The Outcome of Hemoperfusion as an Adjuvant Therapy in Patients with Severe COVID-19 Pneumonia

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Abstract

Background: Coronavirus disease-2019 (COVID-19) pneumonia can result in cytokine release syndrome and a high mortality rate. In addition to anti-viral medications, immunomodulators, and systemic corticosteroids, cytokine removal therapy, also known as hemoperfusion, might have a role in improving patient outcomes.

Methods: This is a retrospective observational study of patients with severe COVID-19 pneumonia who received hemoperfusion using HA 330® in addition to conventional treatment compared to conventional treatment alone during May 2021 – June 2022. The primary outcome was the 28-day survival rate.

Results: 155 patients were included; 98 patients in the hemoperfusion group; and 57 patients in the conventional treatment group. Patients who received hemoperfusion had a higher Sequential Organ Failure Assessment score (10±3.3 vs. 7±2.9; p<0.001). There was no significant difference in the 28-day survival rate between the two groups (54.1% vs. 42.1%; p=0.198). Hemoperfusion for 24-48 hours significantly improved PaO2/FiO2 ratio (P=0.001) and reduced high-sensitivity C-reactive protein (p<0.001) and ferritin levels (P=0.003). Acute kidney injury was associated with an increased risk of 28-day mortality (Hazard ratio (95% confidence interval): 4.72 (2.87 to 7.77); p<0.001). The most common cause of death was bacterial pneumonia.

Conclusions: Hemoperfusion using HA330® was not associated with an improvement in 28-day survival in patients with severe COVID-19 pneumonia during the delta variant outbreak.

Keywords: dialysis; coronavirus 2019; renal replacement therapy; AKI; RRT; kidney failure; hemodialysis

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ผลลัพธ์ของการรักษาด้วยฮีโมเพอร์ฟิวชั่นในผู้ป่วยโรคโควิด-19 ที่มีปอดอักเสบรุนแรง

รุจิรดา ธีระบุญชัยกุล, วรรณิยา มีนุ่น

งานโรคไต กลุ่มงานอายุรศาสตร์ โรงพยาบาลราชวิถี

บทคัดย่อ

บทนำ: โรคติดเชื้อโคโรน่าไวรัส 2019 ทำให้เกิด cytokine release syndrome และเพิ่มมความเสี่ยงต่อการเสียชีวิต มีการศึกษาพบว่าการรักษาด้วยฮีโมเพอฟิวชั่นเพื่อขจัดไซโตไคน์อาจช่วยลดอัตราการเสียชีวิต

ระเบียบวิธีวิจัย: การศึกษาข้อมูลย้อนหลังในผู้ป่วยปอดติดเชื้ออย่างรุนแรงจากโคโรน่าไวรัส 2019 ระหว่างเดือนพฤษภาคม พ.ศ. 2564 ถึง มิถุนายน พ.ศ. 2565 เพื่อเปรียบเทียบอัตราการรอดชีวิตในวันที่ 28 ของการนอนโรงพยาบาล ระหว่างกลุ่มผู้ป่วยที่ได้รับการรักษาด้วยฮีโมเพอฟิวชั่นร่วมกับการรักษาตามปกติ และกลุ่มผู้ป่วยที่ได้รับการรักษาตามปกติอย่างเดียว

ผลการศึกษา: มีผู้ป่วยปอดติดเชื้อโคโรน่าไวรัสรุนแรงจำนวนทั้งหมด 155 ราย 98 รายอยู่ในกลุ่มที่ได้รับฮีโมเพอฟิวชั่นด้วย HA 330® และ 57 รายอยู่ในกลุ่มที่ได้รับการรักษาตามปกติ กลุ่มผู้ป่วยที่ได้รับการรักษาด้วยฮีโมเพอฟิวชั่นมีความรุนแรงของโรคมากกว่า และไม่พบความแตกต่างกันของอัตราการรอดชีวิตในวันที่ 28 ระหว่างทั้งสองกลุ่ม (ร้อยละ 54.1 เทียบกับ ร้อยละ 42.1; P=0.198) หลังการทำฮีโมเพอฟิวชั่นพบว่าผู้ป่วยมีค่า PaO2/FiO2 เพิ่มขึ้น (P=0.001) และ มีระดับ high sensitivity c-reactive protein (P<0.001) และ ferritin ลดลงอย่างมีนัยสำคัญ (P=0.003) ภาวะไตวายเฉียบพลันเป็นปัจจัยเสี่ยงที่สำคัญต่ออัตราการเสียชีวิตที่ 28 วัน (Hazard ratio (95% confidence interval: 4.72 (2.87-7.77); P<0.001) สาเหตุหลักของการเสียชีวิตคือปอดติดเชื้อแบคทีเรีย

สรุป: การทำฮีโมเพอฟิวชั่นด้วย HA 330® ไม่สัมพันธ์กับอัตราการรอดชีวิตที่เพิ่มขึ้น ณ.วันที่ 28 ของการนอนโรงพยาบาลในผู้ป่วยที่เป็นโรคปอดติดเชื้ออย่างรุนแรงจากโคโรน่าไวรัส 2019 ในช่วงที่มีการระบาดของสายพันธ์เดลต้า

คำสำคัญ: ปอดบวม; โควิด; โควิด 19; ฟอกเลือด; ฟอกไต; ปอดอักเสบ

Introduction

In March 2020, World Health Organization (WHO) declared SARS-CoV-2, COVID-19 infection, a global pandemic. Severe cases of COVID-19 have a 67% failure rate due to multi-organ dysfunction syndrome (MODS) and 49% mortality.[1] MODS, including acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI), can lead to morbidity and mortality.[2] The cause of MODS in severe COVID-19 infection is due to the imbalance of immune system response, leading to hyperinflammation known as cytokine storm syndrome (CRS).[3] CRS in severe COVID-19 patients occurs when the body produces an aberrant, rapid, excessive, and prolonged inflammatory response to cytokines, leading to hyperinflammation, extensive endothelial dysfunction with capillary leakage, disseminated intravascular hypercoagulation, and subsequently MODS[2,4] An increase in interleukin-2, interleukin-6 (IL-6), interleukin-7, c-reactive protein (CRP), interferon-gamma, and tumor necrosis factor-alpha have been reported.[5,6]

Hemoperfusion is one of the extracorporeal blood purification methods that remove soluble inflammatory mediators and endotoxins by binding to the adsorbent membrane filter.[7] The Handbook of COVID-19 Prevention

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and Treatment from Zhejiang University School of Medicine, China published in 2020 recommended the use of blood purification methods such as plasma exchange and hemoperfusion for early and midterm treatment of CRS in severe and critically severe COVID-19 infection.[5] Additionally, the Food and Drug Administration has temporarily authorized the emergency use of CytoSorb® device for hemoperfusion in the management of CRS in COVID-19 patients.[8] HA 330® is a highly biocompatible neutron-macroporous resin adsorbing beads made of styrene-divinylbenzene copolymer with a high surface area (500 Da-60 kDa), It can remove substances with a molecular weight of 10-60 kDa.[2,9] Several studies that evaluated the use of HA 330® in patients with CRS in acute inflammatory conditions such as sepsis, acute lung injury, hepatitis, and pancreatitis demonstrated an improvement in inflammatory markers.[5,7,9] A decrease in 28-day mortality has also been reported in patients with sepsis and acute lung injury after 3 days of hemoperfusion treatment compared to usual care.[5,7]

Other types of cartridges that may have therapeutic benefits in COVID-19 infection include PMX-hemoperfusion®, CytoSorb®, and HA380®. Two studies have shown a reduction in mortality rate by 37-43% compared with conventional treatment.[3,10] However, the positive outcome of hemoperfusion could not be confirmed in other studies.[1,11-15] The present retrospective study evaluated the 28-day survival rate after hemoperfusion in patients with severe COVID-19 pneumonia compared to conventional treatment alone.

Materials and Methods

Study design and setting

This retrospective cohort study was conducted at Rajvithi Hospital, Bangkok, Thailand. A medical chart review of patients with COVID-19 pneumonia who were admitted to the medical intensive care unit between May 2021 and June 2022 was performed. During the data collection period, the predominant strain of COVID-19 was the delta variant. The study was approved by the ethical committee of Rajavithi Hospital (approval number 65115) and was performed in accordance with the Helsinki Declaration. Informed consent was not required.

Participants

A medical chart review was performed on 283 patients. The inclusion criteria were age ≥18 years old, having confirmed COVID-19 pneumonia by reverse transcriptase polymerase chain reaction, and findings on the chest X-ray consistent with COVID-19 pneumonia. The exclusion criteria were patients that did not require mechanical ventilation with a Sequential Organ Failure Assessment (qSOFA) score <1, received <3 hours of hemoperfusion treatment had incomplete data and had COVID-19 pneumonia during the hospital outbreak. The patients were classified into two groups: the hemoperfusion group (received hemoperfusion in addition to conventional treatment); and the conventional treatment group (received conventional treatment alone). The patients were normally prescribed hemoperfusion after the infectious disease specialist confirmed a diagnosis of severe COVID-19 pneumonia. The study flowchart is shown in **Figure 1**.

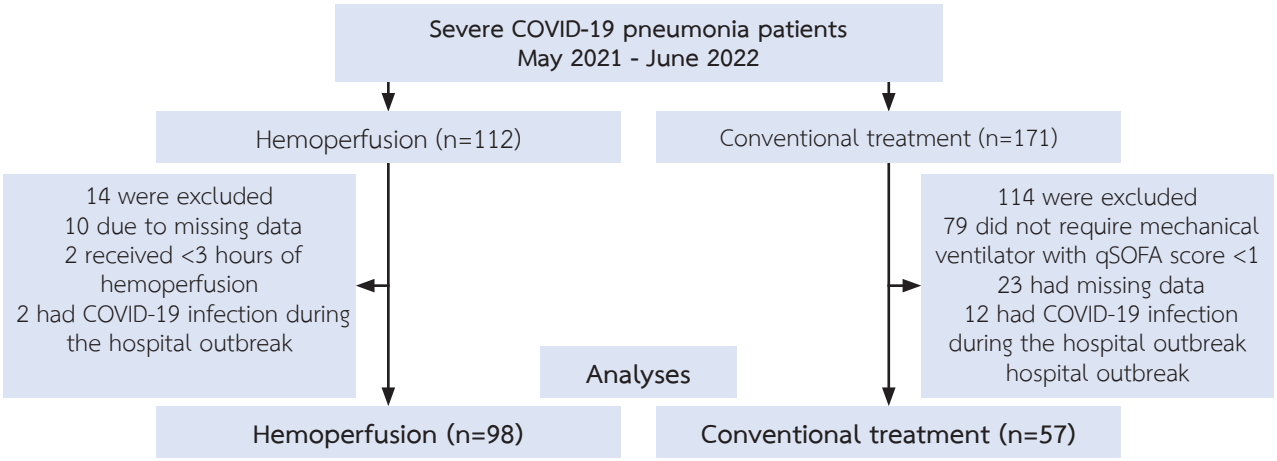

Figure 1 Study Flowchart

Hemoperfusion

Hemoperfusion was started with HA330® cartridge (Jafron, ASTROMED.CO.LTD, China). Unfractionated heparin 5,000 units was used to prime the circuit followed by flushing with normal saline. The blood flow rate ranged between 150 to 200 ml/min and the duration of treatment lasted at least 3 hours. The duration of treatment for each patient was determined by the primary nephrologists.

Data collection

Demographic data, clinical parameters, laboratory data were collected. The anti-viral medications available at the time of the study were favipiravir, lopinavir/ritonavir; LPV/r, and remdesivir, and the immunomodulators were baricitinib and tocilizumab. The SOFA score was calculated for all patients. The PaO2/FiO2 ratio was used to identify the severity of hypoxemic respiratory failure. The data on serum levels of inflammatory markers including IL-6, ferritin, high-sensitivity-CRP (hs-CRP), and D-dimer at baseline and after 24-48 hours of the last session of hemoperfusion were collected. The chest-X-ray image was imported into a computer-aided detection system (Lunit INSIGHT CXR, Lunit inc. J.F.ADVANCE MED), which gave the information on the probability score of abnormal lesions expressed as number (%).[16] The overall accuracy was 97-99%, sensitivity 43.8% and specificity 59.8%.

Outcomes

The primary outcome was patient survival on the 28th day of admission. The secondary outcomes were factors associated with survival.

Sample size calculation

The data from Mikaeili H, et al was used for sample size calculation with a 2-sided α level of 0.05 and power of 80%.[10] The calculation was based on a missing data of 40% resulting in a sample size of 77 patients for each group.

Statistical analyses

Continuous data were presented as mean ± standard deviation or median (interquartile range). Student t-test or Mann-Whitney U test were used to compare the differences between the two groups. Categorical data were presented as numbers (%). The difference between the two groups was compared using a Chi-square test. Survival was analyzed by the Kaplan-Meier curve and Cox proportional hazard regression models. The multivariate models were developed by adjusting for covariates with a p-value <0.2 from the univariate models. A p-value of <0.05 was considered significant. Statistical analysis was performed by Stata version 15.1 (StataCorp LLC).

Results

Characteristics, laboratory data, and outcomes of all patients according to the treatment group are shown in **Table 1**. Patients in the conventional treatment group were substantially older than the hemoperfusion group. Both groups showed similar comorbid conditions including diabetes, and chronic kidney disease stages 5 and 5D. The hemoperfusion group had a higher SOFA score, and worse P/F ratio and received more potent anti-viral medications, immunomodulators, and systemic corticosteroids. Data of the hemoperfusion group according to survival at day 28 are shown in **Table 2**

Table 1 Baseline demographics, clinical data, and outcome according to the treatment group

Parameters	Hemoperfusion (n=98)	Conventional treatment (n=57)	*p*-value
Age (year)	56.34 ± 14.93	61.81 ± 15.99	0.034*
Male sex	50 (51%)	32 (56.1%)	0.538
Comorbidities			
• Chronic kidney disease stage 5	11 (11.2%)	5 (8.8%)	0.628
- Hemodialysis	6 (6.1%)	2 (3.5%)	0.478
- Peritoneal dialysis	2 (2%)	2 (3.5%)	0.578
- Non-dialysis	3 (3.1%)	1 (1.8%)	0.621
• Kidney transplant recipients	2 (2%)	0 (0%)	0.278
• COPD and chronic lung disease	1 (1%)	1 (1.8%)	0.696
• Cardiovascular disease	2 (2%)	0 (0%)	0.278
• Stroke	3 (3.1%)	5 (8.8%)	0.121
• Diabetes mellitus	39 (39.8%)	23 (40.4%)	0.946
• Obesity[a]	8 (8.2%)	4 (7%)	0.797
• Liver cirrhosis	0 (0%)	1 (1.8%)	0.188
• Pregnancy	6 (6.1%)	0 (0%)	0.057
• HIV infection	0 (0%)	1 (1.8%)	0.188
• Malignancy	5 (5.1%)	1 (1.8%)	0.298
• Received immunosuppression (excluding kidney transplant recipients)	3 (3.1%)	0 (0%)	0.182
Time from positive PCR to admission (hours)	1 (0, 2)	0 (0, 1)	<0.001*
• ≤ 24 hours	69 (70.4%)	48 (84.2%)	0.054
• > 24 hours	29 (29.6%)	9 (15.8%)	0.054
Severity of sepsis syndrome			
• qSOFA[b] score available	58 (59.1%)	31 (54.3%)	0.931
- qSOFA score	1 (1, 1)	1 (1, 2)	0.009*
- < 2	51 (52%)	18 (31.6%)	0.013*
- ≥ 2	7 (7.1%)	13 (22.8%)	0.005*
• SOFA[c] score available	40 (40.8%)	26 (45.6%)	0.560
- SOFA score	10.57 ± 3.34	7.58 ± 2.93	<0.001*
- < 2	0 (0%)	0 (0%)	N/A
- 2-7	7 (7.1%)	13 (22.8%)	0.005*
- 8-11	21 (21.4%)	10 (17.5%)	0.560
- > 11	12 (12.2%)	3 (5.3%)	0.156
Oxygen support within the first 24 hours of admission			
• Cannula	19 (19.4%)	10 (17.5%)	0.777
• Mask with bag	1 (1%)	0 (0%)	0.444
• Bi-level positive airway pressure	3 (3.1%)	1 (1.8%)	0.621
• High-flow nasal cannula	35 (35.7%)	20 (35.1%)	0.937
• Mechanical ventilator	40 (40.8%)	26 (45.6%)	0.560
Anti-viral medications and/ or immunomodulators			
• Remdesivir	24 (24.4%)	5 (8.7%)	0.008*
• Baricitinib	35 (35.7%)	8 (14%)	0.005*
• Tocilizumab	10 (10.2%)	1 (1.7%)	0.082

Parameters	Hemoperfusion (n=98)	Conventional treatment (n=57)	*p*-value
Systemic corticosteroids			
• Methylprednisolone	74 (75.5%)	19 (33.3%)	<0.001*
• Dexamethasone	24 (24.5%)	37 (64.9%)	<0.001*
• Prednisolone	0 (0%)	1 (1.8%)	0.188
PaO2/FiO2 ratio and inflammatory markers			
• PaO_2/FiO_2 ratio			
- Day 1-2	126 (92, 158)	206 (107, 285)	0.008*
- Day 3-4	237 (155, 308)	217 (168, 312)	0.899
• Interleukin-6 (pg/ml)			
- Day 1-2	49.66 (7.34, 82.42)	39.17 (8.39, 109.3)	0.941
- Day 3-4	29.1 (6.27, 1232)	0.69 (0.69, 0.69)	0.134
• hs-CRP (mg/L)			
- Day 1-2	10.5 (5.57, 15.72)	10.42 (2.17, 14.68)	0.194
- Day 3-4	5.38 (2.46, 8.9)	5.45 (2.66, 8.15)	0.834
• Ferritin (mg/ml)			
- Day 1-2	1394 (643, 2897)	1365 (403, 2719)	0.408
- Day 3-4	1559 (678, 3661)	1588 (530, 3015)	0.442
• D-dimer (mg/L)			
- Day 1-2	1.96 (0.92, 4.33)	2.45 (1.09, 9.37)	0.308
- Day 3-4	2.43 (1.2, 6.41)	3.11 (1.35, 9.96)	0.383
Consolidation on chest-X-ray (%)			
• Day 1-2	98 (94, 99)	97.22 (64.0, 99.0)	0.244
• Day 3-4	98 (95, 99)	97.16 (83.7, 98.7)	0.380
Acute kidney injury	50 (51%)	22 (38.6%)	0.135
Acute kidney injury requiring dialysis	25 (25.5%)	1 (1.8%)	<0.001*
• Dialysis withdrawal within 28 days	22 (22.4%)	1 (1.8%)	0.001*
• Death-censored dialysis withdrawal within 28 days	20 (20.4%)	1 (1.8%)	0.001*
• Dialysis dependent on day 28	3 (3.1%)	0 (0%)	0.182
Survival on day 28			
• All patients	53 (54.1%)	24 (42.1%)	0.150
• With acute kidney injury	14 (14.3%)	2 (3.5%)	0.034*
• With acute kidney injury requiring dialysis	5 (5.1%)	1 (1.8%)	0.298
• With chronic kidney disease stage 5	6 (6.1%)	4 (7%)	0.827
• With a kidney transplant	0 (0%)	0 (0%)	N/A

Data are presented as mean ± standard deviation or median (interquartile range) or number (%)

[a] defined as body weight >90 kg or body mass index≥ 30 kg/m^2

[b] quick Sequential Organ Failure Assessment score was calculated based on respiratory rate, systolic blood pressure, and Glasgow Coma Score

[c] Sequential Organ Failure Assessment score was calculated using PaO2/FiO2 ratio, platelet count, total bilirubin, Glasgow Coma Score, creatinine, and mean arterial pressure and/or dose of vasopressor

hs-CRP, high sensitivity c-reactive protein; *p-value < 0.05

Table 2 Hemoperfusion treatment and clinical parameters of the hemoperfusion group according to survival outcome

Factors	Hemoperfusion (n=98)		
	Survivors (n=53)	Non-survivors (n=45)	*p*-value
Start hemoperfusion within the first 48 hours of admission	35 (66%)	25 (55.6%)	0.289
Duration of hemoperfusion per session			
• 3 hours	2 (3.8%)	6 (13.3%)	0.085
• 4 hours	51 (96.2%)	39 (86.7%)	0.085
Number of hemoperfusion			
• 1 session	3 (5.7%)	6 (13.3%)	0.190
• 2 sessions	23 (43.4%)	20 (44.4%)	0.917
• 3 sessions	26 (49.1%)	17 (37.8%)	0.262
• 4 sessions	1 (1.9%)	1 (2.2%)	0.907
• 5 sessions	0 (0%)	1 (2.2%)	0.275
Requiring intermittent hemodialysis			
• Due to acute kidney injury	5 (9.4%)	20 (44.4%)	<0.001*
• Due to CKD stage 5D	5 (9.4%)	4 (8.9%)	0.926
Severity of sepsis syndrome			
• qSOFA[a] score			
- Score < 2	35 (66%)	16 (35.6%)	0.003*
- Score ≥ 2	6 (11.3%)	1 (2.2%)	0.081
• SOFA[b] score			
- Score 2-7	3 (5.7%)	4 (8.9%)	0.536
- Score 8-11	8 (15.1%)	13 (28.9%)	0.097
- Score > 11	1 (1.9%)	11 (24.4%)	0.001
PaO2/FiO2 ratio and inflammatory markers - mean difference[c] (95% confidence interval)			
• PaO_2/FiO_2 ratio (n=41)	66 (-50.69, 182.69)	71.68 (28.32, 115.05)	0.904
• Interleukin-6 (pg/ml) (n=8)	-177.4 (-886.3, 531.4)	320.9 (-363.2, 1005)	0.144
• hs-CRP (mg/L) (n=98)	-7.91 (-10.03, -5.79)	-6.56 (-9.44, -3.69)	0.442
• Ferritin (mg/ml) (n=96)	804 (-327, 1936)	3700 (982, 6417)	0.052
• D-dimer (mg/L) (n=86)	1.06 (-1.84, 3.97)	0.38 (-4.18, 4.94)	0.791
Consolidation in CXR – mean difference (95% confidence interval)			
• Before vs. after 24-48 hours of hemoperfusion (n=97)	7.6 (-1.58, 16.77)	3.89 (-2.46, 10.23)	0.506
• Before vs. day 28 of admission (n=41)	8.98 (-2.89, 20.85)	0	0.812

Data are presented as mean ± standard deviation or median (interquartile range) or number (%) unless specified otherwise

[a] quick Sequential Organ Failure Assessment score was calculated based on respiratory rate, systolic blood pressure, and Glasgow Coma Score

[b] Sequential Organ Failure Assessment score was calculated using PaO2/FiO2 ratio, platelet count, total bilirubin, Glasgow Coma Score, creatinine, and mean arterial pressure and/or dose of vasopressor

[c] Mean difference represented the change from baseline after 24-48 hours of hemoperfusion

CXR, chest-X-ray; hs-CRP, high sensitivity c-reactive protein; *p-value <0.05

Kaplan-Meier curves showed no difference in 28-day survival between the hemoperfusion group and the conventional treatment group (54.1% vs. 42.1%; *p*=0.198) **(Figure 2)**. There was also no difference in the survival in the subgroup of patients who had more severe disease (SOFA score ≥ 8) (*p*=0.996) **(Figure 3)**.

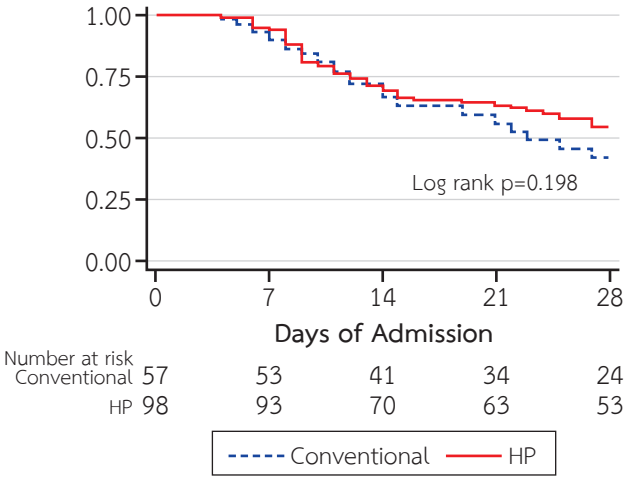

Figure 2 Kaplan-Meier survival curve of 28-day survival for all patients
HP, hemoperfusion

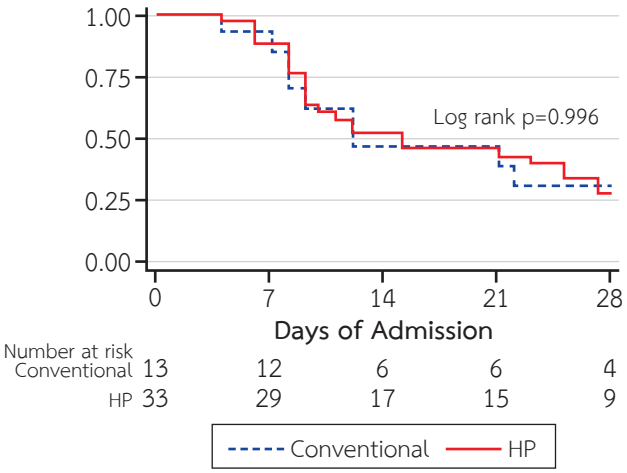

Figure 3 Kaplan-Meier survival curve of 28-day survival for the subgroup of patients with SOFA score ≥8
HP, hemoperfusion

The severity of hypoxemia, the levels of inflammatory markers, and chest X-ray findings before and after hemoperfusion are shown in **Table 3**. P/F ratio and hs-CRP improved considerably after 24-48 hours of hemoperfusion. There were no significant changes in the findings of the chest X-ray after hemoperfusion.

Table 3 Severity of hypoxemia, inflammatory markers, and chest-X-ray findings after hemoperfusion

Factors	Hemoperfusion (n=98)			
	Before	After	*p*-value	Mean difference (95% CI)
Parameter and inflammatory markers				
• PaO_2/FiO_2 ratio (n=41)	139.85 ± 62.29	210.01 ± 112.56	0.001*	70.16 (28.6, 111.7)
• IL-6 (ng/ml) (n=8)	208.7 ± 226.15	342.73 ± 621.59	0.484	134.03 (-294, 562)
• hs-CRP (mg/L) (n=98)	11.88 ± 8.97	4.59 ± 5.38	<0.001*	-7.29 (-9.01, -5.57)
• Ferritin (mg/ml) (n=96)	2943 ± 5107	5045 ± 8155	0.003*	2101 (730, 3472)
• D-dimer (mg/L) (n=86)	6.46 ± 11.36	7.22 ± 8.96	0.553	0.76 (-1.77, 3.29)
Consolidation on CXR (%)				
• Before vs. after 24-48 hours of hemoperfusion (n=97)	86.17 ± 28.73	92.05 ± 15.12	0.042*	0.06 (0, 0.12)
• Before vs. day 28 of admission (n=41)	79.85 ± 35.01	88.61 ± 18.57	0.134	0.09 (-0.03, 0.2)

IL-6, interleukin 6; hs-CRP, high sensitivity c-reactive protein; CXR, chest-X-ray; CI, confidence interval

Cox proportion hazards competing risk regression analyses were performed to determine the predictors associated with 28-day survival **(Table 4)**. In univariate analysis, age ≥60 years, underlying chronic lung disease, AKI, requiring mechanical ventilation within the first 24 hours of admission, SOFA score >11, P/F ratio 101-200,

hemoperfusion 4 hours/session, and consolidation on chest-X-ray >75% were associated with decreased 28-survival. In multivariate analysis, only age ≥60 years, AKI, and requiring mechanical ventilation within the first 24 hours of admission, were negative predictive risk factors for 28-day survival.

Table 4 Factors associated with 28-day survival

Characteristics	Univariate analysis		Multivariate analysis	
	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Age ≥60 years	1.97 (1.24, 3.12)	0.004*	2 (1.03, 3.89)	0.041*
COPD and chronic lung disease	11.43 (2.63, 49.59)	0.001*	-	-
Type 2 diabetes mellitus	0.81 (0.51, 1.29)	0.386	-	-
Obesity[a]	0.39 (0.12, 1.23)	0.108	-	-
CKD stage 5				
• Hemodialysis	0.69 (0.22, 2.18)	0.526	-	-
• Peritoneal dialysis	0.39 (0.05, 2.79)	0.347	-	-
• Non-dialysis	0.91 (0.22, 3.71)	0.897	-	-
Kidney Transplant Recipients	2.66 (0.65, 10.85)	0.172	-	-
Acute kidney injury	4.72 (2.87, 7.77)	<0.001*	4.28 (1.78, 10.27)	0.001*
Acute kidney injury requiring dialysis	1.14 (0.066, 1.97)	0.648	-	-
SOFA[b] score				
• Score 8-11	2.07 (0.91, 4.72)	0.082	-	-
• Score > 11	4.16 (1.71, 10.16)	0.002*	-	-
Requiring mechanical ventilation within the first 24 hours of admission	2.26 (1.13, 4.51)	0.021*	2.87 (1.27, 6.45)	0.011*
PaO_2/FiO_2 ratio				
• > 300	1 (reference)			
• 201 ≤ 300	3.61 (0.43, 30.03)	0.234	-	-
• 101-200	7.53 (1.01, 56.27)	0.049*	-	-
• ≤ 100	6.97 (0.92, 52.91)	0.06	-	-
Consolidation on CXR				
• ≤ 50%	1 (reference)			
• 51-74%	1.54 (0.32, 7.4)	0.593	-	-
• ≥ 75%	2.38 (1.09, 5.19)	0.029*	0.72 (0.36, 1.4)	0.321
Hemoperfusion	0.75 (0.48, 1.17)	0.207	-	-
Duration of hemoperfusion				
• 3 hours per session	1 (reference)			
• 4 hours per session	0.41 (0.17, 0.97)	0.043*	-	-
Number of hemoperfusion				
- 2 sessions	1 (reference)			
- 3 sessions	0.81 (0.42, 1.55)	0.521	0.71 (0.36, 1.4)	0.321

[a] defined as body weight >90 kg or body mass index ≥30 kg/m^2

[b] Sequential Organ Failure Assessment sco re was calculated using PaO_2/FiO_2 ratio, platelet count, total bilirubin, Glasgow Coma Score, creatinine, and mean arterial pressure and/or dose of vasopressor

CXR, chest-X-ray; HR, hazard ratio; CI, confidence interval; *p-value <0.05

The causes of death are shown in **Table 5**. The most common cause of death for both groups was bacterial pneumonia (p=0.642). The conventional treatment group had a significantly higher incidence of mortality from ARDS compared with the hemoperfusion group (15.8% vs. 4.1%; p=0.011).

Table 5. Cause of death for all patients

Cause of death	Hemoperfusion (n=53)	Conventional treatment (n=24)	*p*-value
Acute respiratory distress syndrome	4 (4.1%)	9 (15.8%)	0.011*
Bacterial pneumonia	31 (31.6%)	16 (28.1%)	0.642
Septic shock (except bacterial pneumonia and fungal infection)	5 (5.1%)	2 (3.5%)	0.645
Fungal infection	6 (6.1%)	5 (8.8%)	0.536
Acute myocardial infarction	1 (1%)	1 (1.8%)	0.696
Stroke	4 (4.1%)	0 (0%)	0.122
Kidney failure (refused dialysis)	14 (14.3%)	4 (7%)	0.173
Others (gastrointestinal bleeding, spontaneous pneumothorax)	0 (0%)	2 (3.5%)	0.062

*p-value < 0.05

Discussion

The present study demonstrated that treatment with hemoperfusion using HA 330® cartridge did reduce the 28-day mortality rate compared with conventional therapy in severe COVID-19 pneumonia during the outbreak of the delta variant. Hemoperfusion for 24-48 hours significantly improved PaO2/FiO2 ratio and reduced inflammatory markers. AKI was an independent risk factor for 28-day mortality.

Current evidence supports the use of immunomodulation in treating critically ill COVID-19 patients with CRS. However, the indication for cytokine removal hemoperfusion as adjuvant therapy remains individualized for patients with severe refractory acute respiratory failure and hyper-cytokinemia.[2] Furthermore, clear threshold levels of inflammatory biomarkers for initiating hemoperfusion have yet to be established, with these levels potentially not being as elevated as in other acute inflammatory conditions.[18] Previous studies suggest that patients with higher baseline cytokine concentrations may benefit more from cytokine removal therapy, experiencing higher rates of cytokine removal.[2,6] However, the short half-life of inflammatory cytokines—mere minutes—leads to rapid rebounds in cytokine levels.[4] Moreover, hemoperfusion can inadvertently remove drugs from circulation, lowering their levels to subtherapeutic ranges.[19,20] Consequently, the efficacy of hemoperfusion varies across studies, necessitating caution in its application.[18]

The previous case-control study on COVID-19 pneumonia patients with CRS and comparable SOFA score and P/F ratio to the present study who underwent hemoperfusion using HA 330® and Mediasorb® for 4 hours per session for at least 3 sessions showed no significant difference in the mortality rates between the hemoperfusion group compared with the non-hemoperfusion group.21 In the single-center randomized controlled trial (CYCOV) conducted by Supady et al. in severe COVID-19 pneumonia patients necessitating veno-venous extracorporeal membrane oxygenation (ECMO), CytoSorb® cartridge was introduced during the first 4 hours of ECMO

initiation compared to ECMO treatment alone. While the patients exhibited similar SOFA scores to the present study (score=9), they showed a poorer P/F ratio (62.7 to 84.2). Remdesivir and tocilizumab were administered to 17% and 55% of patients, respectively. Notably, the CytoSorb® group experienced a significantly lower survival rate (CytoSorb® 18% vs. ECMO alone 76%; p=.0016). Septic shock (41.1%) emerged as the leading cause of death in both groups.[22]

In contrast, Surasit et al. conducted a prospective cohort study on severe COVID-19 pneumonia patients with a P/F ratio <200 who underwent hemoperfusion using HA 330® for 4 hours per session. The study compared the outcomes of patients who received ≥3 sessions of hemoperfusion versus those who received <3 sessions. The study cohort had a relatively lower SOFA score at baseline (3.53 to 4.3) than the present study and received early hemoperfusion within 8-15 hours of admission. The group that received ≥3 sessions of hemoperfusion had a lower 28-day mortality rate (adjusted hazard ratio 0.033 (95% CI 0.004 to 0.264); p=0.001).[23] Similarly, Mikaeili et al. conducted a prospective cohort study involving severe COVID-19 pneumonia patients with a P/F ratio < 200 who underwent hemoperfusion using HA 330® for at least 3 sessions of 4 hours each. The baseline APACHE II score ranged from 8 to 9, indicating less severity compared to the present study. Patients who received tocilizumab were excluded from the analysis. The study revealed that the hemoperfusion group exhibited a significantly lower mortality rate compared to the non-hemoperfusion group (37.1% vs. 63.6%; p=0.03).[10]

In the present study, patients exhibited high baseline SOFA scores, similar to Abdullayev et al. and CYCOV, and hemoperfusion failed to reduce mortality.[21,22] Bacterial pneumonia and septic shock were the most common cause of death in the present study and CYCOV study.[22] While hemoperfusion could facilitate endotoxin removal, the timing of hemoperfusion was crucial. Another potential factor contributing to the ineffectiveness of hemoperfusion was the variability in the treatment regimens used among different patients in the present study and that by Abdullayev et al.[21]

The present study revealed an improvement in the P/F ratio and hs-CRP following hemoperfusion which is consistent with other studies. For instance, Abdullayev et al. reported significant improvements in CRP and fibrinogen levels, while Mikaeili et al. demonstrated improvements in SpO2 and P/F ratio.[10,21] However, the present study could not demonstrate improvements in other inflammatory markers post-hemoperfusion. This discrepancy could be attributed to other co-existing conditions such as infection, liver injury, and blood transfusion.[24] Elevated D-dimer levels could be linked to thrombotic complications associated with COVID-19 infection.[25] The present study did not show any improvement in chest X-ray findings after hemoperfusion. Consolidations seen on chest X-rays could be the result of various pathologies, for example, pneumonia, heart failure, volume overload, and interstitial lung disease.

In the previous systematic review, AKI was reported in 35 out of 64 COVID-19 infected patients (56.2%), with an overall mortality rate of 66.2%.[26] One study indicated that AKI stage 3 had a hazard ratio for in-hospital death of 4.724.[4] This finding aligns with that of Abdullayev et al. and the present study, which reported AKI in 50% and 46.2% of severe COVID-19 patients, respectively.[21] Furthermore, the hemoperfusion group had a higher proportion of patients undergoing kidney replacement therapy compared to the conventional treatment (25.5% vs. 1.8%; p<0.001), and this was associated with a decrease in survival (44.4% vs. 9.4%; p<0.001).

The present study had several limitations. There were substantial differences in the baseline characteristics of the patients. The study was conducted in only one institution. Several data were missing including the history of COVID-19 vaccination, P/F ratios, and IL-6 levels.

In conclusion, adjuvant therapy with hemoperfusion using HA 330® was not associated with an improvement in 28-day survival in COVID-19 patients with severe pneumonia during the outbreak of the delta variant. Hemoperfusion resulted in an improvement in P/F ratio and inflammatory markers and AKI was an independent risk factor for mortality.

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