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# Effect of hemoperfusion in critically ill COVID-19 patients: a case series from a single-center hospital in Indonesia

Aldrich Kurniawan[1], Dwi Lestari Partiningrum[1,2], Ivona Olivera[3], Steffani Sanjaya[3], Josephine Djunarko[3], Nurul Hasanah Yusri[3], Kevin Tandarto[3]

*[1] Department of Internal Medicine, Columbia Asia Hospital, Semarang, Indonesia*
*[2] Nephrology and Hypertension Division, Internal Medicine Department, Faculty of Medicine Diponegoro University, Semarang, Indonesia*
*[3] Intensive Care Unit, Columbia Asia Hospital, Semarang, Indonesia*

## Abstract

Hemoperfusion (HP), a blood filtration method targeting the removal of toxins and inflammatory elements, was investigated in this study. The objective was to present the observations in four individuals with confirmed COVID-19 who underwent several rounds of HP utilizing the HA330 cartridge at a hospital in Indonesia.

Case studies: We report four cases of COVID-19 patients who underwent HP. The decision to start HP in COVID-19 patients hinges on severe illness and specific indications such as refractory hypercytokinemia or cytokine storm syndrome, despite conventional treatments. Inclusion criteria were evidence of organ dysfunction; particularly the lungs, kidneys, or liver; and significant inflammatory markers or laboratory abnormalities. The four cases described here received HP as a supplementary treatment for COVID-19. However, only two of these patients successfully finished three cycles of HP, and just one exhibited improvement and was eventually declared to have recovered.

Conclusions: The rationale behind HP in COVID-19 patients lies in its potential to mitigate the cytokine storm, a hallmark of severe disease. COVID-19 is known to trigger an excessive inflammatory response, leading to organ damage and respiratory distress. HP, through the use of devices such as the HA330 cartridge, aims to remove inflammatory cytokines and toxins from blood circulation. Utilizing at least three sessions of HA-330 HP in addition to standard treatment in severe COVID-19 demonstrated a beneficial effect on decreasing inflammatory biomarkers, although it did not affect mortality rates.

**Key words:** hemoperfusion; severe COVID-19; therapeutic; cytokines; mortality.

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## Introduction

The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a pandemic in March 2020. COVID-19 is characterized by a spectrum of symptoms. It presents as an acute respiratory illness that can rapidly progress to respiratory failure, accompanied by multi-organ dysfunction leading to mortality. Elevated mortality rates are frequently observed in elderly patients and those with underlying comorbidities [1–3].

While not conclusive, one of the primary issues encountered is the presence of a cytokine storm, frequently observed in the advanced stages of COVID-19 infection, which can lead to severe inflammation in critically ill patients. This cytokine response may serve as a key modulator in the occurrence of multiple organ dysfunction, acute respiratory distress syndrome (ARDS), multiple organ failure, and rapid mortality [4–5]. Based on the pathophysiology of the COVID-19 disease progression, reducing viral load through antiviral administration, and addressing the inflammatory response with pharmacological and mechanical approaches has become one of the therapeutic management options for critically ill COVID-19 patients experiencing severe complications. Hemoperfusion (HP) can be employed to address various medical conditions and ailments involving the accumulation of toxins or harmful substances in the bloodstream. These include drug poisoning, food poisoning, overdoses, renal failure, and sepsis. This therapy aims to cleanse the blood of harmful substances by passing it through a specialized filter. HP has demonstrated efficacy in stabilizing plasma cytokine levels in individuals experiencing sepsis and septic shock. During the COVID-19 pandemic, research indicated a correlation between COVID-19 infection

and cytokine storm, posing considerable challenges in management of the disease. [6–7].

HP is a blood filtration process designed to eliminate toxins and inflammatory factors from the body. It is hypothesized to alleviate severe and critical COVID-19 symptoms by mitigating the dysregulation of the "cytokine storm". This is a condition where cytokines, which act as inflammatory mediators, are produced excessively due to an imbalance in pro- and anti-inflammatory responses during severe infections. This dysregulation can lead to multi organ dysfunction syndrome (MODS), including conditions such as ARDS and acute kidney injury (AKI) [8–9]. Initiating HP in COVID-19 cases depends on the severity of the illness and specific factors such as persistent hypercytokinemia or cytokine storm syndrome, despite standard therapies. Criteria for consideration also involve indications of organ dysfunction; particularly affecting the lungs, kidneys, or liver; as well as notable inflammatory markers or abnormal lab results [9–10]. The aim of this study was to assess the clinical findings and treatment outcomes of confirmed COVID-19 patients who underwent HP using the HA330 cartridge (Jafron Biomedical, Guangdong, China) at a single-center hospital in Indonesia.

## Case presentation

*Case 1*

A 54-year-old male presented with severe COVID-19 pneumonia. The patient complained of fever, cough, and shortness of breath for 3 days. A polymerase chain reaction (PCR) test confirmed the diagnosis as positive. The patient had a medical history of hypertension and diabetes mellitus. A thoracic computed tomography (CT) scan revealed severe pneumonia. Initial therapy included favipiravir 1600 mg twice daily on the first day followed by 600 mg twice daily, dexamethasone 6 mg once daily, enoxaparin 1 mg/kg subcutaneous injection, amlodipine 10 mg daily, metformin 3×500 mg oral, and gliclazide 80 mg daily. The patient's shortness of breath worsened on the third day of treatment. Oxygen supplementation was provided through a non-rebreathing mask (NRM) at 15 liters per minute (lpm). Additional therapy using remdesivir 200 mg IV as a single dose with a 100 mg maintenance dose starting day 2, tocilizumab 2×400 mg IV, and convalescent plasma was administered. On the fourth day of treatment, the decision to perform HP 3 times over 6 to 8 hours using the HA330 cartridge (Jafron Biomedical, Guangdong, China) was made.

The first HP was conducted on the sixth day of treatment while the patient was experiencing shortness of breath, using NRM at 15 lpm and with oxygen saturation at 81%. The second HP took place on the seventh day, with the patient's clinical condition showing improvement with the use of NRM at 15 lpm and oxygen saturation ranging from 90–95%. The third HP was performed on the eighth day with the patient using NRM at 15 lpm and oxygen saturation at 96–97%. On the eleventh day of treatment, improvements were observed in D-dimer and C-reactive protein (CRP) levels compared to previous assessments, and there was a significant decrease in interleukin (IL)-6 levels. The patient was discharged from the hospital on the twentieth day of treatment.

*Case 2*

A 49-year-old male presented with primary complaints of intermittent dyspnea and fluctuating fever. PCR swab results confirmed a positive diagnosis of COVID-19. The patient had a medical history of hypertension, diabetes mellitus, and coronary artery blockage, was regularly treated with clopidogrel 75 mg daily, bisoprolol 2.5 mg daily, atorvastatin 20 mg daily, metformin 3×500 mg daily, and valsartan 80 mg daily. Upon arrival, the patient exhibited an oxygen saturation level of 77%, leading to oxygen supplementation with NRM at 15 lpm. Initial treatment included remdesivir 200 mg IV as a single dose and a 100 mg maintenance dose starting on day 2, moxifloxacin 2×400 mg IV, and edoxaban 1×60 mg daily. A thoracic CT scan revealed bilateral severe viral pneumonia with moderate pulmonary fibrosis.

The patient's condition deteriorated on the seventh day of treatment, with severe dyspnea and oxygen saturation dropping to 50% with NRM at 15 lpm. Consequently, the patient was transferred to the intensive care unit (ICU) for non-invasive ventilator (NIV) support. Therapy was escalated with meropenem 500 mg IV every 8 hours, convalescent plasma, tocilizumab 8 mg/kg IV single dose, and secretome infusion. The patient showed some improvement on the fifteenth day of treatment, but still required NIV, with radiological improvements prompting the plan for HP. On the eighteenth day of treatment, HP using the HA330 cartridge (Jafron Biomedical, Guangdong, China) was initiated, with a program duration of 6 hours. On the twentieth day, the second HP, lasting 8 hours, was performed. During the second HP, the patient experienced a decrease in consciousness, prompting cessation of the procedure. Subsequently, there was a decline in oxygen saturation, followed by apnea, and ultimately, cardiac arrest, leading to the patient's demise.

*Case 3*

A 73-year-old woman infected with COVID-19 presented with a one-week history of coughing and weakness. The patient had a history of hypertension and was on routine medication. Upon arrival, her oxygen saturation was 55%, and she was given oxygen supplementation with NRM at 15 lpm. Initial treatment included enoxaparin (1 mg/kg subcutaneus administration) and remdesivir (200 mg IV as a single dose and 100 mg maintenance dose starting on day 2). A thoracic CT scan revealed severe bilateral viral pneumonia. On the second day of treatment, the patient deteriorated, with oxygen saturation ($SpO_2$) dropping to 59% despite NRM at 15 lpm. Consequently, the patient was transferred to the ICU and received oxygen supplementation through NIV. Additional therapies included convalescent plasma, tocilizumab 8 mg/kg IV single dose, and intravenous immunoglobulin (IVIG). The patient's condition continued to worsen from the second to the seventh day of treatment.

The first HP was performed on the ninth day of treatment, with an 8-hour program. The second HP took place on the tenth day, with a 6-hour program. The third HP was conducted on the thirteenth day, lasting 6 hours. The patient did not exhibit significant clinical improvement following HP, and instead experienced a decline in oxygen saturation and required an increasing level of oxygen pressure support. The patient's health further declined, ultimately resulting in her passing on the eighteenth day of medical care.

*Case 4*

A 49-year-old male presented with a 5-day history of cough, nasal congestion, and nausea. No dyspnea or fever was reported. Upon arrival, oxygen saturation was 95%, and PCR testing confirmed a positive diagnosis of COVID-19. Initial therapy included remdesivir 200 mg IV as a single dose with 100 mg maintenance dose starting day 2; moxifloxacin 2×400 mg IV; and oxygen supplementation with a nasal cannula at 4 lpm. Radiographic imaging revealed moderate bilateral viral pneumonia. On the seventh day of treatment, the patient experienced a decline in condition, with oxygen saturation dropping to 89–92% despite NRM at 15 liters per minute, accompanied by worsening chest x-ray findings. The patient continued to deteriorate from days 7 to 9, necessitating transfer to an isolated ICU. Additional therapies included enoxaparin, tocilizumab 8 mg/kg IV single dose, convalescent plasma, and IVIG. The high-flow nasal cannula (HFNC) was initiated, but as the patient's condition worsened, NIV was employed. HP therapy was planned.

The first HP was conducted on day 11 for 8 hours. Post the first session, the patient complained of dyspnea with NIV usage. On day 12, a targeted 6-hour HP program was initiated. However, during the procedure, the patient's condition deteriorated, and oxygen saturation decreased to 79–80%, leading to the cessation of HP. Tocilizumab 8 mg/kg IV single dose was added to the treatment regimen. The patient developed sepsis with a decline in consciousness, experiencing continuous deterioration. On the fifteenth day of treatment, the patient was pronounced deceased.

## Discussion

HP is a method of blood purification that can be utilized independently or in combination with other therapies like hemodialysis (HD), continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO). The use of HP, particularly with resin-containing cartridges in conjunction with CRRT and ECMO, has demonstrated positive outcomes such as improved $SpO_2$, reduced levels of inflammatory markers such as IL-6 and CRP, and a potential preventive effect on intubation [11,12]. Additionally, there are case reports indicating that HP on its own has shown favorable results; specifically, the HA-330 cartridges (Jafron Biomedical, Guangdong, China), that contain adsorbing beads made of neutro-macroporous resin, which is a styrene-divinylbenzene copolymer with a loading capacity of 330 mL. These resin beads, with an average diameter of 0.8 mm and a pore size distribution of 500 Da to 60 kDa, are capable of effectively removing medium-sized molecules such as cytokines and complements, having a molecular weight within the range of 10–60 kDa [13,14]. The success of HP procedures in COVID-19 patients relies on several key factors. Prompt initiation of HP at the appropriate disease stage is crucial, along with careful patient selection based on severity and biomarker profiles. Adherence to established treatment protocols, including session frequency and duration, is vital. Comprehensive medical support, such as mechanical ventilation and fluid management, complements HP. Regular monitoring during sessions ensures safety and allows for timely adjustments. A skilled healthcare team proficient in HP techniques and COVID-19 management is indispensable. Additionally, adequate availability of equipment and trained personnel is essential for seamless implementation. This integrated approach optimizes HP's efficacy in COVID-19 treatment. In this study, a total of four patients

**Table 1.** Laboratory indicators of the patients.

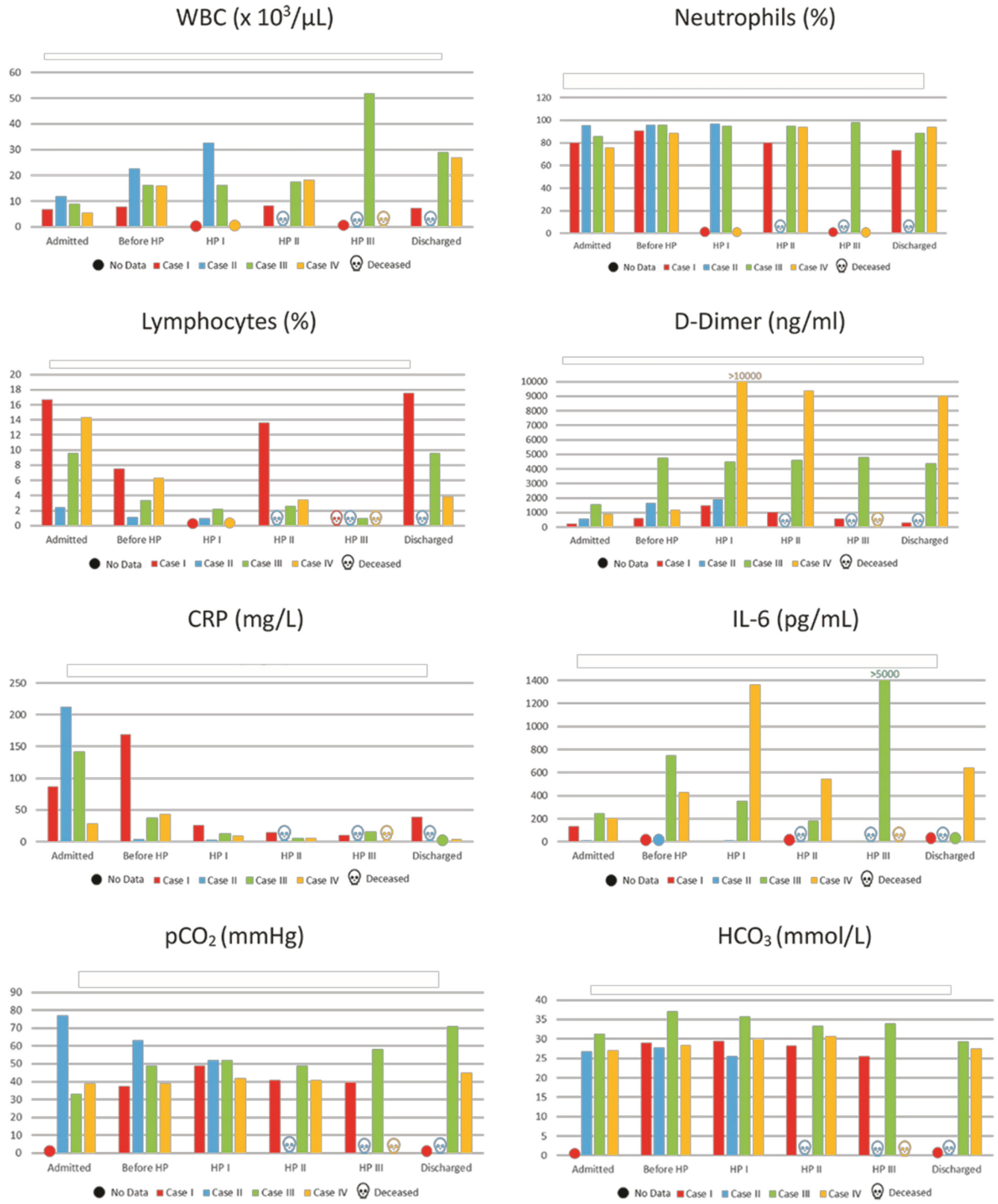
| Laboratory Indicators | Admitted | Before HP | HP I | HP II | HP III | Deceased |
|---|---|---|---|---|---|---|
| WBC I | 6.71 | 7.72 | - | 8.17 | - | 7.19 |
| WBC II | 11.8 | 22.62 | 32.62 | | Deceased | |
| WBC III | 8.77 | 16.15 | 16.22 | 17.63 | 51.90 | 28.94 |
| WBC IV | 5.51 | 15.95 | - | 18.22 | Deceased before HP III | 26.86 |
| Neutrophils I | 80.2 | 90.6 | - | 80.1 | - | 73.6 |
| Neutrophils II | 95.3 | 95.7 | 96.9 | | Deceased | |
| Neutrophils III | 85.6 | 95.8 | 94.7 | 95.0 | 98.3 | 88.3 |
| Neutrophils IV | 75.9 | 88.5 | - | 93.8 | - | 94.0 |
| Lymphocytes I | 16.7 | 7.5 | - | 13.6 | Deceased before HP III | 17.5 |
| Lymphocytes II | 2.4 | 1.1 | 1.0 | | Deceased | |
| Lymphocytes III | 9.6 | 3.3 | 2.2 | 2.6 | 1.0 | 9.6 |
| Lymphocytes IV | 14.3 | 6.3 | - | 3.4 | Deceased before HP III | 3.9 |
| D-dimer I | 245.94 | 594.18 | 1473.37 | 1028.24 | 577.52 | 301.87 |
| D-dimer II | 566.78 | 1648.58 | 1911.15 | | Deceased | |
| D-dimer III | 1526.80 | 4713.39 | 4472.08 | 4558.56 | 4745.56 | 4342.75 |
| D-dimer IV | 920.80 | 1167.88 | > 10000 | 9390.23 | Deceased before HP III | 8986.59 |
| CRP I | 87.2 | 169.3 | 25.8 | 15.1 | 10.3 | 39.2 |
| CRP II | 212.2 | 3.9 | 3.0 | | Deceased | |
| CRP III | 141.6 | 36.8 | 12.2 | 4.8 | 15.1 | - |
| CRP IV | 28.7 | 43.2 | 9.4 | 5.3 | Deceased before HP III | 3.7 |
| IL-6 I | 133.2 | No data | < 1.50 | - | < 1.50 | - |
| IL-6 II | 12.85 | No data | 12.66 | | Deceased | |
| IL-6 III | 247.1 | 748.6 | 354.1 | 184.9 | > 5.000 | - |
| IL-6 IV | 202.6 | 429.5 | 1363 | 547.5 | Deceased before HP III | 644.9 |
| pH I | | 7.494 | 7.385 | 7.445 | 7.414 | - |
| pH II | 7.493 | 7.442 | 7.449 | | Deceased | |
| pH III | 7.59 | 7.49 | 7.44 | 7.44 | 7.42 | 7.22 |
| pH IV | 7.45 | 7.47 | 7.46 | 7.48 | Deceased before HP III | 7.44 |
| $pO_2$ I | | 49 | 123 | 59 | 75 | - |
| $pO_2$ II | 77 | 63 | 52 | | Deceased | |
| $pO_2$ III | 160 | 42 | 52 | 53 | 55 | 15 |
| $pO_2$ IV | 104 | 48 | 53 | 46 | Deceased before HP III | 32 |
| $pCO_2$ I | | 37.4 | 49.0 | 40.7 | 39.5 | - |
| $pCO_2$ II | 77 | 63 | 52 | | Deceased | |
| $pCO_2$ III | 33 | 49 | 52 | 49 | 58 | 71 |
| $pCO_2$ IV | 39 | 39 | 42 | 41 | Deceased before HP III | 45 |
| $HCO_3$ I | | 29.0 | 29.4 | 28.2 | 25.5 | |
| $HCO_3$ II | 26.8 | 27.8 | 25.5 | | Deceased | |
| $HCO_3$ III | 31.2 | 37.1 | 35.8 | 33.3 | 33.9 | 29.3 |
| $HCO_3$ IV | 27.1 | 28.4 | 29.9 | 30.6 | Deceased before HP III | 27.5 |
| $FiO_2$ I | | 80 | 83 | 90 | 83 | - |
| $FiO_2$ II | 100 | 95 | 94 | | Deceased | |
| $FiO_2$ III | 100 | 91 | 100 | 88 | 92 | 100 |
| $FiO_2$ IV | 63 | 100 | 100 | 100 | Deceased before HP III | 70 |
| Lactate I | - | 2.56 | 4.87 | 1.71 | 2.26 | - |
| Lactate II | 3.82 | 3.22 | 4.19 | | Deceased | |
| Lactate III | 2.8 | 2.5 | 2.4 | 2.2 | 2.9 | 10.4 |
| Lactate IV | 2.7 | 4.6 | 2.2 | 2.4 | Deceased before HP III | 4.5 |

CRP: C-reactive protein; $FiO_2$: fraction of the oxygen; $HCO_3$: bicarbonate; HP: hemoperfusion; IL: interleukin; $pCO_2$: carbon dioxide partial pressure; $pO_2$: oxygen partial pressure; WBC: white blood cell. I: first patient; II: second patient; III: third patient; IV: fourth patient.

underwent HP as an adjunctive therapy for COVID-19. Only two out of the four patients completed three cycles of HP, and only one patient showed improvement and was declared recovered (Figure 1, Table 1).

Extracorporeal blood purification has been suggested as a potential treatment for severe COVID-19 by removing pro-inflammatory cytokines. HP, a blood purification therapy introduced in the early 1960s to enhance hemodialysis efficiency for reducing uremia, involves the passage of blood through a cartridge containing a sorbent material [10]. Through a physicochemical process, this material selectively retains specific molecules. HP has been employed not only for uremia but also for treating drug and chemical intoxication and fulminant hepatic encephalopathy. Over time, its applications have expanded to include the

**Figure 1.** Laboratory indicators of the patients.




CRP: C-reactive protein; HP: Hemoperfusion; WBC: white blood cells; pCO2: partial pressure of carbon dioxide.

management of acute inflammatory conditions such as sepsis, pancreatitis, and acute lung injury [14,15].

A mortality rate of 75% was identified from the cases we observed. This result was consistent with a study by Manalili *et al*., where a mortality rate of 62.1% was reported among 66 patients [14]. However, other studies indicate varying mortality rates ranging from 25–80% [11–14]. The variability in these results in COVID-19 patients may be attributed to differences in sample sizes, the patients' conditions at the time of initiation of HP, and the presence of comorbidities [14]. The high mortality rate in this study can also be linked to the critical condition of patients at the time of HP. In the case of the three deceased patients, HP was performed after a decline in their condition, with oxygen supplementation provided through non-invasive ventilation. The introduction of early HA-330 HP alongside standard therapy demonstrated an improvement in organ failure severity and potentially lowered mortality rates. The decision to undergo HA-330 HP was based on the assessment of the caregiving team. In our study, some early HP was not implemented due to limited resources; thus, it was reserved for cases where standard therapy failed to alleviate COVID-19 symptoms [15,22]. Research suggests that both early and late HP may alleviate COVID-19 symptoms, but there is a lack of large-scale randomized control trials (RCTs) to evaluate these outcomes. According to research by Soleimani *et al*., there was no significant difference in the mortality rate between severe COVID-19 patients undergoing HP and those who do not; as well as those undergoing plasmapheresis [15,16]. Nevertheless, the therapeutic effects of HP indicate an improvement in $SpO_2$ and a reduction in the levels of inflammatory cytokines such as CRP and IL-6 [17].

In this study, one out of four patients showed improvement. In the case of the patient who showed improvement, HP was performed on the sixth day of treatment, and the patient received oxygen supplementation with NRM. This finding aligns with research by Esmaeili *et al*., where the implementation of HP in the early stages of ARDS, when oxygen saturation with oxygen mask supplementation was below 90%, could prevent disease progression into severe ARDS. It helped stabilize oxygen saturation, prevented the need for ventilator use and intubation, and improved clinical conditions [18].

This is attributed to the mechanism of adsorption during HP, which captures inflammatory cytokines from the bloodstream, preventing these cytokines from adhering to the walls of alveoli and pulmonary arteries. As a result, this process can reduce the incidence and progression of ARDS [19]. In this patient, a decrease in CRP and IL-6 levels was also observed post-HP. Similar results were found in a case report by Shadvar *et al.,* where clinical improvement and respiratory marker improvement were noted after the first HP, accompanied by a reduction in CRP, ferritin, and procalcitonin after the second HP [20]. Clinical improvement was noted along with a decrease in IL-1, IL-6, IL-8, and TNF-α levels. Despite the reduction in inflammatory cytokines, HP was unable to decrease mortality rates and IL-6 levels in patients with septic shock [15].

In this study, regrettably, three out of four patients who underwent HP succumbed to their condition. Only one out of the three deceased patients successfully completed three cycles of HP, while the other two did not complete the procedure due to unstable hemodynamics and respiratory failure. According to a study by Abbasi *et al*., a higher mortality rate was observed in patients who had already been on mechanical ventilator support compared to before the use of mechanical ventilators in patients undergoing HP therapy. The primary causes of death in that study were respiratory failure and sepsis [21]. It aligns with our cases, as in the three deceased patients, HP was initiated after more than ten days of treatment. During HP, the patients were already in a state of sepsis and severe respiratory failure, requiring oxygen supplementation through non-invasive ventilation. Consequently, the higher risk of mortality suggests that HP may not provide significant benefits in such advanced stages of the disease.

Recent findings indicate that commencing HP early in COVID-19 cases can lead to positive results, potentially enhancing organ function and reducing mortality rates. Hence, it is imperative to promptly identify patients who could benefit from HP and start treatment. Healthcare providers should vigilantly monitor COVID-19 patients for signs of severe illness, such as worsening respiratory distress, organ dysfunction, and elevated inflammatory markers, to aid in earlier identification. Subsequent research should focus on large-scale RCTs to thoroughly assess the impact of early HP commencement on COVID-19 patient outcomes. These trials should encompass diverse patient groups and consider various factors like disease severity and treatment approaches. Additionally, comparative research between early and late HP initiation could offer valuable insights into optimal treatment timing for COVID-19 [11,21,22]. The elevated mortality rate may be influenced by the timing and the patient's condition at the initiation of HP.

However, this study is limited by its small sample size, highlighting the need for further research to explore the impact of HP as a therapy for COVID-19.

## Conclusions

Incorporating a minimum of three HA-330 HP sessions alongside standard therapy in severe cases of COVID-19, showed a positive impact on reducing the inflammatory biomarkers but not mortalities. Nevertheless, the findings were influenced by baseline confounding factors and a restricted sample size. Subsequent large-scale RCTs are necessary to validate these findings.

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### Authors' contributions

All the authors contributed equally to this research.

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## Corresponding author

Aldrich Kurniawan Liemarto, MD
Siliwangi Street No.143, Kalibanteng Kulon,
West Semarang District,
Semarang City, Central Java 50145, Indonesia.
Tel: (024) 86008600
Fax: (024) 86008600
Email: aldrich.kurniawan86@gmail.com

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