"Early Hemoperfusion Application in Severe and Critical COVID-19 Treatment : a Randomized, Controlled Trial"

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Abstract:

Background: Hemoperfusion is an extracorporeal apheresis method widely used in combination therapy for severe forms of COVID-19. However, limited evidence from randomized clinical trials exists to support this practice.

Methods: In this single-center study, patients with severe COVID-19 requiring ICU admission were randomly assigned (1:1) to receive HA-330 hemoperfusion in combination with standard severe COVID-19 treatment (Intervention group) or standard therapy alone (Control group). Both groups received tocilizumab intravenously if their clinical conditions worsened within 24 to 48 hours. The primary outcome was mortality from any cause within 28 days after randomization. Secondary outcomes included mechanical ventilator-free days, daily C-reactive protein (CRP) levels, oxygenation (defined by PaO2/FiO2 ratio), daily sequential organ failure assessment (SOFA) score, and severity score of lung infiltration on chest X-rays (CXR RALE score).

Results: A total of 28 patients underwent randomization, with 14 (50%) receiving HA-330 hemoperfusion and 14 (50%) without it. Within 24 to 48 hours, only 9 out of 14 patients (64.3%) in the control group experienced clinical worsening and were subsequently administered intravenous tocilizumab. At 28 days after randomization, the mortality rate was significantly lower in the intervention group compared to the control group (28.57% vs. 78.57%, p=0.021), with a hazard ratio of death of 0.26 (95%

confidence interval = 0.08-0.8, p=0.021). The median mechanical ventilator-free days, daily CRP levels, SOFA score, and CXR RALE score were comparable in both groups.

Conclusion: Among patients with severe forms of COVID-19, the early application of HA-330 hemoperfusion might reduce the mortality rate. However, these results should be further confirmed in a large-scale study.

Trial registration: Thai Clinical Trials Registry (TCTR20211102004). Registered on November 2, 2021.

Keywords: Hemoperfusion. Extracorporeal apheresis. COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been identified as the cause of coronavirus disease 19 (COVID-19), which is currently recognized as a worldwide emergency outbreak disease [1]. COVID-19 presents with a wide spectrum of symptoms, ranging from mild to severe illness. Patients with severe forms of COVID-19 may develop serious conditions of uncontrolled systemic hyperinflammation due to an overproduction of pro-inflammatory cytokines (especially tumor necrosis factor-alpha [TNF-α], interleukin [IL]-1β, IL-6), leading to acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), multiple organ failure (MOF), and even death [2]. Therefore, several treatments based on reducing cytokine signaling pathways, such as corticosteroids, interleukin (IL)-1, IL-6, and Janus Kinase (JAK) inhibitors, have been used with promising results and have provided better clinical outcomes [3].

Extracorporeal blood purification (EBP) using different methods, such as the hemoperfusion technique, is proposed as a promising therapy for the elimination of inflammatory mediators in an effort to restore immune balance [4]. Recently, they have been suggested in the consensus conference of Acute Disease Quality Initiative as possible adjuvant therapeutic tools in critically ill COVID-19 patients [5].

HA-330 hemoadsorbent is a synthetic resin hemofilter composed of polystyrene divinylbenzene copolymer developed to non-selectively eliminate 10-60 kDa molecules, including interleukin (IL)-6 [6]. As shown in previous observational and prospective cohort studies [7,8], the early use of HA-330 perfusion in addition to standard therapy improves organ failure outcomes and may indirectly reduce the mortality rate. However, the lack of confirmation by randomized control studies complicates the interpretation of these results.

Based on these considerations, we performed an open-label, randomized, controlled trial to evaluate the efficacy of early additional HA-330 hemoperfusion therapy compared to standard therapy for severe and critical COVID-19 patients in a single referral center in Thailand.

Methods

Study Design

We conducted a single tertiary-center, open-label, randomized, controlled trial to demonstrate the efficacy of additional hemoperfusion in severe COVID-19 patients. All adult patients (≥15 years of age) who were confirmed to have SARS-CoV-2 infection and were admitted to the ICU designated for airborne infection isolation at Nakornping Hospital, Chiang Mai, Thailand, between November 8, 2021, and May 31, 2022, were

considered eligible for this study. The study protocol and all other relevant documents were reviewed and approved by an institutional review board and the Medical Research Committee for Research Ethics of Nakornping Hospital (Certificate No. 105/64). The trial was registered with the Thai Clinical Trials Registry (TCTR20211102004) on November 2, 2021.

Participants

Eligible participants were recruited into the study when they met all of the inclusion criteria. The inclusion criteria were as follows: 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 according to the Surviving Sepsis Campaign guideline for COVID-19, first update 2021 [9],3) received intravenous remdesivir and corticosteroids (at least 6 mg/day of dexamethasone) for more than 24 hours, 4) evidence of a hyperinflammatory state, defined as C-reactive protein (CRP) ≥ 75 mg/L or serum ferritin ≥ 300 ng/mL or serum interleukin [IL]-6 level ≥ 20 pg/mL, 5) evidence of arterial hypoxemia, defined as PaO2 / FiO2 ≤ 300 and/or room air pulse oxygen saturation < 92%.

Exclusion criteria included terminal diseases, pregnancy, a history of HA-330 allergy, recent myocardial infarction, and do-not-resuscitate patients.

The research was carried out in accordance with a named standard. In case, the patients were unstable and they were unable to provide informed consent, legal representatives were informed and had to give consent before the initiation of randomization.

Randomization and Masking

All participants were randomly assigned (1:1) to receive either early additional HA-330 hemoperfusion with standard severe COVID-19 therapy or standard therapy alone. The block randomization method was used to randomize subjects into two equal groups, using a block size of four. Allocation was controlled by other investigators who were not involved in the COVID-19 ICU team and concealed using opaque numbered sealed envelopes. Further details are described in the study protocol.

Due to impracticability for a blinding procedure, neither participants nor care providers were masked to the treatment.

Treatment and Procedures

After initiating standard treatment, which included intravenous remdesivir, at least 6 mg per day of dexamethasone, intravenous antibiotics for empirical severe bacterial pneumonia treatment, and standard supportive care (including oxygen supplementation, standard venous thromboembolism prophylaxis, and noninvasive or invasive mechanical support when indicated), HA-330 hemoperfusion was applied in the intervention group within 8 hours after randomization. Femoral or internal jugular venous catheterization was performed in this group, and hemoperfusion was started at a blood flow rate of 150-200 ml/min. The hemoperfusion cartridge used in this study was the Jafron® (HA-330) hemoperfusion machine, administered 4 hours per session daily for 3 consecutive days. Before connection to the participants, we used 5000 IU unfractionated heparin to prime the circuit. Most of the patients received systemic

anticoagulant for venous thromboembolism prophylaxis, Therefore, there was no systemic anticoagulant administration during the hemoperfusion treatment.

Each participant in both groups was closely monitored throughout 24-48 hours after randomization. If their clinical status worsened, defined as a deterioration of hypoxemia (reduction of PaO2/FiO2 or oxygen saturation from baseline), an increase in CRP levels, or a 50% increase in pulmonary infiltrates, the monoclonal antibody-based (anti-IL-6 receptor antibody) therapy tocilizumab was administered intravenously at a dose of 400-800 mg (depending on weight) as soon as possible. The study protocol is briefly demonstrated in Figure 1.

Daily blood samples were collected, and chest imaging was performed for each patient from randomization until at least 5 days after protocol initiation. Our blood tests included white blood cell count, absolute lymphocyte count, thrombocyte count, hyperinflammatory markers (CRP, LDH, ferritin), arterial blood gas, serum BUN/Creatinine, and liver function tests. The severity of chest imaging was recorded daily using the CXR RALE score [10], which was interpreted by a single investigator.

Outcome measures

The primary efficacy endpoint was mortality from any cause within 28 days after randomization. Secondary endpoints included the sequential organ failure assessment (SOFA) score, C-reactive protein (CRP) levels, oxygenation (defined by the PaO2/FiO2 ratio), severity score of lung infiltration on the chest X-ray (CXR RALE score) after 24, 48, 72, 96, and 120 hours, development of acute kidney injury (AKI) at 72 and 144 hours, ICU or hospital length of stay, and mechanical ventilator-free days.

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 within the 28-day period.

Sample Size Estimation

Based on our previous prospective cohort study [8], the 28-day mortality rate of patients with severe COVID-19 could be reduced by 96.7% (Hazard ratio 0.033) after the addition of HA-330 adsorption to standard therapy. We estimated a 2-sided α level of 0.05 and a power of 80% to detect a difference in the 28-day mortality rate between the interventional group and the control group after using HA-330 hemoperfusion.To account for a potential 20% dropout rate, at least 12 patients will be recruited per each group. We planned to perform a prespecified interim efficacy when the first 6 randomized patients had been followed through day 28.

Statistical Analysis

Descriptive demographics of the patient population were calculated for each group. Categorical parameters were reported as absolute numbers and percentages. Continuous data were presented as mean ± SD or median with interquartile range (IQR). To compare non-normally distributed continuous variables, the Mann–Whitney U test was used. Fisher's exact test was performed to compare the frequency of categorical variables. Intention-to-treat analysis was used to report the efficacy outcome.

The time-to-event analysis of the primary outcome, 28-day mortality, was performed using the Cox proportional hazard regression model and Kaplan-Meier curve (with the log-rank test). The test for a difference between treatment groups was based on the corresponding two-sided 95% confidence interval (CI). At the time of the interim efficacy analysis, a two-sided P value of less than 0.05 was needed to demonstrate early efficacy (superiority of hemoperfusion group over control group). Four parameters of secondary outcomes were analyzed using a mixed-effects regression model for 0-7 days of repeated measured data, including inflammatory marker (CRP), oxygenation level (PaO2/FiO2), chest X-ray infiltration score (RALE score), and sequential organ severity failure (SOFA).

STATA software (StataCorp LLC, College Station, TX, USA) version 15.1 was used to perform the statistical analyses, and a significance level of 0.05 was considered statistically significant.

Results

Patient demographics and clinical characteristics at baseline:

Of 270 patients with severe COVID-19 admitted to the ICU were screened, only 28 patients were finally included in the intention to treat analysis, as shown in Figure 2. Fourteen (50%) of the 28 patients were randomly assigned to receive early HA-330 hemoperfusion in combination with standard therapy, while the other 14 (50%) continued with standard therapy without HA-330 hemoperfusion.

The baseline characteristics of the participants in the two groups were balanced (Table 1). Approximately 80% of the trial population was male. The mean age of the

study participants was 65 years, with no significant difference between both groups. The most common coexisting condition was hypertension (50%). Other patient demographics, including height, body mass index (BMI), symptoms at admission, vital signs, and oxygen saturation, showed no significant difference between both groups. The median time from diagnosis to randomization was 3.5 days. COVID-associated acute respiratory distress syndrome (ARDS) based on the Berlin definition [11] was presented in 64.3% of the participants. The mean severity of ARDS, classified according to PaO2/FiO2, was moderate to severe (PaO2/FiO2 = 114.7). Approximately 80% of these patients required invasive mechanical ventilation at the initial ICU admission.

Laboratory tests at baseline: inflammatory markers, chest x-ray

After randomization, we conducted tests for arterial blood gas, blood chemistries (including urea, creatinine, and liver function tests), complete blood count (CBC), chest X-ray, and inflammatory markers (including CRP, ferritin, LDH, and IL-6 levels). The mean CRP level was 125.2 mg/L, and the mean IL-6 level was 162.7 pg/mL, with no significant difference between both groups. The remaining parameters were balanced and showed no statistically significant differences.

Treatment modalities and hemoperfusion

At baseline, all patients were receiving intravenous remdesivir, corticosteroids (at least 6 mg/day of dexamethasone), and prophylactic anticoagulation. Among them, 64.3% were being supported with invasive mechanical ventilation, and 25% were on high-flow nasal cannula therapy. In the intervention group, HA-330 hemoperfusion was

applied early after randomization. The mean time from severe pneumonia diagnosis to the first hemoperfusion was 28.9 hours.

After randomization, the clinical worsening was closely monitored. Only 9 out of 14 patients (64.3%) in the control group showed deterioration within 24 to 48 hours, and as a result, tocilizumab was administered intravenously at a dose of 400-800 mg (depending on weight). The mean time for tocilizumab prescription in these participants was 37.2 hours.

No immediate complications related to hemoperfusion, such as local puncture site bleeding and thromboembolism, occurred. Transient hypotension during the procedure was experienced by 2 participants, but these adverse events were relieved after fluid resuscitation. Furthermore, no life-threatening complications were observed in both groups.

Clinical outcomes

Results for the primary and secondary outcomes are shown in Table 2. Death from any causes through day 28 occurred in 28.6% of the patients in the intervention group and 78.6% of those in the control group (Hazard ratio = 0.26 [95% CI = 0.08 – 0.81; P=0.021]). The Kaplan-Meier curve indicated that cumulative survival was higher in the intervention group compared to the control group (as shown in Figure 3). The ICU mortality was also lower in the hemoperfusion group (Hazard ratio = 0.25 [95% CI = 0.067 – 0.929; P=0.039]), but the hospital mortality in the hemoperfusion group showed improvement without statistical significance (Hazard ratio = 0.38 [95% CI = 0.136 – 1.06; P=0.065]). The median number of ventilator-free days at 28 days after

randomization was 18.6 days (IQR 0-29.4), with no statistical difference between both groups.

Regarding secondary outcomes, the mixed effect model was used to analyze the sequential organ failure assessment (SOFA) score, inflammatory marker (CRP), oxygenation level (PaO2/FiO2), and chest X-ray infiltration scoring (RALE score). During the 7 days of treatment, these clinical parameters in both groups improved without statistical difference, as shown in Table 2 and Figure 4.

As for safety outcomes, we found that the incidence of nosocomial infection was higher in the control group without statistical significance (28.5% vs. 35.7%, p=1.0). The incidence of acute kidney injury at day 3 and day 6 after randomization was also not different in both groups.

Discussion

Some patients with severe COVID-19 may progress to critical illness due to an uncontrolled inflammatory state contributing to multi-organ failure and death [2]. In this randomized, controlled trial, early additional HA-330 hemoperfusion application in severe COVID-19 resulted in reduced 28-day mortality compared with the control group (28.6% vs. 78.6%, Hazard ratio = 0.26; P=0.021). This finding was consistent with the hypothesis of a treatment benefit from extracorporeal apheresis in the treatment of the hyperinflammatory state in severe COVID-19 [12]. Compared with the control group, which included approximately 60% of patients who received intravenous tocilizumab due to clinical deterioration, hemoperfusion also exhibited lower hyperinflammatory cytokine levels (CRP), reduction of chest X-ray infiltration, and improvement of arterial hypoxemia (increased PaO2/FiO2 ratio) without statistical difference. We also found a

higher incidence of nosocomial infection after treatment in the control group than the hemoperfusion group, but this adverse outcome could not reach statistical significance (28.5% vs. 35.7%, p=1.0). These favorable outcomes can be explained by lower clinical deterioration and incidences of superimposed infection after treatment in the hemoperfusion group compared with the control group.

Hemoperfusion can remove inflammatory markers and consequently reduce plasma cytokine levels through hemoadsorption into either charcoal or resin beads contained in an adsorbent cartridge. This technique can be used in selected patients with systemic inflammatory syndrome, such as refractory septic shock or severe COVID-19 [13,14]. The HA-330 hemofilter, composed of neutral microporous resin that adsorbs pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, showed favorable outcomes in severe or critical cases of COVID-19 [15]. In our previous study [8], the early use of HA-330 hemoperfusion in addition to standard therapy improved organ failure outcomes and might reduce the mortality rate. However, our study had limitations for interpretation due to the small sample size and lack of confirmation by randomization. On the other hand, a recent trial by Supady et al. [16], which studied the efficacy of hemoperfusion in severe COVID-19 patients requiring ECMO support, had a significantly lower survival rate compared to the control group (18% vs. 76%, p=0.0075). This unfavorable outcome may have resulted from high severity of the COVID-19 patients and the delayed hemoperfusion at the time of initiation. Thus, it is reasonable to assume that considering the timing of hemoperfusion and the severity of the disease could benefit the selected COVID-19 patients.

The strengths of our study include the prospective randomized controlled design and completion of 28-day follow-up in all participants. The study was also conducted using a personalized approach and designed according to real-life practice. All treatment decisions were controlled by a COVID-19 expert blinded to the treatment allocation. However, there are some limitations. First, this randomized, controlled trial was open-label, which may have introduced ascertainment bias during the treatment process. Nevertheless, we used the same treatment protocol conducted and adjusted by only one COVID-19 expert due to the impracticality of making the design double-blinded. Second, the IL-6 level was not checked daily due to the lack of benefit for monitoring from a previous study [16]. We still suggest that appropriate surrogate markers, such as CRP, chest imaging, and arterial oxygenation, are well-correlated with clinical manifestation after treatment. Third, the sample size was still small due to the limitation of hospital facility. However, the number of participants was still adequate to evaluate the clinical outcomes definitively. Fourth, only one type of hemoperfusion cartridge (HA-330) was used due to the lack of accessibility to other types. Finally, our study could not compare the efficacy of intravenous tocilizumab with hemoperfusion. The mean time from severe pneumonia diagnosis to tocilizumab initiation was approximately an 8-hour delay compared to the hemoperfusion group, which may have affected this study's outcome.

Conclusion:

In patients with severe forms of COVID-19, the early application of HA-330 hemoperfusion may reduce the mortality rate. However, this result should be further confirmed in a large-scale study.

Declarations

Ethical Approval

Ethics approval was obtained from an institutional review board and the Medical Research Committee for Research Ethics of Nakornping Hospital (Certificate No. 105/64). Written inform consent or agreement to participate was obtained from each patient or the patient's surrogate.

Author contributions

KS, NS helped in conceptualization. KS, NS contributed to methodology. KS conducted study and data collection. KS contributed to data analysis. KS, NS helped in writing—original draft preparation. KS, NS contributed to writing—review and editing. NS helped in supervision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Table 1. Baseline clinical characteristics

Clinical characteristics	Hemoperfusion group (n=14)	Control group (n=14)	p-value
Male Gender n (%)	9 (64.3%)	13 (92.9%)	0.17
Age（yr）, mean ± SD	64.4 ± 12.2	65.8 ± 12.4	0.38
Height（cm）, mean ± SD	160.5 ± 5.2	161.8 ± 8.7	0.32
Body weight（kg）, mean ± SD	59.8 ± 13.9	57.4 ± 13.1	0.68
Body mass index（BMI）, mean ± SD	23.3 ± 6.1	21.9 ± 4.3	0.77
Day from onset to pneumonia diagnosis (Day), median (IQR)	2 (1,4)	2 (1,5)	0.72
Day from admission to pneumonia diagnosis (day), median (IQR)	1.5 (0,4)	0 (0,1)	0.055
Day from diagnosis to randomization (day), median (IQR)	3.5 (2,6)	3.5 (2,5)	0.89
Symptoms of COVID, n (%)			
- Fever	9 (64.3%)	10 (71.43%)	1.0
- Cough	7 (50%)	10 (71.43%)	0.44
- Dyspnea	14 (100%)	13 (92.86%)	1.0
- Purulent sputum	3 (21.43%)	2 (14.29%)	1.0
- Sore throat	0 (0 %)	3 (21.43%)	0.22
- Rhinorrhea	1 (7.14%)	0 (0 %)	1.0
- Muscle pain	1 (7.14%)	0 (0 %)	1.0
Vital signs, mean ± SD			
- SBP (mmHg)	138.4 ± 25	122.8 ± 21.6	0.96
- DBP (mmHg)	79.1 ± 14.4	70.9 ± 9.7	0.96
- PR (/min)	89.6 ± 26.6	102.3 ± 30.4	0.09
- RR (/min)	31 ± 21.2	28.1 ± 7.21	0.68
- Body temperature (^{o}C)	36.9 ± 1.1	37 ± 1.0	0.47
- Oxygen saturation room air (%), mean ± SD	83.1 ± 7.95	79.4 ± 13.6	0.81
Comorbidities, n (%)			
- DM type2	6 (42.86%)	6 (42.86%)	1.0
- Hypertension	8 (57.14%)	6 (42.86%)	0.71
- Dyslipidemia	3 (21.43%)	3 (21.43%)	1.0
- COPD	2 (14.29%)	0 (0%)	0.48
- CKD	3 (21.43%)	4 (28.57%)	1.0
- Others	7 (50%)	6 (42.86%)	1.0
Respiratory support at ICU admission, n (%)			0.52
- Low flow oxygen cannula	-	-	
- Oxygen mask with bag	1 (7.14%)	2 (14.29%)	
- High flow nasal cannula (HFNC)	5 (35.71%)	2 (14.29%)	
- Non-invasive ventilator (NIV)	-	-	

- Invasive mechanical ventilator	8 (57.14%)	10 (71.43%)	
Invasive mechanical ventilation , n(%)	10 (71.43%)	11 (78.57%)	1.00
COVID-associated ARDS (CARD), n (%)	10 (71.43%)	8 (57.14%)	0.70
COVID ARDS Severity, n (%) - Mild - Moderate - Severe	 0 7 (63.64%) 3 (27.27%)	 1 (12.50%) 4 (50 %) 3 (37.50%)	0.60
PaO2 / FiO2 (Initial ARDS diagnosis)**,** median (IQR)	126.45 (96.1 , 147.7)	99.98 (54 , 172.4)	0.86
Initial ARDS respiratory support - High flow nasal cannula (HFNC) - Invasive mechanical ventilator	 1 (10%) 4 (40%)	 1 (12.50%) 6 (75%)	0.22
Antibiotics, n (%) 1 = Cef-3 + azithromycin 2 = Meropenem + azithromycin 3 = meropenem	 6 (42.86%) 3 (21.43%) 5 (35.71%)	 4 (28.57%) 3 (21.43%) 7 (50%)	0.88
Remdesivir (n%) - Time from severe pneumonia , median IQR (hours)	14 (100%) 1 (1 , 2)	14 (100%) 1.125 (1 , 4.33)	0.57
Corticosteroid, n (%) - Dexamethasone 12 mg/day - Dexamethasone 20 mg/day - Hydrocortisone 100 mg IV q 8 hr **- Time from severe pneumonia (hours)** , median IQR (hours)	14 (100%) 1 (7.14%) 13 (92.86%) 0 1.25 (1 , 11)	14 (100%) 0 13 (92.86%) 1 (7.14%) 1.125 (1 , 8.5)	1.00 0.85
Baricitinib (n%)	2 (15.38%)	1 (7.14%)	0.60
Hemoperfusion, n (%) severe pneumonia to first HP , mean ± SD (hours)	14 (100%) 28.9 ± 14	- -	
Tocilizumab (n%) - Time from severe pneumonia , mean ± SD (hours)	0 (0%) -	9 (64.3%) 37.18 ± 15	0.001
Laboratory test (Day0)			
Arterial blood gases - PaO_2 (mmHg), median (IQR) - $PaCO_2$ (mmHg) , mean ± SD - PaO_2 / FiO_2 , median (IQR) - pH value, median (IQR)	 91.85 (76 , 150.5) 32.7 ± 8.7 155.55 (126.7 , 221) 7.435 (7.399,7.483)	 73.6 (49.3 , 102.7) 33 ± 6.1 130.25 (75.8 , 307) 7.368 (7.317,7.454)	 0.27 0.45 0.49 0.06
LFT , median (IQR) - Alanine aminotransferase (IU/L) - Alkaline phosphatase (IU/L),	 27 (19 , 40) 73 (54 , 99)	 40 (23 , 84) 91.5 (76 , 176)	 0.08 0.01

- Total bilirubin (mg/dL)	0.46 (0.35,0.56)	0.995 (0.76,1.54)	0.01
- C-reactive protein (mg/L), mean ± SD	120.2 ± 42.1	130.2 ± 51.1	0.29
- Ferritin, median (ng/mL) (IQR)	1,296 (455 , 1824)	1,399 (1024 , 1810)	0.41
- LDH, median (U/L) (IQR)	406 (289 , 485)	433 (352 , 539)	0.21
- Fibrinogen, (mg/dL) mean ± SD	516.9 ± 122	401.9 ± 180.1	0.94
- Interleukin-6 (pg/mL) , median (IQR)	49.3 (16.1,469.2)	276.1 (121,2071)	0.07
Complete blood count (Day0)			
- WBC, median (IQR)	8,850 (8000 , 10500)	11,800 (7800,16100)	0.53
- Absolute lymphocyte count , median (IQR)	801.9 (714,1067)	545.6 (360.5,933.8)	0.24
- Platelet, median (IQR)	231,000 (174,000 , 293,000)	210,000 (127,000 , 263,000)	0.23
Renal functions (Day0) , median (IQR)			
- Blood urea nitrogen (mg/dL)	28.4 (18.8 , 44.8)	23.6 (16.3 , 64.6)	0.94
- Serum creatinine (mg/dL)	1.22 (0.67 , 1.78)	1.14 (0.83 , 2.67)	0.66
Chest X-ray : RALE (Day0) , median (IQR)	11.5 (7 , 14)	16.5 (7 , 24)	0.30
SOFA score , median (IQR)	3 (2 , 6)	6.5 (3 , 12)	0.06
Respiratory SOFA score , median (IQR)	2 (2 , 3)	3 (1 , 4)	0.18

Table 2. Clinical outcomes

Clinical outcomes after HA-330 hemoperfusion	**HA-330 Hemoperfusion group (n=14)**	**Control group (Non HA-330) (n=14)**	**P-value**
Primary outcomes			
28-day mortality	4 (28.6%)	11 (78.6%)	0.021
Hazard ratio = 0.26 (95 % CI = 0.08 – 0.81 ; P=0.021)			
Invasive mechanical ventilator day , median (IQR)	4.665 (0 , 6.88)	5.895 (1.75 , 10.9)	0.37
Ventilator free day , median (IQR)	24.81 (0 , 30)	0 (0 , 26.42)	0.18
Causes of death - Severe COVID-19 respiratory failure - Sepsis related to secondary infection	 2 (14.3%) 2 (14.3%)	 4 (28.36%) 7 (50%)	0.044
Secondary outcomes			
SOFA score (D3), median (IQR)	3 (2, 6)	6 (2, 9)	0.36
SOFA score (D6), median (IQR)	4 (2, 8)	3.5 (2.5, 11)	0.45
CRP level (D3), median (IQR)	36.7 (24.9, 62.36)	73.6 (45, 93.7)	0.11
CRP level (D6), median (IQR)	14.1 (6.7, 37.4)	23.92 (6.14, 35.07)	0.94
Chest X-ray pattern by RALE score (D3), median (IQR)	9.5 (5, 15)	14 (6, 20)	0.47
Chest X-ray pattern by RALE score (D6), median (IQR)	9 (4, 17.5)	8 (5, 16)	0.85
PaO_2 / FiO_2 (D3), median (IQR)	222.98 (181.5, 418.7)	310.3 (127.1, 346)	0.85
Respiratory SOFA (D3)	2 (0, 3)	1 (1, 3)	0.88
Clinical deterioration (n%)	0 (0%)	9 (64.3%)	0.001
Acute kidney injury at Day3 , (n%)	0 (0%)	2 (14.3%)	0.48
Acute kidney injury at Day6 , (n%)	2 (14.29%)	0 (0%)	0.48
Nosocomial infection, (n%)	4 (28.54%)	5 (35.71%)	1.00

ICU length of stay (days) median (IQR)	11.73 (6.67, 15.1)	8.5 (7, 12.25)	0.45
Hospital length of stay (days) median (IQR)	11.73 (9.17, 15.1)	8.5 (7, 16.5)	0.40
ICU mortality (n%)	3 (21.43%)	9 (64.3%)	0.054
	Hazard ratio = 0.25 (95 % CI = 0.067 – 0.929 ; P=0.039)		
Hospital mortality (n%)	6 (42.86%)	10 (71.43%)	0.25
	Hazard ratio = 0.38 (95 % CI = 0.136 – 1.06; P=0.07)		

Figure legend

Figure 1. Treatment protocol and randomization

Figure 2. Study profile

Figure 3. Kaplan-Meier curves for survival in the intervention (hemoperfusion) group and control group

Figure 4 : Longitudinal outcomes in both groups (solid line = intervention or hemoperfusion group , Dash line= control group). **A-D** represent SOFA score, CRP, CXR-RALE score, PaO2/FiO2 from day1 to day7 after randomization, respectively.