

The Efficacy of Early Additional Hemoperfusion Therapy for Severe COVID-19 Patients: A Prospective Cohort Study

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Keywords

Hemoperfusion therapy · Severe COVID-19 · Survival

Abstract

Introduction: Currently, the effect of hemoperfusion on outcome in severe COVID-19 patients is still unknown. Therefore, we aimed to investigate the effects of early HA-330 hemoperfusion in severe COVID-19 patients. **Methods:** We conducted a single center, prospective cohort study on patients who were diagnosed with severe COVID-19 patients and admitted to ICU. Patients in hemoperfusion group (defined as patients who were treated with hemoperfusion therapy at least 3 sessions in combination with standard therapy) were compared with the control group (defined as patients who received standard treatment alone or received less than 3 sessions of hemoperfusion therapy). The primary outcome was daily sequential organ failure assessment (SOFA) scores. Secondary outcomes were all-cause mortality at 28 days, mechanical ventilator-free day, daily C-reactive protein (CRP), oxygenation (defined by PaO₂/FiO₂ ratio), and severity score of lung infiltration on the chest X-ray (CXR RALE score). All outcomes were adjusted by regression analysis to reduce the confounders due to some difference in baseline characteristics. **Results:** A total number of 29 severe and critical COVID-19 confirmed pa-

tients were enrolled. Fifteen patients were defined as hemoperfusion group and 14 were control group. The median of CRP and SOFA score at the baseline (the day after severe pneumonia diagnosis or before hemoperfusion) in hemoperfusion and control groups were comparable, 96.79 mg/L and 87.3 mg/L, $p = 0.53$, 3.53 ± 0.99 versus 4.3 ± 1.89 , $p = 0.15$, respectively. Clinical improvement associated with decreased SOFA score and improvement of CXR RALE score were found in hemoperfusion group compared to control group ($p = 0.008$ and $p = 0.005$, respectively). The 28-day mortality rate was significantly lower in hemoperfusion group compared to control group (6.67% vs. 85.71%, $p < 0.001$) and the adjusted hazard ratio of death was 0.017 (95% confidence interval = 0.008–0.351, $p = 0.008$). **Conclusions:** The addition of early HA-330 hemoperfusion to standard therapy improved severity of organ failure and might reduce the mortality rate. However, the results were affected by the baseline confounders and limited sample size.

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Introduction

COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) has been declared as worldwide emergency outbreak disease. The COVID-19

patients represent a wide spectrum of symptoms ranging from mild to severe forms. Some patients may progress to critical illness due to uncontrolled inflammatory state (also called hyperinflammatory state) contributing to multi-organ failure and death [1].

Hyperinflammatory state caused by uncontrolled overproduction of pro-inflammatory cytokines (esp. interleukin [IL]-1 β , IL-6) can result in multiple organ failure including acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI) and has been associated with high mortality rate [2]. Therefore, immunomodulatory agents such as corticosteroid, tocilizumab might exert an effect in controlling this hyperinflammatory response and provide additional improvements in clinical outcomes [3].

Based on this concept, implementation of extracorporeal therapies to elimination of extra-inflammatory mediators such as hemoperfusion technique can be one of the COVID-19 treatment options. Hemoperfusion devices can adsorb and remove both pro-inflammatory and anti-inflammatory cytokines nonselectively. Thus, these techniques have been advocated as adjunctive treatments in COVID-19 patients to mitigate maladaptive inflammation and prevent multiple organ failure [4].

HA-330 hemoadsorbent which can efficiently eliminate 10–60 kDa molecules [5], including the cytokines IL-6 has been allowed from the Emergency Use Authorization authority to use as a device for treatment of severe COVID-19 with hyperinflammatory state [6]. Here, we performed a prospective cohort study to investigate the efficacy of HA-330 hemoperfusion in combination with standard therapy in severe COVID-19 patients.

Methods

Study Design

We conducted a single tertiary-center prospective cohort study to compare the efficacy of additional hemoperfusion on cases with confirmed SARS-CoV-2 infection (positive reverse transcriptase polymerase-chain-reaction) and admitted in ICU designed for the airborne infection isolation in Nakornping hospital, Chiang Mai, Thailand between April 7, 2021, and May 31, 2021. Only patients who were classified as severe COVID-19 infection and not eligible to inclusion criteria were considered eligible for this study. The study design is presented in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram (online suppl. Fig. S1; see www.karger.com/doi/10.1159/000521713 for all online suppl. material). The study was approved by the Medical Research Committee for Research Ethics of Nakornping hospital (Certificate No. 045164).

Participants

COVID-19 patients were recruited into the study when they met the inclusion criteria. Inclusion criteria were (1) adults ≥ 15 years old with confirmed SARS-CoV-2 infection by reverse transcriptase polymerase-chain-reaction, (2) classified as severe or critical COVID-19 infection according to surviving campaign guideline for COVID-19 first update 2021 [7], (3) diagnosed as severe pneumonia (according to ATS IDSA criteria 2007), (4) hypoxemic respiratory failure with PaO₂ to FiO₂ ratio less than 200, and (5) evidence of systemic inflammation defined as C-reactive protein (CRP) ≥ 30 mg/L. Exclusion criteria were terminal diseases, pregnancy, history of HA-330 allergy, recent myocardial infarction, history of any shock for >12 h after severe pneumonia diagnosis and do-not-resuscitate patients (Fig. 1).

When eligibility criteria were not met, HA-330 hemoperfusion was performed on the same day along with the standard treatment including antiviral agents (mostly remdesivir), corticosteroid, respiratory support, and any other supportive treatments according to standard COVID-19 guidelines. We defined this group as the hemoperfusion group if HA-330 hemoperfusion was performed daily for at least 3 sessions. Patients who received the standard treatment alone or received HA-330 hemoperfusion less than 3 sessions of hemoperfusion were classified as “control group.” The decision to receive HA-330 hemoperfusion was based on the judgment of caregiver team. All patients who received HA-330 hemoperfusion gave informed consent before the first session of procedure.

Treatments

All patients received antiviral agents (mostly remdesivir 200 mg first dose then 100 mg daily dose for 5 days), 6–20 mg per day of dexamethasone and standard of care including oxygen supplementation, noninvasive or invasive mechanical support when indicated. When each patient fits in our inclusion criteria, they were assessed to perform HA-330 hemoperfusion as soon as possible after the diagnosis of severe pneumonia. The patient was administered hemoperfusion through femoral vein at a blood flow rate of 150–200 mL/min. The hemoperfusion cartridge used in our study was performed by Jafron® (HA-330) hemoperfusion machine 4 h per session daily for 3 consecutive days. We used 5,000 IU unfractionated heparin for priming the circuit and closed vital sign monitoring throughout the session. We did not use heparin for loading dose and maintenance of dose with the reason of nursing work load. However, we did not find any premature circuit clotting during our study.

Blood sample was first collected from each patient when severe pneumonia was diagnosed or before 1st session of hemoperfusion and then daily checked until at least day 5 of severe pneumonia or day 5 after the first hemoperfusion. Our blood tests included white blood cell count, absolute lymphocyte count, thrombocyte count, hyperinflammatory markers (CRP, LDH), arterial blood gas, serum BUN/creatinine, and liver function test. Daily chest X-ray also performed and was recorded as severity scoring of lung infiltration on the chest radiograph (CXR RALE score) [8].

Outcome Measures

We observed the clinical progression of severe COVID-19 patients during their hospital admission and compared the outcome between hemoperfusion and control group. The primary outcome was sequential organ failure assessment (SOFA) score on day 3 to day 7 after diagnosis of severe pneumonia. Prespecified secondary outcomes were all-cause mortality during 28 days, timing from

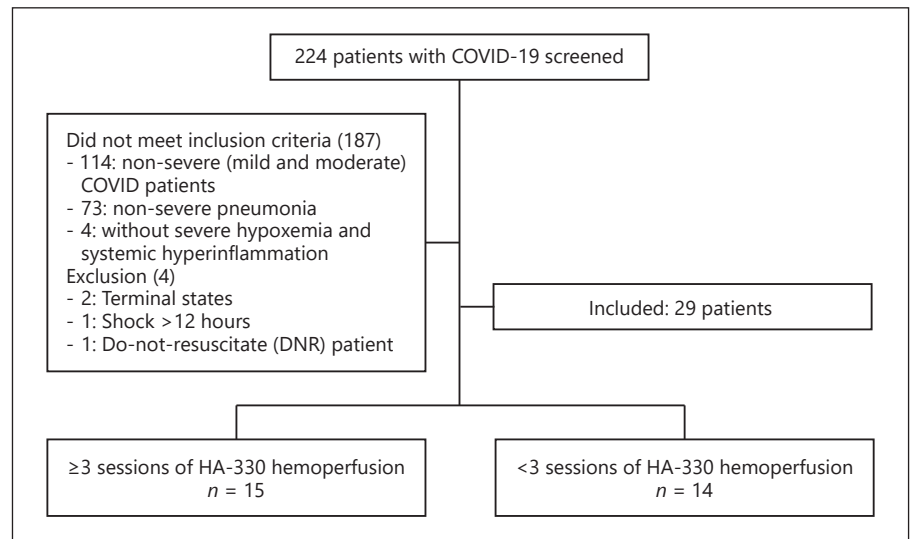


Fig. 1. Flowchart of the study.

ICU admission to intubation, mechanical ventilator-free day, AKI development, and ICU or hospital length of stay. For patients who died, the number of ventilator-free days was 0; for patients who were alive, the ventilator-free days were the days when invasive mechanical ventilation was not required for 28 days. We also monitored daily inflammatory markers (CRP), lung infiltration CXR score (RALE), and oxygenation assessment ($\text{PaO}_2/\text{FiO}_2$ ratio), which were defined as secondary outcomes.

Sample Size Estimation

We used data from a collection of 3 case reports from China by Peng et al. [9] for our sample size calculation. We originally estimated a 2-sided α level of 0.05 and power of 80% to detect a difference of mean SOFA score between before and after 3 sessions of HA-330 hemoperfusion (from 15.45 to 14.25), at least 11 patients in each group were required for an enrollment.

Statistical Analysis

Categorical parameters were summarized as absolute numbers and percentages. Continuous data are shown as mean $\pm$ SD or median + interquartile range. For comparison the non-normal continuous variables, Mann-Whitney U test was used. Fisher's exact test was performed for comparing the frequency of categorical variables.

Four parameters of primary outcomes were analyzed with mixed-effects regression model for 0–7 days repeated measured data including inflammatory marker (CRP), oxygenation level ($\text{PaO}_2/\text{FiO}_2$), infiltration scoring of chest X-ray (RALE score), and organ severity failure (SOFA) and presented with β -coefficient and 95% confidence intervals (CIs) adjusted with potential confounders. For the secondary outcomes of timing from ICU admission to intubation and 28-day mortality, the Cox proportional hazard regression model and Kaplan-Meier curve (with the log-rank test) were also applied to calculate the hazard ratio and 95% CIs adjusted with potential confounders. STATA software (StataCorp LLC, College Station, TX, USA) version 15.1 was used to perform the statistical analyses, and 0.05 was considered as statistically significant level.

Results

Patient Demographics and Clinical Characteristics at Baseline

Of 224 patients who were admitted with COVID-19 infection, 29 patients were classified as severe COVID-19 patients and considered in this cohort (Fig. 2). Nineteen (65.5%) were treated with HA-330 hemoperfusion at least one session, but only 15 (51.7%) patients completely assessed 3 sessions of HA-330 hemoperfusion. The clinical and demographic characteristics are described in Table 1. The mean age was significantly lower in hemoperfusion group compared with control group (54.5 vs. 64.3; $p = 0.046$). Body weight and body mass index in hemoperfusion group were more than control group (79.5 vs. 63.4; $p = 0.009$ and 29.1 vs. 24; $p = 0.003$, respectively). The day from onset and the day from admission to severe pneumonia diagnosis were not different between the groups. We observed significant higher respiratory rate in the hemoperfusion group than the control group suggesting more pronounced respiratory difficulties. The comorbidities between groups were not different. The hemoperfusion group had slightly higher COVID-associated ARDS incidence than the control group without statistical significance (86.7% vs. 64.3%, $p = 0.17$). The severity of ARDS classified according to $\text{PaO}_2/\text{FiO}_2$ was moderate to severe in both groups ($\text{PaO}_2/\text{FiO}_2$: 121.25 vs. 119.5; $p = 0.86$). The mean SOFA score was also comparable in both groups (3.53 vs. 4.3; $p = 0.18$).

Treatment Modalities and Hemoperfusion

The standard treatment including antibiotic agents, antiviral agents, corticosteroids, tocilizumab (anti-IL6),

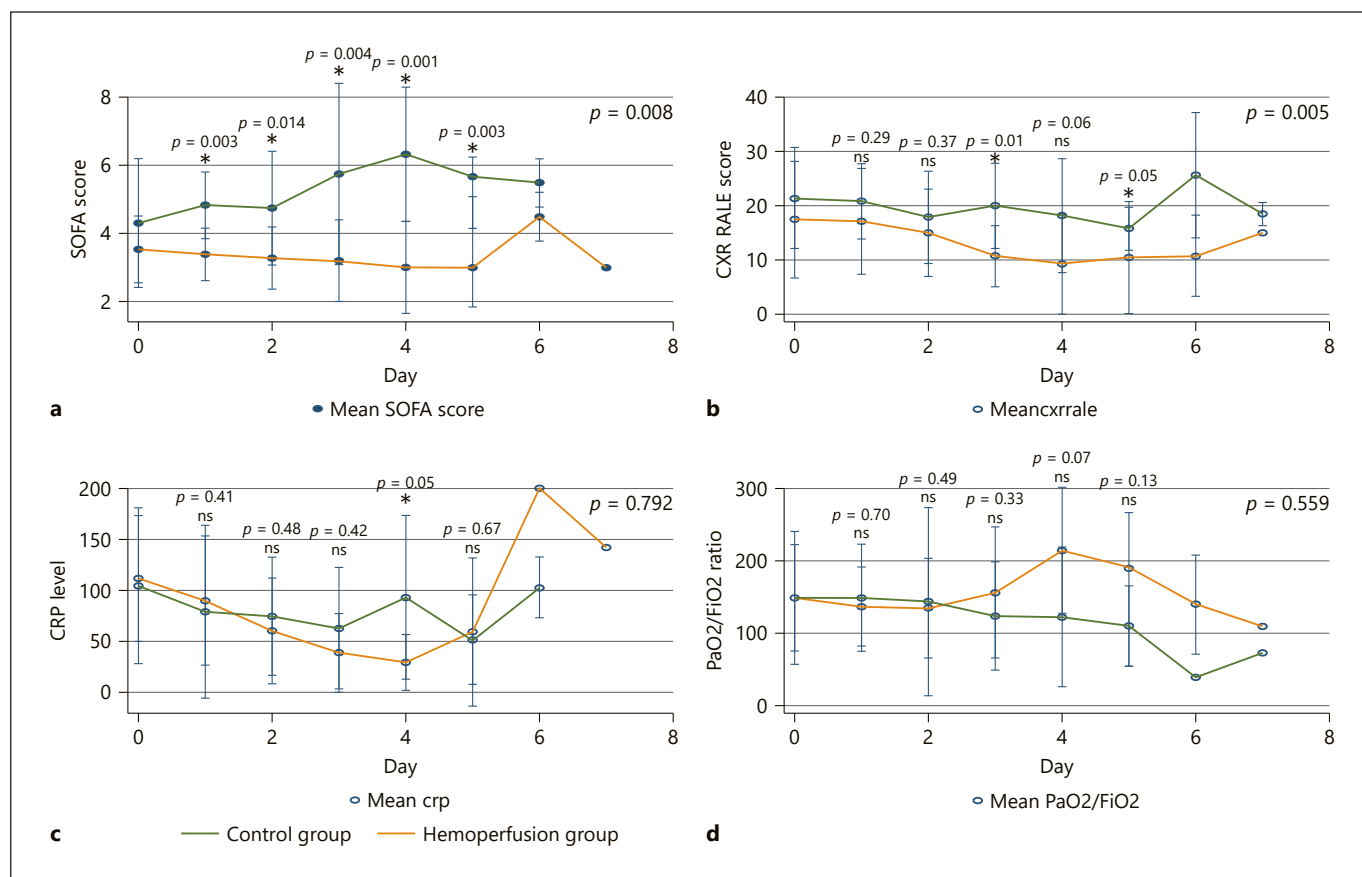


Fig. 2. Longitudinal biomarkers and outcomes of severe COVID-19 patients who completed at least 3 sessions of HA-330 hemoperfusion (hemoperfusion group) compared with control group. **a** Represents SOFA score at day 1 to day 6 comparison between 2 groups with the score statistically significantly lower in hemoperfusion group. **b–d** Represent daily chest X-ray RALE score, CRP level, and PaO₂ to FiO₂ ratio, respectively.

and initial respiratory supports were not different in both groups. HA-330 hemoperfusion option was considered after the diagnosis of severe pneumonia. The median time from severe pneumonia diagnosis to 1st hemoperfusion was shorter in the hemoperfusion group than the control group (24 h vs. 108 h; $p = 0.02$) but the median time from onset or from ICU admission to the first hemoperfusion was not different.

We observed no complication related to bleeding or thromboembolism. There were 3 cases who developed bradycardia and hypotension during the procedure, but these adverse events were mitigated after adequate fluid administration. Two patients experienced shivering during the sessions that were relieved after keeping warm and anti-shivering medication (intravenous chlorpheniramine or pethidine). No life-threatening complications occurred.

Laboratory Tests at Baseline: Inflammatory Markers, Chest X-Ray, and Arterial Blood Gas

Before the first session of hemoperfusion on the day after diagnosis of severe pneumonia, we checked arterial blood gas, blood chemistries (including urea, creatinine, and liver function test), inflammatory markers (CRP, ferritin, and LDH), CBC, and chest X-ray. Only hemoglobin level in hemoperfusion group was higher significantly (14.39 vs. 11.82 g/dL; $p = 0.002$). The rest of parameters were not statistically different.

Clinical Outcomes

Mixed effect model was used to analyze the organ severity failure (SOFA), inflammatory marker (CRP), oxygenation level (PaO₂/FiO₂), and infiltration scoring of chest X-ray (RALE score). Compared with control groups, we observed that complete at least 3 sessions of HA-330

Table 1. Baseline clinical characteristics

Clinical characteristics	Hemoperfusion group (n = 15)	Control group (n = 14)	p value
Male, n (%)	12 (80.0)	7 (50.0)	0.095
Age, year, mean $\pm$ SD	54.5 $\pm$ 14.4	64.3 $\pm$ 10.2	0.046
Height, cm, mean $\pm$ SD	164.8 $\pm$ 8.2	162.1 $\pm$ 8.3	0.40
Body weight, kg, mean $\pm$ SD	79.5 $\pm$ 17.2	63.4 $\pm$ 13.6	0.009
BMI, mean $\pm$ SD	29.1 $\pm$ 4.5	24.0 $\pm$ 3.7	0.003
Day from onset to severe pneumonia diagnosis, day, median (IQR)	5 (3, 9)	7 (4, 8)	0.54
Day from admission to severe pneumonia diagnosis, day, median (IQR)	2 (1, 4)	2 (0, 3)	0.66
Symptoms of COVID, n (%)			
Fever	14 (93.3)	12 (85.7)	0.47
Cough	10 (66.7)	9 (64.3)	0.60
Dyspnea	15 (100.0)	12 (85.7)	0.22
Purulent sputum	2 (13.3)	1 (7.1)	0.53
Sore throat	2 (13.3)	1 (7.1)	0.53
Rhinorrhea	4 (26.7)	0 (0)	0.057
Headache	1 (6.7)	0 (0)	0.52
Muscle pain	2 (13.3)	2 (14.3)	0.67
Fatigue	0 (0)	3 (21.4)	0.100
Nausea/vomiting	0 (0)	2 (14.3)	0.22
Diarrhea	2 (13.3)	1 (7.1)	0.53
Red eye	0 (0)	2 (14.3)	0.22
Anosmia	0 (0)	1 (7.1)	0.48
SARS-COV-2 PCR: cycle time	23.8 $\pm$ 11.9	21.4 $\pm$ 3.9	0.74
Vital signs, mean $\pm$ SD			
SBP, mm Hg	119.4 $\pm$ 18.5	116.3 $\pm$ 20.7	0.67
DBP, mm Hg	71.5 $\pm$ 12.7	69.4 $\pm$ 13.8	0.66
PR (/min)	92.9 $\pm$ 17.6	84.6 $\pm$ 18.3	0.23
RR (/min)	27.5 $\pm$ 7.1	22.7 $\pm$ 5.2	0.047
Body temperature, °C	37.3 $\pm$ 1.1	37.4 $\pm$ 0.9	0.99
Oxygen saturation room air, %, mean $\pm$ SD	85.7 $\pm$ 9.6	84.1 $\pm$ 8.5	0.64
Comorbidities, n (%)			
DM type2	4 (26.7)	5 (35.7)	0.45
Obesity	3 (20.0)	0 (0)	0.13
Hypertension	6 (40.0)	7 (50.0)	0.43
Dyslipidemia	4 (26.7)	1 (7.14)	0.19
CKD	0 (0)	2 (14.3)	0.22
Others	2 (13.3)	3 (21.4)	0.47
Respiratory support at ICU admission, n (%)			
Low flow oxygen cannula	3 (20.0)	2 (14.3)	0.70
Oxygen mask with bag	2 (13.3)	0 (0)	
HFNC	5 (33.3)	6 (42.9)	
NIV	0 (0)	0 (0)	
Invasive mechanical ventilator	5 (33.3)	6 (42.9)	
COVID-associated ARDS (CARD), n (%)	13 (86.7)	9 (64.3)	0.17
COVID ARDS severity, n (%)			
Mild	1 (6.7)	0 (0)	0.25
Moderate	7 (46.7)	3 (21.4)	
Severe	5 (33.3)	6 (42.9)	
PaO ₂ /FiO ₂ (initial ARDS diagnosis), median (IQR)	121.25 (71.2, 177.0)	119.5 (79.9, 160.0)	0.86
Initial ARDS respiratory support			
Low flow oxygen cannula	0 (0)	1 (6.7)	0.11
Oxygen mask with bag	0 (0)	0 (0)	
HFNC	7 (46.7)	2 (14.3)	
NIV	0 (0)	0 (0)	
Invasive mechanical ventilator	5 (33.3)	6 (42.9)	

Table 1 (continued)

Clinical characteristics	Hemoperfusion group (n = 15)	Control group (n = 14)	p value
Antibiotics, n (%)			
No antibiotics	1 (6.7)	6 (42.9)	0.12
Ceftriaxone	6 (40)	2 (14.3)	
Ceftriaxone + azithromycin	5 (33.3)	2 (14.3)	
Piperacillin/tazobactam	1 (6.7)	2 (14.3)	
Meropenem	2 (13.3)	2 (14.3)	
Antiviral agents, n (%)			
Favipiravir 1,600 mg/day	2 (13.3)	6 (42.9)	0.086
Favipiravir 2,000 mg/day	0	0	
Remdesivir	13 (86.7)	8 (57.1)	
Corticosteroid, n (%)			
Dexamethasone 6 mg/day	0	1 (7.1)	0.68
Dexamethasone 12 mg/day	3 (20.0)	6 (42.9)	
Dexamethasone 18 mg/day	0	1 (7.1)	
Dexamethasone 20 mg/day	12 (80.0)	5 (35.7)	
Tocilizumab, n (%)	2 (13.3)	1 (7.14)	0.53
Hemoperfusion, n			
0	0	10	
1	0	4	
2	0	0	
3	10	0	
4	3	0	
5	2	0	
Time from severe pneumonia to first HP, hours, median (IQR)	24 (6, 48)	108 (63, 252)	0.020
Time from onset to 1st hemoperfusion (IQR)	8 (4, 10)	15 (9, 19)	0.15
Time from ICU admission to 1st hemoperfusion (IQR)	1.13 (0.86, 1.92)	0.82 (0.4, 8.9)	0.48
<i>Laboratory test (baseline)</i>			
Arterial blood gases			
PaO ₂ , mm Hg, median (IQR)	70.8 (60, 97)	72 (62.9, 99.4)	0.75
PaCO ₂ , mm Hg, mean (SD)	34.1 (4.3)	34.1 (8.1)	0.98
PaO ₂ /FiO ₂ , median (IQR)	140.7 (78.1, 177)	133 (79.9, 160)	0.73
pH value, mean (SD)	7.42 (0.6)	7.44 (0.06)	0.43
Liver function test, median (IQR)			
Alanine aminotransferase, IU/L	31 (27, 47)	35 (22, 56)	0.97
Alkaline phosphatase, IU/L	66 (57, 113)	59.5 (40, 88)	0.50
Total bilirubin, mg/dL	0.69 (0.38, 0.9)	0.53 (0.35, 0.86)	0.84
Inflammatory markers			
CRP, median (IQR)	96.79 (65, 197)	87.3 (37.6, 185.6)	0.53
Ferritin, median (IQR)	1,544 (1,145, 2,882)	1,214 (985, 2,244)	0.59
LDH, mean (SD)	460.9 (148.7)	525.4 (192.12)	0.37
Complete blood count			
Hemoglobin, g/dL, mean (SD)	14.39 (1.61)	11.82 (2.34)	0.002
White blood cell, median ×10 ³ (IQR)	9.8 (7.7, 12.4)	8.9 (6.7, 12.3)	0.87
Absolute lymphocyte count, median (IQR)	904 (627, 1,147.3)	984 (550.4, 1,193)	0.95
Platelet, median ×10 ³ (IQR)	188 (163, 226)	193 (133–295)	0.95
Renal functions			
Blood urea nitrogen, mg/dL, median (IQR)	18 (12.9, 21)	20 (16.4, 32.3)	0.31
Serum creatinine, mg/dL, median (IQR)	1.03 (0.74, 1.2)	1 (0.81, 1.19)	0.82
Urine output, mL/day, median (IQR)	1,800 (1,400, 2,500)	1,250 (600, 2,300)	0.59
Chest X-ray: RALE score, median (IQR)	16 (8, 25)	22 (15, 27)	0.15
SOFA score, mean ± SD	3.53±0.99	4.3±1.89	0.18
Respiratory SOFA score, mean ± SD	3.07±0.8	2.92±1.04	0.63

IQR, interquartile range; BMI, body mass index; HFNC, high flow nasal cannula; NIV, noninvasive ventilator.

Table 2. Clinical outcomes

Clinical outcomes after HA-330 hemoperfusion (day 4)	Hemoperfusion group (n = 15)	Control group (n = 14)	p value
Primary outcome			
SOFA score (day 3), mean±SD	3.2 (±1.21)	5.75 (±1.21)	0.004
SOFA score (day 4), mean±SD	3 (±1.35)	6 (±1.97)	0.001
Secondary outcome			
CRP level (D3), median (IQR)	26.15 (22.03, 44.97)	39.4 (11.63, 90.77)	0.42
CRP level (D4), median (IQR)	21.6 (13.48, 34.25)	58.99 (25.67, 179.12)	0.049
Chest X-ray pattern by RALE score (day 3), mean (SD)	10.73 (5.65)	20 (7.87)	0.002
Chest X-ray pattern by RALE score (day 4), median (IQR)	6.5 (4, 10)	18 (11, 27)	0.057
PaO ₂ /FiO ₂ (day 3), median (IQR)	132.5 (84.7, 215.25)	101 (67.85, 161.05)	0.33
PaO ₂ /FiO ₂ (day 4), median (IQR)	191.8 (182.74, 235.38)	126.6 (59.7, 126.6)	0.07
Respiratory SOFA (day 3), mean (SD)	2.93 (1.03)	3.25 (0.71)	0.45
Respiratory SOFA (day 4), mean (SD)	2.67 (1.07)	3.33 (1.03)	0.23
AKI on day 3, n (%)	0 (0)	2 (14.29)	0.23
Serum creatinine on day 30 (mg/dL), median (IQR)	0.73 (0.62, 0.81)	1.85 (1.12, 2.58)	0.07
Required mechanical ventilation, n (%)	9 (60)	14 (100)	0.011
	Risk ratio = 0.6 (95% CI 0.397–0.907)		
Time to mechanical ventilation	HR = 0.5 (95% CI = 0.196–1.27), p = 0.15		
Mechanical ventilation-free day, days, median (IQR)	25 (20.29, 30)	0 (0, 0)	0.001
ICU length of stay, days, median (IQR)	9.75 (6, 21.06)	9.03 (5, 14.33)	0.35
Hospital length of stay, days, median (IQR)	15.83 (10, 22.71)	14.36 (9.6, 20.75)	0.41
ICU mortality, n (%)	2 (13.33)	12 (85.71)	<0.001
	Risk ratio = 0.16 (95% CI 0.42–0.58)		
Hospital mortality, n (%)	2 (13.33)	13 (92.86)	<0.001
	Risk ratio = 0.14 (95% CI 0.04–0.53)		
28-day mortality, n (%)	1 (6.67)	12 (85.71)	<0.001
	Risk ratio = 0.08 (95% CI 0.012–0.523)		
	HR = 0.033 (95% CI = 0.004–0.264), p = 0.001		

IQR, interquartile range; HR, hazard ratio.

hemoperfusion (hemoperfusion group) was associated with decreased SOFA score and improved chest X-ray infiltration (decreased RALE score) significantly by using mixed effect model repeated measurement with baseline variable adjustment (Adj. β -coefficient = -1.28 ; $p = 0.008$ and Adj. β -coefficient = -6.93 ; $p = 0.005$, respectively). CRP and level of hypoxemia (PaO₂ to FiO₂ ratio) also showed clinical improvement in the hemoperfusion group, but they could not reach statistical significance (Adj. β -coefficient = -6.93 ; p value = 0.005 and Adj. β -coefficient = 15.86 ; $p = 0.56$, respectively). On day 30, we found that median serum creatinine level of hemoperfusion group tend to lower than control group without statistical difference ($p = 0.07$) (Table 2). All of outcome parameters were shown in Table 2 and Figure 2a–d.

To evaluate the efficacy of at least 3 sessions HA-330 hemoperfusion (hemoperfusion group) on 28-day mortality, log-rank test and cox-regression analysis were conducted on survival time of severe and critical COVID-19

patients. After variable adjustment, the hazard ratio for 28-day mortality was 0.033 (95% CI = 0.004 – 0.264 , $p = 0.001$). The Kaplan-Meier curve indicated that cumulative survival was higher in hemoperfusion group compared to control group (as shown in Fig. 3a). We also found that patients in this group had more mechanical ventilator-free day (median 25 days vs. 0 day, $p = 0.001$). The Kaplan-Meier curve indicated that cumulative intubation rate had a trend to lower in hemoperfusion group compared to control group (as shown in Fig. 3b). AKI was not statistically different in both groups (0% vs. 14.29% , $p = 0.22$).

Discussion

In summary, patients who received at least 3 sessions of HA-330 hemoperfusion (hemoperfusion group) exhibited lower organ failure severity (decreased SOFA score), im-

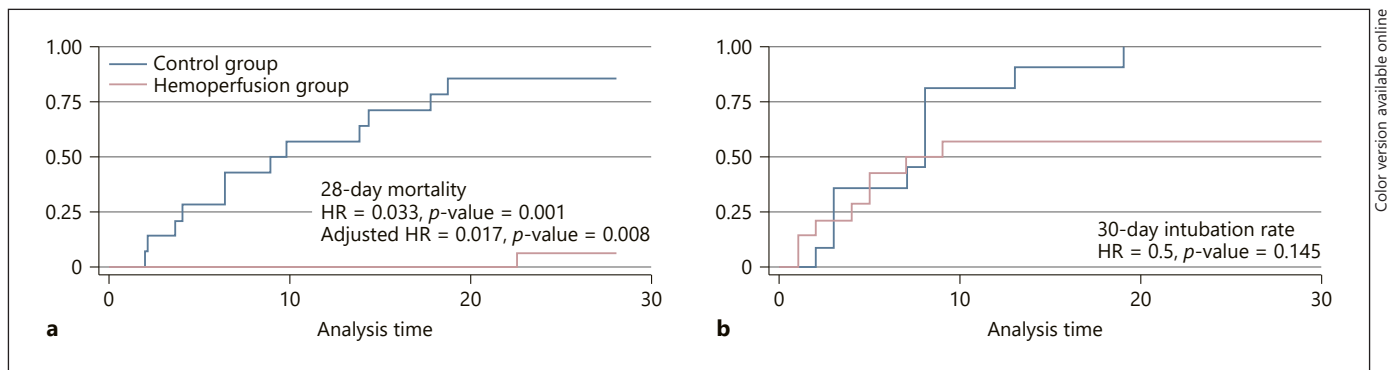


Fig. 3. The Kaplan-Meier curve for cumulative 28-day survival (**a**) and 30-day intubation rate (**b**) of patients in hemoperfusion group versus control group.

provement of chest X-ray infiltration, decreased hyperinflammatory marker (CRP) compared to control group (Fig. 2a–c; Table 2). Our interesting findings were lower 28-day mortality and higher mechanical ventilator-free day that were observed among the patients in hemoperfusion group (Fig. 3a–b; Table 2). These outcomes can be explained by the improvement of hyperinflammatory state that resulted in mitigating of organ failure and reduction in mortality rate eventually. Severe COVID-19 usually presents as acute severe pneumonia from developing a dysregulated immune response like sepsis. This overwhelming hyperinflammatory response is termed “cytokine storm” that characterized by high levels of pro-inflammatory cytokines (e.g., IL-1 β , IL-6, and TNF) and correlated directly with the severity of lung injury in patients with severe COVID-19 [9, 10]. The hyperinflammatory state is associated with multi-organ dysfunction including AKI, ARDS, etc. and correlated with poor outcomes. To mitigate excessive inflammation, the use of hemoperfusion to remove pro-inflammatory cytokines from the blood is one of potential approach [11]. In this form of extracorporeal blood purification, the patient’s blood is circulated through a sorbent containing column with nonselectively adsorbs, and therefore removes endogenous and exogenous molecules, usually targeting cytokines, endotoxin, pathogens, or combination, depending on the type of sorbent. HA-330 includes a neutral microporous resin that adsorbs pro-inflammatory cytokines such as TNF- α , IL-1, IL-6 [12]. Using HA-330 as hemoperfusion may be beneficial for the treatment of COVID-19 cytokine storm and may result in decreased mortality [13]. There are some studies which have the positive effects of hemoperfusion in COVID-19 patients [14]. In Esmaeili Vardanjani et al. [15] study, hemoperfusion with CRRT was effective in

ceasing ARDS progression, decreasing intubation, and reducing the mortality. In the study of De Rosa et al. [16] study, hemoperfusion with polymyxin was associated with organ failure recovery and hemodynamic improvement. Our study has the same results as the previous studies. The mortality rate was significantly lower in hemoperfusion group. Furthermore, it was observed that intubation rate might be reduced significantly after performing hemoperfusion in COVID-19 patients using high flow nasal cannula or noninvasive ventilation. Our study outcome contrast to the recent trial by Supady et al. [17], which explored the effect of hemoperfusion in the severe COVID-19 patients requiring ECMO support. In this study, the hemoperfusion group has significant lower survival rate compared to the control group, 18% versus 76%, $p = 0.0075$. The result of this study might emphasize that timing of hemoperfusion and severity of patients are the key factors for patient selection. The effect of earlier hemoperfusion therapy in less severity COVID-19 patients should be explored more in the future trial. Our strength in this study was the pragmatic design that was conducted as same as real-life practice. We also prospectively observed daily parameters to compare the outcomes between 2 groups. In addition, considering several factors (such as high costs of hemoperfusion cartridges, stability of patients, availability of the ICU teams), we could not implement this treatment option for every patient and may become bias of our study. However, we had adjusted some different of baseline variables using regression analyses that should affirm more reliable of study results. There are some limitations in this study. First, this study was not a randomized control trial. We decided to conduct prospective cohort study instead of using randomized study design because the critical COVID-19 patients usually need-

ed prompt decision with early treatment in order to stop the disease progression. The high cost of HA-330 hemoperfusion was also another barrier of conduction RCT design especially limited resource setting. Therefore, the prospective study with regression analysis for comparing 2 groups of patients was practical, feasible, and may be another choice to apply the novel treatment in real clinical practice during the pandemic. Second, with the limitation of study which was not randomized controlled trial, the selection bias may be unavoidable as indicated in some imbalance of prognostic factors at the baseline. However, the severity score (SOFA score) at the time of treatment initiation between both groups was comparable. Third, the IL-6 level could not be checked in this study because of test unavailability in our center which might have some affect if it is found differences between groups. Fourth, only one type of hemoperfusion cartridge (HA-330) was used due to lack of accessibility to other types of cartridges at the study period. Fifth, it is still unclear for the optimal sessions of hemoperfusion. We set at least 3 sessions of hemoperfusion based on the duration of severe COVID-19 was in the range of 72 h. Currently, we still do not know the optimal session and duration of HA-330 hemoperfusion. We performed 2 additional analyses. The first analysis was the comparison between patients with any sessions of hemoperfusion versus no hemoperfusion and the second one was the comparison between patients with at least 3 sessions of hemoperfusion versus no hemoperfusion. The mortality outcomes were still better in hemoperfusion group than no hemoperfusion group in both analyses (online suppl. Fig. S2, S3). We also stratified the number of hemoperfusion by study group in online supplementary Table S1.

Conclusions

In severe COVID-19 patients, the addition of at least 3 sessions of HA-330 hemoperfusion to standard-19 therapy improved severity of organ failure and might reduce the mortality rate. However, the results were affected by the baseline confounders and limited sample size. Future large-scale RCT is needed to confirm the conclusion.

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Statement of Ethics

The study was reviewed and approved by the Medical Research Committee for Research Ethics of Nakornping hospital (Certificate No. 045164). The investigators informed patients or their surrogates concerning the study orally and written informed consent were given before entry into the study.

Conflict of Interest Statement

None of the authors have any conflicts to disclosure.

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Author Contributions

K.S. and N.S. were responsible for study concept and design. K.S. was responsible for the acquisition, analysis, or interpretation of data. K.S. and N.S. were responsible for drafting the manuscript. K.S. and N.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. K.S. and N.S. interpreted the findings, contributed to writing the manuscript, and approved the final version for publication.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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