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RESEARCH ARTICLE

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Direct hemoperfusion using a polymyxin B-immobilized polystyrene column for COVID-19

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Abstract

Objective: To evaluate the efficacy and safety of direct hemoperfusion using a polymyxin B-immobilized polystyrene column (PMX-DHP) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-positive pneumonia patients.

Methods: This study was a case series conducted at a designated infectious diseases hospital. Twelve SARS-CoV-2-positive patients with partial pressure of arterial oxygen/percentage of inspired oxygen (P/F) ratio < 300 were treated with PMX-DHP on two consecutive days each during hospitalization. We defined day 1 as the first day when PMX-DHP was performed. PMX-DHP efficacy was assessed on days 7 and 14 after the first treatment based on eight categories. Subsequently, improvement in P/F ratio and urinary biomarkers on

days 4 and 8, malfunctions, and ventilator and extracorporeal membrane oxygenation avoidance rates were also evaluated.

Results: On day 14 after the first treatment, disease severity decreased in 58.3% of the patients. P/F ratio increased while urine β2-microglobulin decreased on days 4 and 8. Cytokine measurement pre- and post-PMX-DHP revealed decreased levels of interleukin-6 and the factors involved in vascular endothelial injury, including vascular endothelial growth factor. Twenty-two PMX-DHPs were performed, of which seven and five PMX-DHPs led to increased inlet pressure and membrane coagulation, respectively. When the membranes coagulated, the circuitry needed to be reconfigured. Circuit problems were usually observed when D-dimer and fibrin degradation product levels were high before PMX-DHP.

Conclusions: Future studies are expected to determine the therapeutic effect of PMX-DHP on COVID-19. Because of the relatively high risk of circuit coagulation, coagulation capacity should be assessed beforehand.

KEYWORDS

cytokine, pneumonia, steroids

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global threat, causing serious illness and death not only among the elderly but also among young people with no history of the disease. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus, binds to the angiotensin-converting enzyme 2 receptor, and it is gradually becoming clear that it causes abnormalities not only in the respiratory system but also in the other systems, including the circulatory, digestive, nervous, hematological, and immune systems.[1]

Although several promising drugs are being tested in clinical trials for COVID-19, a definitive treatment has not yet been established.[2] The involvement of increased cytokine levels has been noted, and anti-inflammatory therapy including corticosteroids or anti-human interleukin (IL)-6 receptor monoclonal antibodies, such as tocilizumab, is expected to be effective in such patients.[3-5] Direct hemoperfusion using a polymyxin B-immobilized polystyrene column (PMX-DHP) is a treatment that selectively adsorbs endotoxins; it is also expected to adsorb a variety of endogenous substances.[6] In our institution, a total of 12 patients with COVID-19 requiring O_2 supplementation have been treated using PMX columns. In this retrospective observational study, we report our experience with circuit coagulation while treating patients with COVID-19 by performing PMX-DHP.

2 | PATIENTS AND METHODS

2.1 | Patient population

The patients included were those whose respiratory samples tested positive for SARS-CoV-2 upon real-time reverse transcription-polymerase chain reaction (RT-PCR)[7] and underwent PMX-DHP during hospitalization at the National Center for Global Health and Medicine between January 30 and April 25, 2020. PMX-DHP was considered when an image of pneumonia consistent with COVID-19 was obtained on a computed tomography (CT) scan of the chest and the partial pressure of arterial O_2/percentage of inspired O_2 (P/F) ratio was less than 300 or O_2 saturation (SpO_2) was 93% or less (room air). Patients aged ≤16 years at the time of obtaining consent were excluded. Demographic data, information on clinical symptoms, and laboratory data were collected. This study was conducted ethically in accordance with the Declaration of Helsinki. The study protocol was approved by the institutional review board (approval no: NCGM-G-003472-02) and written informed consent for publication was obtained from each patient.

2.2 | Clinical procedure

A temporary blood access catheter was inserted, and extracorporeal circulation was established. PMX-DHP

was performed using Toraymyxin PMX-20R (Toray Industries, Tokyo, Japan) at a blood flow rate of 100 ml/min for 3 hours on two consecutive days for each patient. Nafamostat mesylate (30 mg/h) or 50 U/kg/h of low-molecular-weight heparin (LMWH) was used for anti-coagulation therapy. In the event of circuit coagulation, a new circuit was primed and re-established after returning blood.

2.3 | Measurement

The efficacy of PMX-DHP was assessed based on the proportion of improvement (decrease) of 1 point or more on days 8 and 15 of the first PMX-DHP regimen in the following eight categorical assessments[8]: (a) no hospitalization and resumption of normal activities; (b) no hospitalization but no resumption of normal activities; (c) hospitalization without a requirement for O_2 supplementation; (d) hospitalization requiring O_2 supplementation; (e) hospitalization requiring nasal high-flow O_2 therapy, noninvasive mechanical ventilation, or both; (f) requirement for invasive mechanical ventilation; (g) requirement for a ventilator and extracorporeal membrane oxygenation (ECMO); and (h) death. We defined disease severity as follows: categories 1-3 as mild, 4-5 as moderate, and 6-8 as severe. The secondary objectives were as follows: improvement in the P/F ratio, improvement in urinary biomarker levels on days 4 and 8; changes in cytokine levels before and after PMX treatment; occurrence of serious adverse events or malfunctions; ventilator avoidance rate; and proportion of ECMO avoidance. Urinary β2-microglobulin (β2MG) and liver-type fatty acid-binding protein (L-FABP) levels were determined using latex-enhanced turbidimetric immunoassays (Denka Seiken and Sekisui Medical, Tokyo, Japan).[9,10] IL-6; IL-1β; IL-8; IL-10; IL-17; platelet-derived growth factor-BB (PDGF-BB); regulated on activation, normal T cell expressed and secreted (RANTES); and vascular endothelial growth factor (VEGF) levels in the serum samples from patients with COVID-19 were analyzed using a Bio-Plex suspension assay kit and array system (BioRad Laboratories, California) according to the manufacturer's instructions. The Bio-Plex analysis of the serum samples was conducted at the National Center for Global Health and Medicine.

2.4 | Statistical analysis

Data are expressed as median (maximum and minimum) values. Patients' baseline characteristics and clinical findings on admission are presented. All analyses were conducted using R software (version 3.5.1., R Core Team, 2018).

TABLE 1 Patients' demographics

Patient number		N = 12
Age		66.5 (36-83)
Sex		Male 9 (75.0%), female 3 (25.0%)
Onset to admission (days)		6.5 (3-16)
BMI		25.4 (19.2-31.9)
Smoking		5 (41.7%)
HTN		5 (41.7%)
DM		3 (25.0%)
SOFA on admission		2 (0-10)
AKI	Stage 1	2 (16.6%)
	Stage 2	1 (8.3%)
	Stage 3	1 (8.3%)
O_2 supplementation (not ventilated), when PMX treatment was initiated		5 (41.7%)
Artificial respiration (not V-V ECMO), when PMX treatment was initiated		5 (41.7%)
V-V ECMO, when PMX treatment was already being used		2 (16.6%)
Disease status (points)	Day 1	5.50 (4-7)
	Day 8	5.33 (3-8)
	Day 15	5.27 (3-8)
Disease status, day 8	Improvement	4 (33.3%)
	Sustained	4 (33.3%)
	Worsening	4 (33.3%)
Disease status, day 15	Improvement	7 (58.3%)
	Sustained	1 (8.3%)
	Worsening	4 (33.3%)
P/F ratio	Day 1	153.9 (69.0-327.1)
	Day 4	214.1 (122.3-438.1)
	Day 8	271.3 (172.8-464.8)
Urinary β2MG (μg/l)	Day 1	16 630 (62-70 725)
	Day 4	3390 (79-11 173)
	Day 8	1698 (30-9435)
Urinary L-FABP (μg/gCre)	Day 1	67.3 (0.1-167.0)
	Day 4	61.7 (12.3-151.6)
	Day 8	87.5 (1.1-803.4)
Ventilator avoidance rate		4/5 (80.0%)
ECMO avoidance rate		3/5 (60.0%)
Mortality		3 (25.0%)

Note: The ventilator avoidance rate is the percentage of patients with an oxygen demand (N = 5) who were able to avoid intubation (N = 4). The ECMO avoidance rate is the percentage of patients who avoided ECMO (N = 3) among those who were already on ventilator management (N = 5).
Abbreviations: AKI, acute kidney injury; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; P/F, PaO_2/FiO_2; VV-ECMO, veno-venous extracorporeal membrane oxygenation.

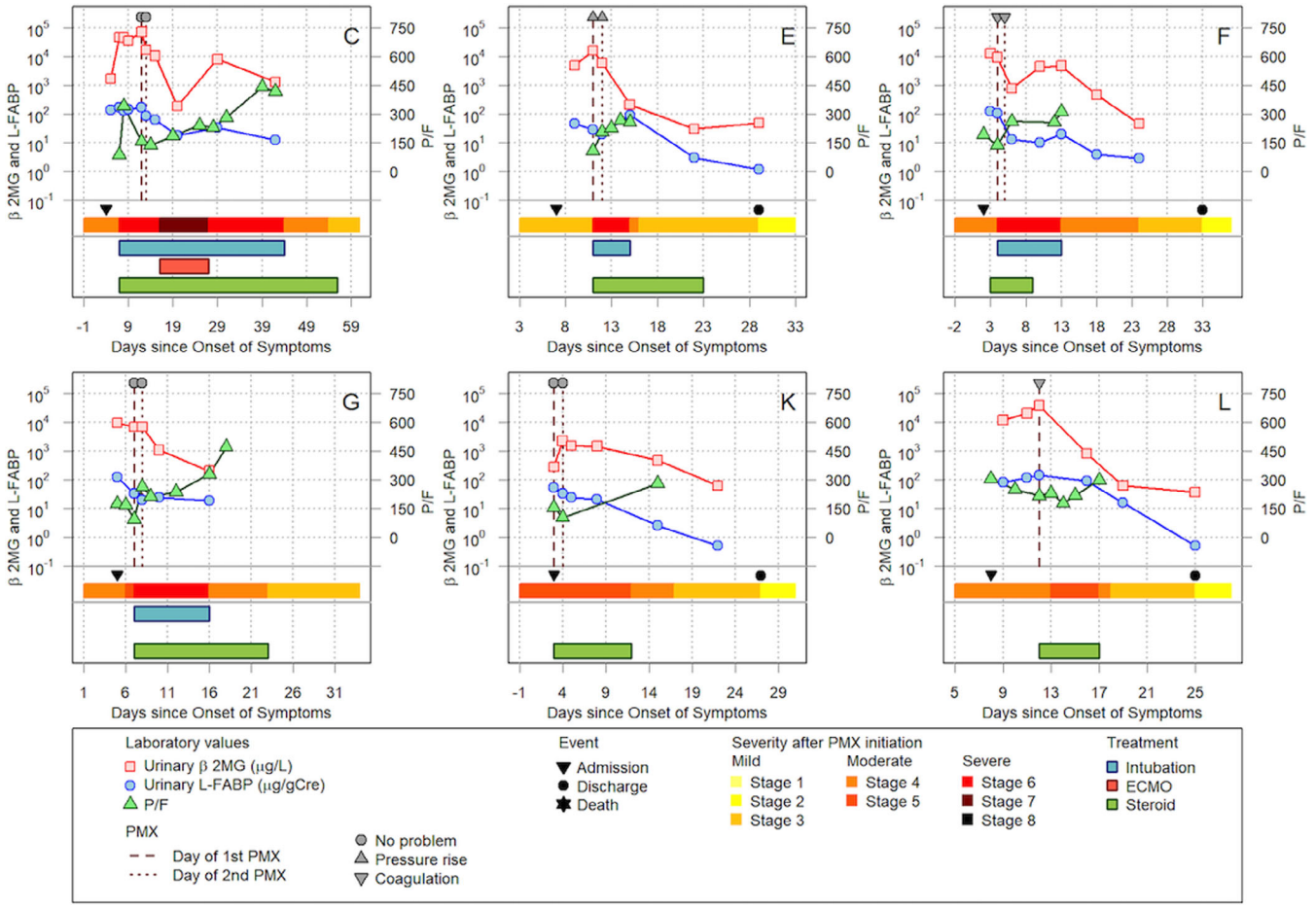

FIGURE 1 Clinical course of the six representative cases. The dates of the first and second PMX regimen and the presence or absence of increased inlet pressure or circuit coagulation events are noted. At the start of the PMX treatment, five patients were on oxygen supplementation (moderate), five were already intubated (severe), and two were very sick and on ECMO (critical). N = 6. PMX, polymyxin B; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy; P/F, PaO_2/FiO_2; β2MG, β2-microglobulin; L-FABP, liver-type fatty acid-binding protein

3 | RESULTS

3.1 | Patients' demographics

Patients' baseline characteristics are shown in Table 1 (N = 12, nine male and three female patients). The mean age, body mass index, and days from onset to admission were 66.5 (36-83) years, 25.4 (19.2-31.9), and 6.5 (3-16) days, respectively. As a coexisting condition, 5 of the 12 patients (41.7%) had hypertension. All (100%) patients had obvious COVID-19 pneumonia on CT and required O_2 supplementation. As shown in Figure 1 and Figure S1, at the start of the PMX treatment, two patients were very sick and had already received ECMO (A and B), five were already intubated (C-G), and five required O_2 supplementation (H-L).

3.2 | Effect of PMX-DHP on the severity of COVID-19

The clinical courses of six representative patients are shown in Figure 1. The remaining six patients are shown in Figure S1. The mean disease statuses on days 1, 8, and 15 were 5.50, 5.33, and 5.27, respectively, with gradual improvement; 33.3% and 58.7% of the patients improved on days 7 and 14, respectively (Table 1). Of the five patients receiving O_2 supplementation (H-L), intubation was avoided in four (I-L, 80%), and ECMO was avoided in three (E-G, 60%) of the five patients (C-G) who were already on ventilation management. Two patients (A, B) were already on ECMO and both unfortunately died. Patient A temporarily received continuous renal replacement therapy (CRRT) with polymethyl methacrylate membranes[11] from day 16 to day 27; as PMX-DHP was

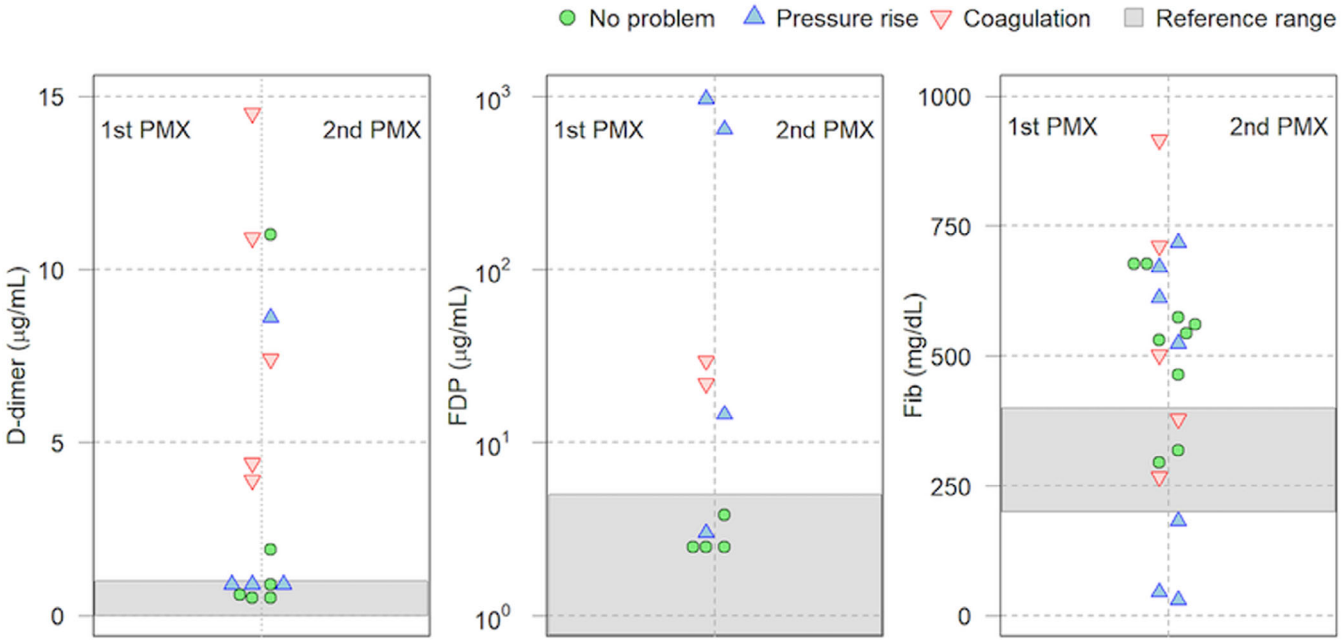

FIGURE 2 Association of coagulation factors with episodes of increased inlet pressure and circuit coagulation during PMX treatment. D-dimer, FDP, and fibrinogen are shown on the vertical axis. The left side shows the first PMX regimen and the right side shows the second PMX regimen. The normal values for each parameter are shown in the gray area: D-dimer, 0-1.0 μg/ml; FDP, 0-4.9 μg/ml; fibrinogen, 200-400 mg/dl. PMX, polymyxin B; FDP, fibrin degradation product; Fib, fibrinogen

performed on day 35, CRRT was completed prior to this treatment.

3.3 | Improved test values and circuit coagulation

Overall, there was an increase in the P/F ratio and a downward trend in urine β2MG levels on days 4 and 8 (Table 1, Figure 1, Figure S1). Urinary L-FABP levels tended to decline after PMX-DHP in 10 patients. There were 22 instances of PMX-DHP, of which seven resulted in increased inlet pressure and five resulted in membrane coagulation, necessitating reconfiguration of the circuit. Interestingly, in all cases of coagulation, after the second reassembly of the PMX circuit, PMX-DHP could be completed without any problems. Such circuit troubles tended to be observed if D-dimer and fibrin degradation product (FDP) levels were high before PMX-DHP (Figure 2). Furthermore, patients who did not experience any problems during the first session of PMX-DHP did not have any circuit problems during the second session of the treatment. Eight of the 12 patients (66.6%) did not receive systemic LMWH; four of the 12 patients (33.3%) received systemic LMWH in the treatment dose. Of the four patients receiving LMWH, two patients experienced circuit coagulation. They both had high D-dimer levels (3.9 and 10.9 μg/ml). The D-dimer levels of the other two patients who did not experience any problems during the procedure were in the normal range (0.6 and 0.5 μg/ml).

3.4 | Effect on cytokines

Serum IL-6, IL-1β, IL-8, IL-10, IL-17, PDGF-BB, RANTES, and VEGF levels were evaluated in six patients (A, B, E, F, I, and J) before and after PMX-DHP. Samples were collected within 6 hours before the first PMX-DHP and within 6 hours after the second PMX-DHP. As shown in Figure 3, IL-6 levels showed an overall downward trend. Except for one patient who died, IL-8, IL-10, and IL-17 levels remained almost unchanged or trended downward. The levels of PDGF-BB, RANTES, and VEGF markers of arteriosclerosis and vascular endothelial injury also showed an overall downward trend after PMX-DHP.

4 | DISCUSSION

Biopsy specimens obtained during the autopsy of a patient who died from severe COVID-19 showed bilateral diffuse alveolar damage (DAD) with cytosolic fibromyxoid exudation on histological examination.[12] PMX itself is used in the treatment of endotoxemia and septic shock caused by gram-negative rods. However, it is also expected to adsorb endogenous substances and cytokines, including tumor

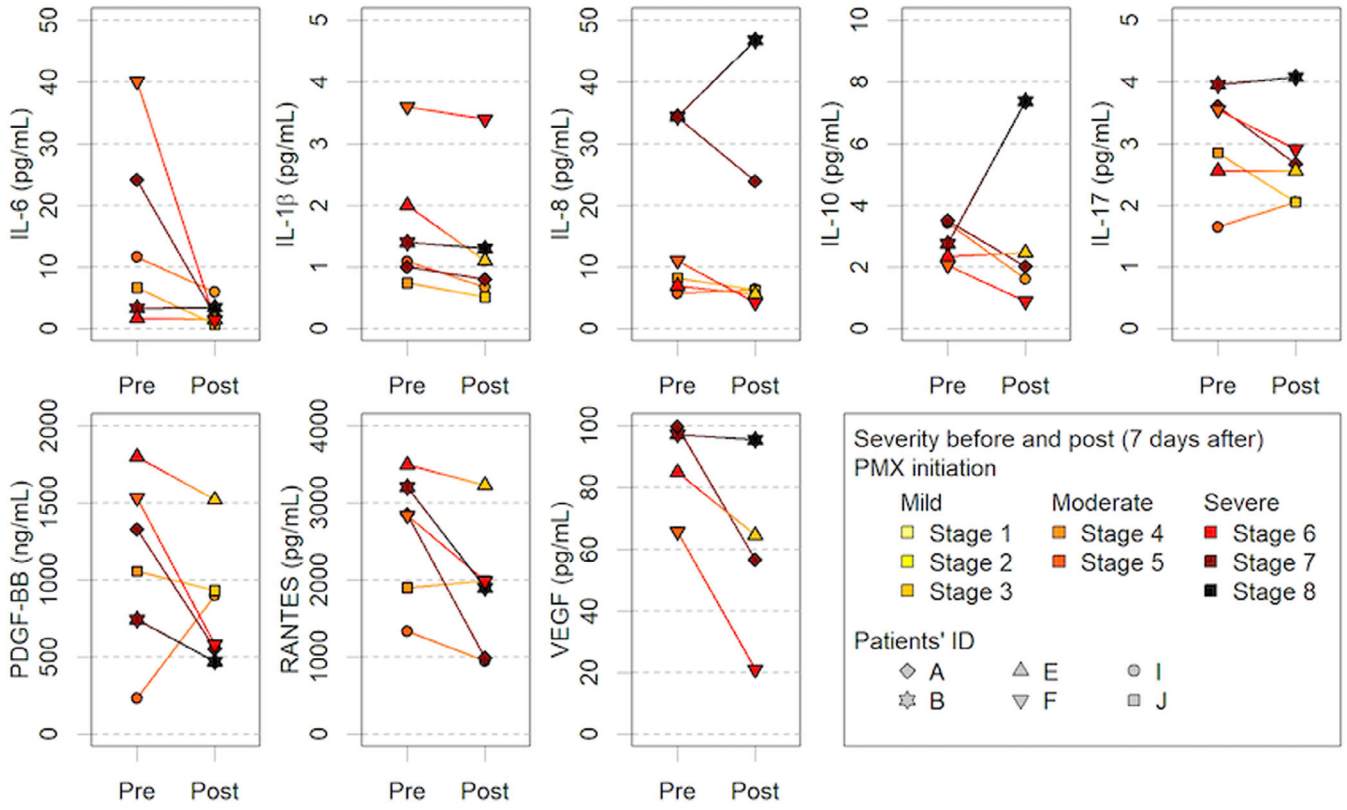

FIGURE 3 Serum cytokines before and after PMX treatment. Serum IL-6, IL-1β, IL-8, IL-10, IL-17, PDGF-BB, RANTES, and VEGF levels were evaluated in six patients (A, B, E, F, I, and J) before and after PMX treatment. Samples were collected within 6 hours before the first treatment and within 6 hours after the second treatment. The same symbol indicates the same patient. Severity is indicated by color. IL-6 showed an overall downward trend. Except for one patient (B) who died, IL-8, IL-10, and IL-17 remained almost unchanged or trended downward in the other patients. The levels of PDGF-BB, RANTES, and VEGF, markers of arteriosclerosis and vascular endothelial injury, also showed an overall downward trend around PMX treatment. The severity after PMX treatment is indicated by the severity on day 8 of the treatment. IL-6, interleukin-6; PDGF-BB, platelet-derived growth factor-BB; RANTES, regulated on activation, normal T cell expressed and secreted; VEGF, vascular endothelial growth factor; PMX, polymyxin B

necrosis factor (TNF)-α, IL-6, and high mobility group protein B1 (HMGB-1),[6,13] and prevent the migration of activated leukocytes to the lungs.[14]

The therapeutic effects of PMX-DHP on DAD, pneumocystis pneumonia, idiopathic pulmonary fibrosis, and various other lung diseases have been reported.[15-17] At present, the only treatments for severely ill patients with COVID-19 pneumonia are highly invasive treatments such as ventilation and ECMO, necessitating a prolonged stay in the intensive care unit which is a major burden on medical facilities. Several membranes, including PMX, may play an important role in the treatment of COVID-19 in terms of cytokine adsorption.[18] Inhibition of viral replication due to antiviral action is expected to be effective when the initial SARS-CoV-2 replication rate is suppressed. However, access to treatment options for preventing the transition from rapidly worsening interstitial pneumonia to DAD is the most unmet medical need as the disease progresses from moderate to severe in patients who are at the onset of requiring O_2. The mechanism of action underlying treatment with PMX has been hypothesized to be a combination of removal of activated leukocytes[14,19] and cytokines[6] that are risk factors for severe COVID-19-related pneumonia, reduction in abnormalities in the coagulation fibrinolytic system, and the rapid decline in lymphocytes during COVID-19, as well as an improvement in oxygenation capacity. We treated one COVID-19 patient having acute respiratory distress syndrome with PMX-DHP and found it to be effective.[20] Since then, we have treated 12 patients. A PMX cartridge (Toraymyxin) was recently approved in Canada for extended-label use in patients with COVID-19.[21] Its use is indicated in patients with acute respiratory distress syndrome or fluid retention, DAD on CT, and P/F ratio < 300. In the US, PMX has been approved by the Food and Drug Administration (FDA) as a compassionate use device for critically ill patients with septic shock who also tested positive for SARS-CoV-2. Currently, four blood purification devices have been approved according to the FDA COVID-19 Emergency

Use Authorizations for Medical Devices, namely, "Spectra Optia" (Terumo BCT) in combination with "Depuro D2000" (Marker Therapeutics AG), "CytoSorb" (CytoSorbents), "Oxiris" (Baxter Healthcare) and "Seraph 100" (ExThera Medical). The functions of each device are different, and include the removal of cytokines or viruses, or plasma exchange. PMX is the only direct hemoperfusion device targeting endotoxin and is also reported to remove activated leukocytes and several cytokines.

While treating patients with COVID-19, we found that the levels of urinary biomarkers, such as β2MG and L-FABP, fluctuated according to the severity of pneumonia.[22] Therefore, data on urinary β2MG and L-FABP levels was obtained to determine the time-course and outcome. Because the lung and kidney are often impaired in multi-organ failure, it is worthwhile to evaluate kidney injury biomarkers while keeping in mind the complications of acute kidney injury.[23] β2MG is a 11 870 Da single-chain polypeptide present on almost all nucleated cells. It is a component of major histocompatibility class (MHC) I molecules and can be expressed in the process of cytokine hyperproduction. It is a marker of tubular function; however, its expression can also be elevated in autoimmune diseases, malignancy, and infection. Because interferon (IFN)α, which plays a critical role in innate immunity, upregulates the expression of MHC class I and β2MG,[24] we assume that the urinary β2MG level may reflect the type 1 IFN response in COVID-19 patients. Therefore, the decrease in the urinary β2MG level after PMX-DHP in most of the patients in the present study suggests a potential cytokine suppressive effect of PMX in COVID-19 patients. Serum β2MG was measured using stored sera within 6 hours before the first PMX-DHP and within 6 hours after the second PMX-DHP. With the exception of Case A, which had a poor prognosis, all cases remained unchanged or showed decreased serum β2MG levels (N = 9, data not shown). L-FABP is expressed in renal proximal tubules and is shed into the urine under hypoxic conditions.[25] To date, L-FABP has been clinically used as a novel biomarker for the detection of acute kidney injury; however, it can also be used as a predictor of severity and mortality in the intensive care unit.[26] Nakamura et al. reported the effect of PMX on urinary L-FABP reduction in patients with septic shock.[27] It was suggested that urinary L-FABP levels were significantly elevated in patients with septic shock and that treatment using PMX was effective in reducing these levels. In the future, larger-scale studies of PMX in COVID-19 patients will need to determine the prognostic effect of treatment using PMX on L-FABP.

Increased thrombotic complications and coagulation disorder are known to occur in COVID-19 patients.[28-30] In our study, the PMX circuit coagulated in five sessions and had to be reassembled. In retrospect, among patients with high D-dimer and FDP levels, episodes of circuit coagulation, especially in membranes, were noted in the first 15 to 30 minutes. Although the membrane itself cannot be examined in detail due to infection control issues, it may be necessary to assess the patients' coagulation status, and if necessary, initiate systemic heparinization before treatment with PMX. We also checked the levels of soluble fibrin (SF) and thrombin-antithrombin (TAT) complex, which are known as factors involved in early coagulation, in three cases. The levels of SF and the TAT complex reflect the coagulation phase and are useful predictors of coagulation.[31] Despite these levels being elevated in all three cases, the circuit did not coagulate in two cases. The D-dimer and FDP levels in these two cases were normal. Compared to COVID-19 survivors, COVID-19 non-survivors have been reported to have significantly higher D-dimer and FDP levels and longer prothrombin time and activated partial thromboplastin time.[32] In our hospital, we consider using LMWH for anticoagulation treatment in patients with moderate-to-severe COVID-19 who require O_2.[33] Nafamostat mesylate acts effectively against COVID-19 by inhibiting the entry of the virus into human cells.[34] An observational study on the compassionate use of nafamosat mesylate and favipiravir in combination therapy in SARS-CoV-2-positive patients has been reported.[35] This effect may be expected when using nafamostat as an anticoagulant in PMX-DHP; however, further studies are obviously needed to confirm this effect. There is a known association between cytokine storms and vascular endothelial injury in COVID-19.[36,37] In the present study, PMX was able to inhibit IL-6,[38] which is one of the cytokines that have been the focus of attention in COVID-19. It was also suggested that PMX may have beneficial effects on the cytokines (PDGF-BB, RANTES, and VEGF) involved in atherosclerosis and vascular endothelial injury, which have been rarely mentioned in reports related to PMX until now.

Our study has some limitations. First, the extremely limited number of cases and the lack of comparators limit the interpretation of the treatment efficacy of PMX in COVID-19. A prospective study comparing the use and non-use of PMX in the treatment of COVID-19 pneumonia is necessary. The duration of PMX-DHP should be 2 hours in general according to the package insert. In contrast, it has been reported that longer (>12 hours) treatment with PMX might be more effective in terms of improving oxygenation.[39-42] Therefore, we decided to extend the duration to 3 hours, but not more, due to the limited medical resources and strict infection control implemented in this study. In addition, various treatments, including steroids and antiviral drugs, were administered to our patients; hence, it is unclear whether

PMX alone was effective. In nine of the 12 cases, steroids and PMX were introduced at the same time (within 24 hours). Of the three patients for whom the time between steroid treatment and initiation of PMX was more than 48 hours, two (Figure S1A, B) died and one (Figure 1C) required ECMO. In the current study, no patients were treated with tocilizumab or convalescent plasma. In terms of controlling cytokines, it was suggested that steroid treatment and PMX might be more effective if started at the same time. However, the indication for steroids in COVID-19 remains controversial and needs to be further investigated.

5 | CONCLUSION

PMX-DHP may have a beneficial effect on patients with COVID-19. Therefore, future prospective studies with a control group are expected to evaluate the therapeutic effect of PMX-DHP in patients with COVID-19. Because of the risk of circuit coagulation during the treatment, it is necessary to evaluate the coagulation status of the patient in advance.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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