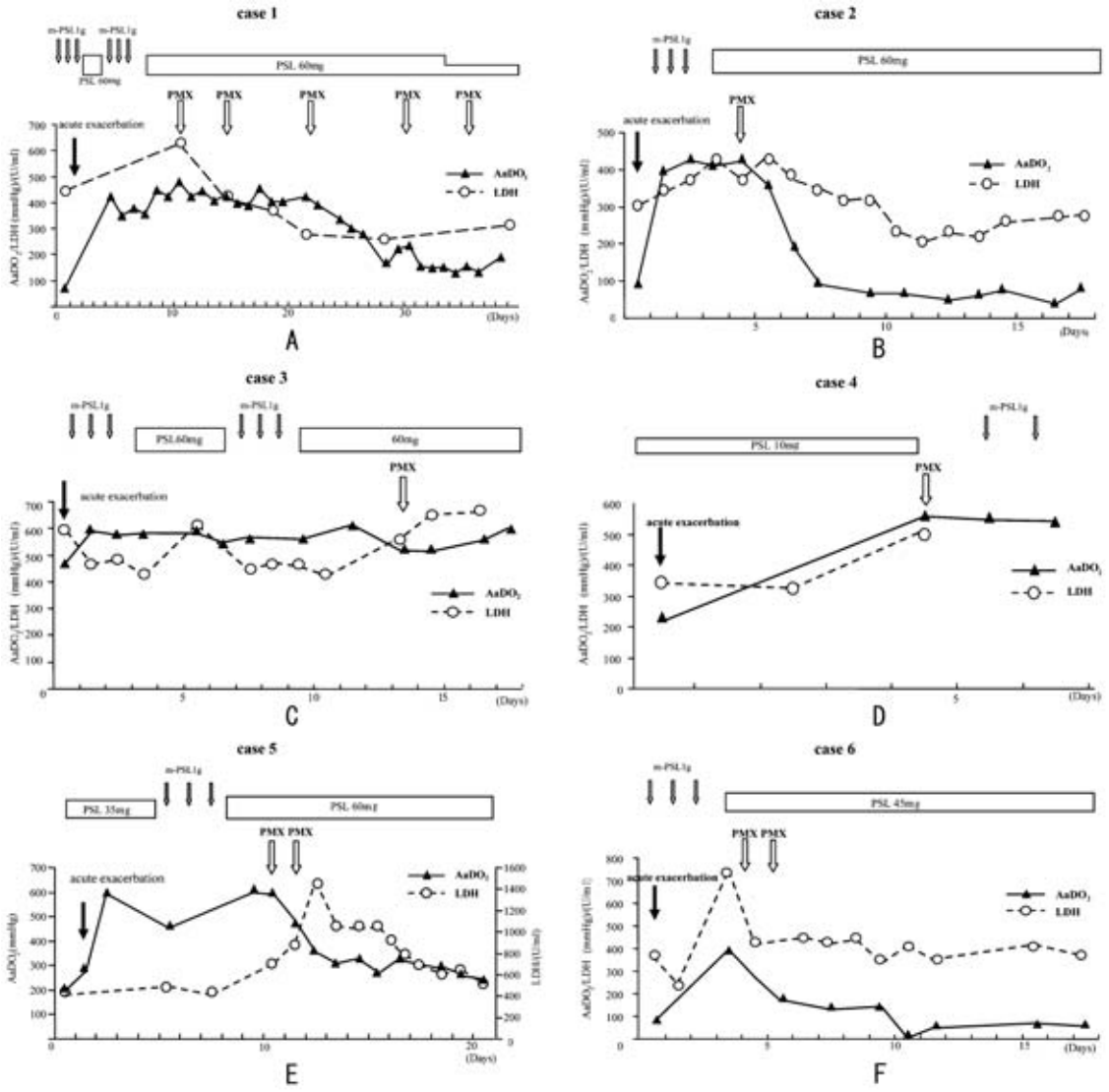

Figure 1. Serial $AaDO_2$ and serum LDH values pre- and post-PMX treatment (cases 1-6). PMX treatment resulted in improved $AaDO_2$ and serum LDH in four (cases 1, 2, 5 and 6) of six patients with acute exacerbation of clinical IPF.

acerbation of IPF (4) in all six patients.

Oxygenation including $AaDO_2$ and P/F ratio was improved during PMX treatment in four of six patients. Those four patients (cases A~F) were successfully weaned from mechanical ventilation and survived more than 30 days after initial PMX treatment. $AaDO_2$, serum KL-6 and LDH were improved in the survivors post PMX treatment.

In case 1, we performed PMX treatment five times for 2

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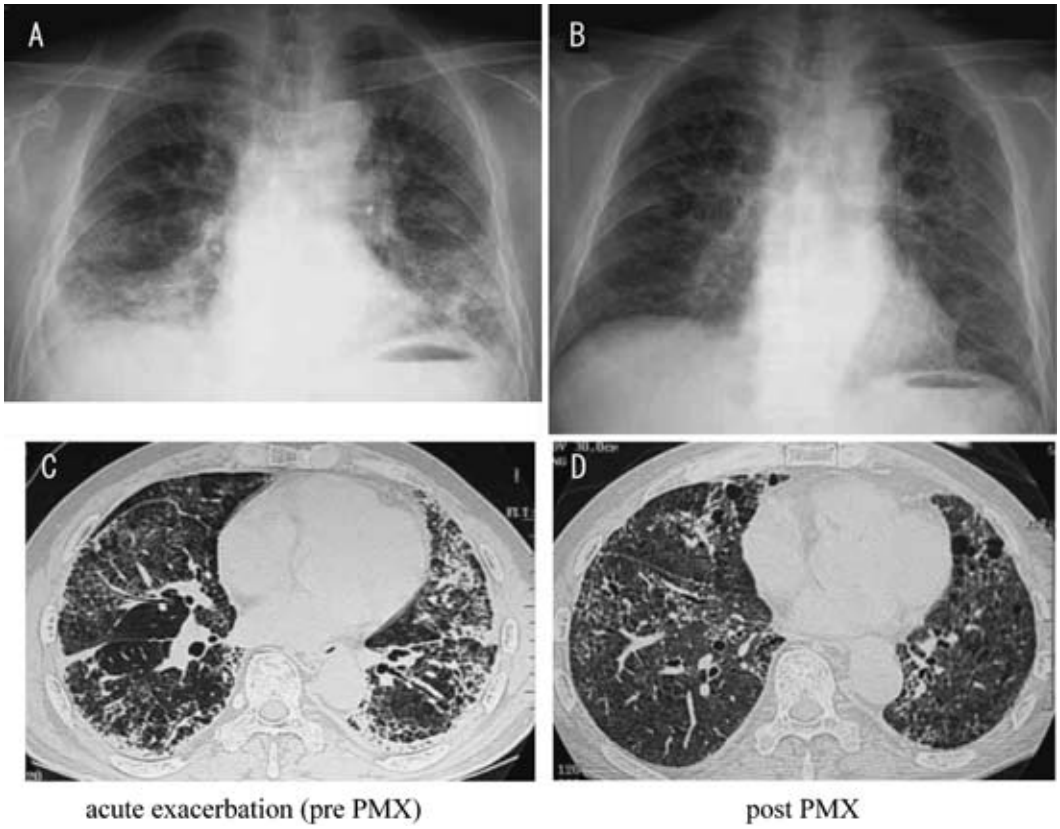

Figure 2. **Chest X-ray and HRCT of case 1. (A) Chest X-ray shows bilateral infiltration in the lower lung at the time of acute exacerbation of clinical IPF. (B) Chest X-ray shows improved bilateral infiltration, and an increase in lung volume after treatment with PMX treatment five times. (C) Reticular and linear patterns with traction bronchoectasis and ground glass attenuation were observed in the acute exacerbation of IPF (before PMX treatment). (D) Ground glass attenuation was resolved after PMX treatment.**

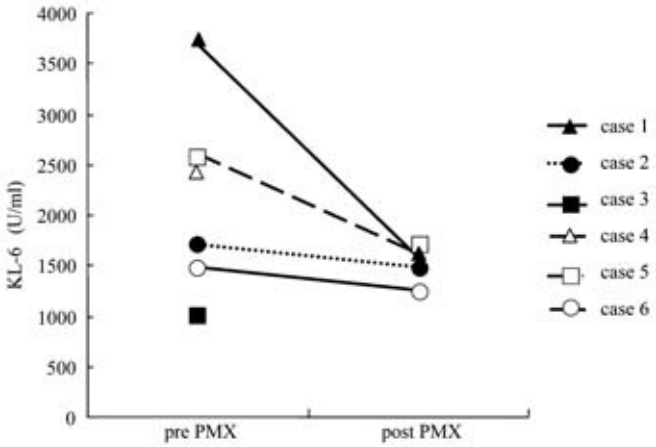

Figure 3. **Serum KL-6 levels pre- and post-PMX-treatment in clinical IPF patients with acute exacerbation. Serum KL-6 levels post PMX were not evaluated in cases 3 and 4.**

hours each. Acute hypoxemic respiratory failure assessed by $AaDO_2$, P/F ratio, serum LDH and KL-6 gradually improved after each PMX treatment (Fig. 1A). Diffuse ground glass attenuation of HRCT resolved after five times treatment with PMX in case 1 (Fig. 2). This patient has survived more than 20 months with oxygen (O_2) therapy. In case 2, we performed PMX treatment once for six hours. As shown in Fig. 1B, $AaDO_2$ and LDH were dramatically improved after PMX treatment. The patient was weaned from mechanical ventilation 8 days after acute exacerbation and survived more than 30 days after PMX treatment. However, this patient died of acute myocardial infarction after 3 months of PMX treatment without evidence of respiratory failure. In cases 3 and 4, we administered PMX treatment once for two hours. In case 3 (Fig. 1C), although PaO_2 and $AaDO_2$ were temporarily improved during PMX treatment, the patient finally died of disseminated intravascular coagulation (DIC) eighteen days after acute exacerbation. In case 4 (Fig. 1D), high-dose corticosteroid therapy was administered after PMX treatment because of a severe esophageal ulcer. $AaDO_2$ was slightly decreased after PMX treatment. However, the patient died of respiratory failure due to progression of IPF seven days after acute exacerbation. Autopsy lung specimens in case 4 showed typical honeycomb change of usual interstitial pneumonia (UIP) with DAD. Treatment with PMX was discontinued because patients died (cases 3 and 4). In cases 5 (Fig. 1E) and 6 (Fig. 1F), we administered PMX treatment twice for 2 hours as originally described (8, 9). $AaDO_2$ and LDH were improved and these patients were weaned from mechanical ventilation and survived more than

30 days post PMX treatment. In the four of six patients who survived, serum KL-6 levels decreased in response to PMX treatment (Fig. 3).

Discussion

In this pilot study, we demonstrated the potential beneficial effect of PMX treatment for acute exacerbations of clinical IPF patients.

The prognosis of IPF is known to be poor. The mean length of survival varies from 3 to 5 years, and the major cause of death is respiratory failure due to IPF progression (1, 2). Respiratory failure may ensue, in which case IPF patients are generally difficult to ventilate and are rarely successfully weaned from mechanical ventilation. In one study of seven mechanically ventilated patients with IPF, six of seven patients died after 3.2±4 days of ventilation (16). Fumeaux et al reported fourteen patients with idiopathic or secondary pulmonary fibrosis died in the ICU after a mean stay of 7.6±4.6 days, despite mechanical ventilation (17). Acute exacerbations of IPF have been described high mortality in several reports (4, 5, 7, 18). Ambrosini et al reported that four of five patients with IPF died a median of 13 days after onset of acute exacerbation (5). Parambil et al recently reported that six of seven patients with acute exacerbation of IPF undergoing surgical lung biopsy died during their hospitalization (7). In the current study, four of six patients with acute exacerbation who required mechanical ventilation survived more than 30 days after the initial PMX treatment, suggesting a clinical benefit of PMX treatment.

Several papers have reported the effect of PMX treatment on oxygenation (8-11). Similar results were observed in this study. In four of six patients, $AaDO_2$ and P/F ratio improved after PMX treatment even though the endotoxin levels were all below the normal range. Aoki et al have suggested that reduction of endotoxin concentration might reduce pulmonary vasoconstriction and intrapulmonary shunting (8). Nakamura et al have reported that the blood metalloproteinase (MMP)-9 level and tissue inhibitor of MMP (TIMP)-1 level were significantly reduced after PMX treatment and were well correlated with improvement of P/F ratio (10). In an animal model of sepsis, PMX has been reported to improve oxygenation through suppression of nitric oxide production (19). The precise mechanisms by which PMX treatment improves oxygenation still remain unsolved. In this pilot study, there was no limitation of patient management without PMX treatment and minor differences in infusion therapy may have affected the oxygenation of patients. However, conventional therapies were not changed at any stage during each PMX treatment, thus allowing the effect of PMX treatment to be evaluated.

Acute exacerbation of IPF is characterized pathologically by DAD, which clinically resembles ALI/ARDS. Complicating factors including inflammatory mediators probably contribute to DAD (20, 21). We measured the serum levels of inflammatory cytokines (IL-6, IL-10), the chemokine IL-8 and plasma plasminogen activator inhibitor 1 (PAI-1) in cases 1, 2 and 4. Serum IL-6, IL-8 and plasma PAI-1 decreased in cases 1 and 2, which responded to PMX treatment (data not shown). Serum levels of the anti-inflammatory cytokine IL-10 increased after PMX treatment in these two patients. It is still unknown whether PMX has an effect on cytokine/chemokine or PAI-1 production. Kushi et al recently reported that improvement of P/F ratio by PMX treatment was related to the decrease in blood neutrophil elastase and IL-8 (11). Inflammatory cells including activated monocytes producing such mediators may be absorbed by PMX treatment (22, 23). Serum LDH has been demonstrated to be a useful indicator of lung damage or inflammation (24). Serum KL-6 has also been reported to be a useful marker of the rapid progression of IPF (15). In this study, these two markers tended to be correlated with $AaDO_2$. The effect of PMX on these markers also remains unclear.

There is some controversy regarding the choice of appropriate cycles and frequencies of PMX treatment. Aoki et al have reported once to seven times for the treatment of sepsis (8). Additionally, PMX treatment once or twice for 4 hours has reportedly improved the survival of sepsis patients (13). A recent paper has suggested that frequent treatment might be effective in severe sepsis patients (25). We performed PMX treatment 1-5 times for 2 or 6 hours, depending on the patient's condition. Further investigation will be needed to determine and confirm the cycles and frequencies of PMX treatment.

The present results suggest that PMX therapy could be of benefit in patients with acute exacerbation of IPF. This study is a pilot study, mainly designed to rescue the patients and to assess the effectiveness of PMX treatment. However, the small number of patients and the absence of control groups are considerable limitations of the study. A randomized controlled study will be needed.

Abbreviations:

$AaDO_2$=alveolar-arterial difference of oxygen
ALI=acute lung injury
ARDS=acute respiratory distress syndrome
DIC=disseminated intravascular coagulation
HRCT= high resolution computed tomography
LDH=lactate dehydrogenase
PAI-1= plasminogen activator inhibitor 1
P/F=arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2)
PMX=polymyxin B-immobilized fiber
UIP= usual interstitial pneumonia

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