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The Role of Early Hemoadsorption in Severe COVID-19 Treatment: A Pilot Randomized Controlled Trial

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Keywords
Hemoadsorption therapy · Severe COVID-19 · Survival

Abstract

Introduction: Hemoadsorption, an extracorporeal apheresis technique, is reportedly used in severe COVID-19 patients. However, limited evidence from randomized clinical trials supports this practice. ***Methods:*** In this single-center study, severe COVID-19 patients requiring ICU admission were randomly assigned (1:1) to receive HA-330 hemoadsorption in combination with standard treatment or standard therapy alone. Both groups received tocilizumab intravenously if their clinical conditions worsened within 24–48 h. The primary outcome was mortality from any cause within 28 days after randomization. Secondary outcomes included mechanical ventilator-free days, daily C-reactive protein levels, oxygenation (defined by PaO_2/FiO_2 ratio), daily sequential organ failure assessment 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 hemoadsorption. Only 9 out of 14 patients (64.3%) in the control group experienced clinical worsening and were subsequently administered intravenous tocilizumab. At 28 days, the mortality rate was significantly lower in the intervention group (28.57% vs. 78.57%, $p = 0.021$), with a hazard ratio of death of 0.26 (95% CI = 0.08–0.81; $p = 0.021$). All of secondary outcomes were comparable in both groups. ***Conclusion:*** Based on our pilot randomized trial, the early application of HA-330 hemoadsorption in patients with severe COVID-19 may establish a favorable outcome in term of mortality. These data provide the initial proof of concept for conducting a large-scale study in the future.

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

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

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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, and even death [2]. Therefore, several treatments based on reducing cytokine signaling pathways, such as corticosteroids, interleukin (IL)-1, IL-6, and Janus kinase inhibitors, have been used with promising results and have provided better clinical outcomes [3].

Extracorporeal blood purification using different methods, such as the hemoadsorption 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].

The HA-330 hemoadsorbent, a synthetic resin hemofilter composed of polystyrene divinylbenzene copolymer, is designed to non-selectively eliminate molecules ranging from 10 to 60 kDa, including inflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8, IL-17, and tumor necrosis factor (TNF)-α. Its application resulted in improved barrier permeability and reduced lung injury in an endotoxin-induced ARDS porcine model [6]. As shown in previous observational and prospective cohort studies of severe COVID-19 patients [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, pilot randomized, controlled trial to evaluate the efficacy of early additional HA-330 hemoadsorption 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 Hemoadsorption in severe COVID-19 patients. All adult patients (≥18 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 Certified Ethical Review Board of Nakornping Hospital approved the study protocol for clinical research (Approval No. 105/64), and written informed consent for publication was obtained from each patient. 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 ≥18 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, the first update 2021 [9], (3) received intravenous remdesivir corticosteroids (at least 6 mg/day of dexamethasone) for more than 24 h, (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 was defined as a PaO_2/FiO_2 ratio ≤300 and/or room air pulse oxygen saturation <92%, or as being compatible with severe pneumonia as defined by the IDSA/ATS 2007 criteria. The exclusion criteria included terminal diseases (defined as conditions that cannot be adequately treated, such as advanced heart disease, advanced-stage cancer, or patients in a moribund state), pregnancy, a history of HA-330 allergy, recent myocardial infarction, prolonged shock lasting more than 12 h, and patients with a do-not-resuscitate order. 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 Hemoadsorption 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 as shown in Figure 1. Due to the impracticability of 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 hemoadsorption was applied in the intervention group within 8 h after randomization. Femoral or internal jugular venous catheterization was performed in this group, and hemoadsorption was started at a blood flow rate of 150–200 mL/min. The hemoadsorption cartridge used in this study was the Jafron® (HA-330), administered 4 h per session daily for 3 consecutive days. Before connection to the participants, we used 5,000 IU unfractionated heparin to prime the circuit. Most of the patients

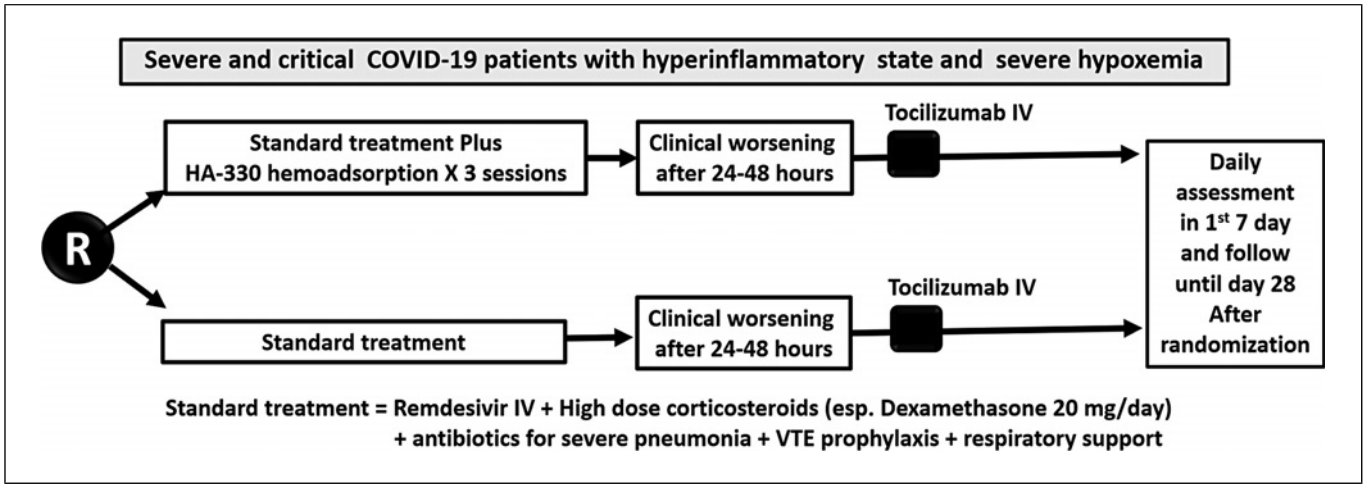

Fig. 1. Study protocol and randomization.

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

Each participant in both groups was closely monitored throughout 24–48 h after randomization. If their clinical status worsened, defined as a deterioration of hypoxemia (reduction of PaO_2/FiO_2 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, CRP levels, oxygenation (defined by the PaO_2/FiO_2 ratio), severity score of lung infiltration on the chest X-ray (CXR RALE score) after 24, 48, 72, 96, and 120 h, development of AKI at 72 and 144 h, 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; 95% CI = 0.004–0.264) with the addition of HA-330 adsorption to standard therapy. However, due to the broad confidence interval, using these data for sample size calculation could introduce errors. Without prior data to base the sample size on, we decided to use a sample size of at least 12 per group for this pilot randomized study, following the feasibility considerations suggested by Julious [11]. We also 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 for the primary outcome, 28-day mortality, was conducted using the Cox proportional hazard regression model. We assessed the assumption of proportional hazards through Schoenfeld Residual plot testing and examined survival curves using the Kaplan-Meier method, with statistical significance determined by 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 hemoadsorption 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 (PaO_2/FiO_2), chest X-ray infiltration score (RALE score), and sequential organ severity failure (SOFA). STATA software (StataCorp LLC,

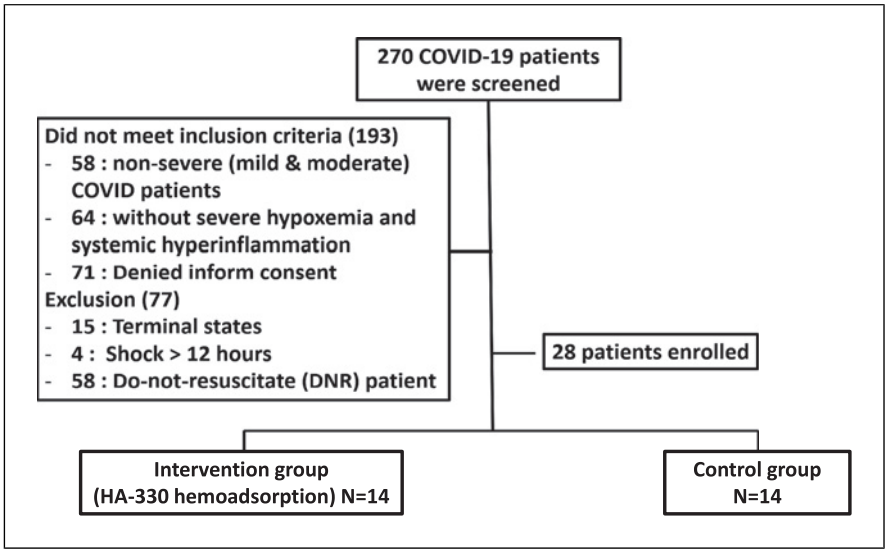

Fig. 2. Study profile.

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 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 hemoadsorption in combination with standard therapy, while the other 14 (50%) continued with standard therapy without HA-330 hemoadsorption.

The baseline characteristics of the participants in the two groups were nearly balanced, as shown in Table 1. Approximately 80% of the trial population was male, and the mean age of the study participants was 65 years, with no significant difference observed between both groups.

Hypertension was the most common coexisting condition among patients (50%). Other patient demographics showed no significant difference between the two groups.

The median time from diagnosis to randomization was 3.5 days. COVID-associated acute respiratory distress syndrome (ARDS), defined by the Berlin criteria [12], was present in 64.3% of participants. The mean severity of ARDS, classified by PaO_2/FiO_2, was moderate to severe (PaO_2/FiO_2 = 114.7). There were no significant differences in respiratory support modalities provided to severe and critical COVID-19 patients in both groups.

Laboratory Tests at Baseline: Inflammatory Markers, Chest X-Ray

After randomization, we conducted tests for arterial blood gas, blood chemistries, complete blood count, chest X-ray, and inflammatory markers (including CRP, ferritin, LDH, and IL-6 levels). The mean CRP level was 125.2 mg/L, with no significant difference between groups. Other parameters were balanced without statistically significant differences.

Treatment Modalities and Hemoadsorption

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 hemoadsorption was applied early after randomization. The mean time from severe pneumonia diagnosis to the first hemoadsorption was 28.9 h. It effectively conveys the information that all details regarding treatment modalities were presented in Table 2. After randomization, the clinical worsening was closely monitored. Only 9 out of 14 patients (64.3%) in the control group showed deterioration within 24–48 h, 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 h.

Table 1. Baseline clinical characteristics

Clinical characteristics	Hemoadsorption group (n = 14)	Control group (n = 14)	p value
Male gender, n (%)	9 (64.3)	13 (92.9)	0.17
Age, mean±SD, years	64.4±12.2	65.8±12.4	0.38
Height, mean±SD, cm	160.5±5.2	161.8±8.7	0.32
Body weight, mean±SD, kg	59.8±13.9	57.4±13.1	0.68
Body mass index, mean±SD, BMI	23.3±6.1	21.9±4.3	0.77
History of COVID-19 vaccination, n (%)	4(28.6)	10(71.4)	0.06
Day from onset to pneumonia diagnosis, median (IQR), days	2 (1, 4)	2 (1, 5)	0.72
Day from admission to pneumonia diagnosis, median (IQR), days	1.5 (0, 4)	0 (0, 1)	0.06
Day from diagnosis to randomization, median (IQR), days	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, mm Hg	138.4±25	122.8±21.6	0.96
DBP, mm Hg	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, ℃	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 type 2	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
COVID-associated ARDS (CARD), n (%)	10 (71.43)	8 (57.14)	0.70
COVID ARDS severity, n (%)			0.60
Mild	0	1 (12.50)	
Moderate	7 (63.64)	4 (50)	
Severe	3 (27.27)	3 (37.50)	
PaO_2/FiO_2 (initial ARDS diagnosis), median (IQR)	126.45 (96.1, 147.7)	99.98 (54, 172.4)	0.86
Laboratory test (day 0)			
Arterial blood gases			
PaO_2, median (IQR), mm Hg	91.85 (76, 150.5)	73.6 (49.3, 102.7)	0.27
$PaCO_2$, mean±SD, mm Hg	32.7±8.7	33±6.1	0.45
PaO_2/FiO_2, median (IQR)	155.55 (126.7, 221)	130.25 (75.8, 307)	0.49
pH value, median (IQR)	7.435 (7.399, 7.483)	7.368 (7.317, 7.454)	0.06
LFT, median (IQR)			
Alanine aminotransferase, IU/L	27 (19, 40)	40 (23, 84)	0.08
Alkaline phosphatase, IU/L	73 (54, 99)	91.5 (76, 176)	0.01

Table 1 (continued)

Clinical characteristics	Hemoadsorption group (n = 14)	Control group (n = 14)	p value
Total bilirubin, mg/dL	0.46 (0.35, 0.56)	0.995 (0.76, 1.54)	0.01
CRP, mean±SD, mg/L	120.2±42.1	130.2±51.1	0.29
Ferritin, median, ng/mL (IQR)	1,296 (455, 1,824)	1,399 (1,024, 1,810)	0.41
LDH, median, U/L (IQR)	406 (289, 485)	433 (352, 539)	0.21
Fibrinogen, mean±SD, mg/dL	516.9±122	94.25 (30.1, 207.1)	0.94
Interleukin-6, median (IQR), pg/mL	49.3 (8.72, 469.2)		0.46
Complete blood count (day 0)			
WBC, median (IQR)	8,850 (8,000, 10,500)	11,800 (7,800, 16,100)	0.53
Absolute lymphocyte count, median (IQR)	801.9 (714, 1,067)	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 (day 0), 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 (day 0), median (IQR)	11.5 (7, 14)	16.5 (7, 24)	0.30
SOFA score, median (IQR)	3 (2, 6)	6 (3, 9)	0.10
Respiratory SOFA score, median (IQR)	2 (2, 3)	3 (1, 4)	0.18

Table 2. Details of treatment modalities in each group

Clinical characteristics	Hemoadsorption group (n = 14)	Control group (n = 14)	p value
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 ventilation	8 (57.14)	10 (71.43)	
Antibiotics, n (%)			0.88
1 = Cef-3 + azithromycin	6 (42.86)	4 (28.57)	
2 = meropenem + azithromycin	3 (21.43)	3 (21.43)	
3 = meropenem	5 (35.71)	7 (50)	
Remdesivir, n (%)	14 (100)	14 (100)	0.57
Time from severe pneumonia, median IQR, h	1 (1, 2)	1.125 (1, 4.33)	
Corticosteroid, n (%)	14 (100)	14 (100)	1.00
Dexamethasone 12 mg/day	1 (7.14)	0	
Dexamethasone 20 mg/day	13 (92.86)	13 (92.86)	
Hydrocortisone 100 mg IV q 8 h	0	1 (7.14)	
Baricitinib, n (%)	2 (15.38)	1 (7.14)	0.60
Hemoadsorption, n (%)	14 (100)	–	
severe pneumonia to first HP, mean±SD, h	28.9±14	–	
Tocilizumab, n (%)	0 (0)	9 (64.3)	0.001
Time from severe pneumonia, mean±SD, h	–	37.18±15	

No immediate complications related to hemoadsorption, 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.

Table 3. Clinical outcomes

Clinical outcomes after HA-330 hemoadsorption	HA-330 hemoadsorption 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, n (%)			
Severe COVID-19 respiratory failure	2 (14.3)	4 (28.36)	0.044
Sepsis related to secondary infection	2 (14.3)	7 (50)	
Secondary outcomes			
SOFA score (D1), median (IQR)	2.5 (2, 7)	8 (3, 10)	0.01
SOFA score (D2), median (IQR)	3 (2, 6)	5 (3, 9)	0.1
SOFA score (D3), median (IQR)	3 (2, 6)	6 (2, 7)	0.42
SOFA score (D4), median (IQR)	2 (2, 6)	4 (2, 8)	0.11
SOFA score (D5), median (IQR)	2 (2, 6)	5 (3, 8)	0.26
SOFA score (D6), median (IQR)	4 (2, 8)	3.5 (2.5, 9.5)	0.56
SOFA score (D7), median (IQR)	5 (3, 10)	3 (2, 6)	0.35
CRP level (D1), median (IQR)	79.5 (61.7, 125.17)	126.3 (79.8, 170.3)	0.18
CRP level (D2), median (IQR)	50.9 (32.4, 99.5)	91.5 (58.8, 144.7)	0.13
CRP level (D3), median (IQR)	36.7 (24.9, 62.36)	73.6 (45, 93.7)	0.11
CRP level (D4), median (IQR)	30.4 (12, 50.1)	41.95 (26.2, 66.8)	0.24
CRP level (D5), median (IQR)	16.2 (10.7, 33.3)	23.4 (17.2, 38.8)	0.44
CRP level (D6), median (IQR)	14.1 (6.7, 37.4)	23.92 (6.14, 35.07)	0.94
CRP level (D7), median (IQR)	10.6 (7.6, 15.6)	15.35 (7.9, 28.7)	0.63
Chest X-ray pattern by RALE score (D1), median (IQR)	8.5 (5.5, 12)	16 (8, 28)	0.08
Chest X-ray pattern by RALE score (D2), median (IQR)	11.5 (5, 14)	13 (6, 20)	0.28
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 (D4), median (IQR)	10 (7, 15)	10 (6, 18)	0.55
Chest X-ray pattern by RALE score (D5), median (IQR)	8 (4, 16)	16 (7, 22)	0.2
Chest X-ray pattern by RALE score (D6), median (IQR)	9 (4, 17.5)	8 (5, 16)	0.85
Chest X-ray pattern by RALE score (D7), median (IQR)	7 (3, 15)	10 (7, 14)	0.37
PaO_2/FiO_2 (D1), median (IQR)	178.2 (100.2, 251.3)	114.4 (78, 182.5)	0.17
PaO_2/FiO_2 (D2), median (IQR)	213.2 (142.3, 417)	162.2 (139.6, 351.7)	0.4
PaO_2/FiO_2 (D3), median (IQR)	223 (181.5, 418.7)	310.3 (127.1, 346)	0.85
PaO_2/FiO_2 (D4), median (IQR)	221 (170.4, 287.8)	218.7 (156, 269.2)	0.87
PaO_2/FiO_2 (D5), median (IQR)	228.9 (156.2, 259.7)	204.8 (151.2, 307.6)	0.92
PaO_2/FiO_2 (D6), median (IQR)	279.3 (167.8, 330)	201.1 (150.9, 237.4)	0.4
PaO_2/FiO_2 (D7), mean±SD	253.4 (±77.4)	215.4 (±104.3)	0.44
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 day 3, n (%)	0 (0)	2 (14.3)	0.48
Acute kidney injury at day 6, n (%)	2 (14.29)	0 (0)	0.48
Nosocomial infection, n (%)	4 (28.54)	5 (35.71)	1.00
ICU length of stay, median (IQR), days	11.73 (6.67, 15.1)	8.5 (7, 12.25)	0.45
Hospital length of stay, median (IQR), days	11.73 (9.17, 15.1)	8.5 (7, 16.5)	0.40

Table 3 (continued)

Clinical outcomes after HA-330 hemoadsorption	HA-330 hemoadsorption group (n = 14)	Control group (non HA-330) (n = 14)	p value
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)		

Clinical Outcomes

The results for the primary and secondary outcomes are presented in Table 3. Death from any cause up to day 28 was observed in 28.6% of 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 illustrates that cumulative survival was higher in the intervention group compared to the control group (refer to Fig. 3). To address the issue of unbalanced baseline characteristics in the data, we applied the Cox proportional hazard model. Even after adjusting for SOFA score, liver function tests, and IL-6 levels, the 28-day mortality in the hemoadsorption group remained significantly lower (hazard ratio = 0.19, 95% CI = 0.04–0.86, p = 0.031), as depicted in Figure 4.

The ICU mortality was also lower in the hemoadsorption group (hazard ratio = 0.25 [95% CI = 0.067–0.929; p = 0.039]), but the hospital mortality in the Hemoadsorption 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 (PaO_2/FiO_2), 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 Tables 1 and 2 and Figure 5.

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 AKI at day 3 and day 6 after randomization was also not different in both groups. During our study, none of the participants experienced coagulation problems. VTE prophylaxis was applied to all patients in accordance with the American Society of Hematology 2021 guidelines recommendation, without any complications.

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 hemoadsorption 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 discovery supports the hypothesis proposing the therapeutic benefits of extracorporeal apheresis in managing the hyperinflammatory state associated with severe COVID-19 [13].

Compared with the control group, which included approximately 60% of patients who received intravenous tocilizumab due to clinical deterioration, hemoadsorption also exhibited lower hyperinflammatory cytokine levels (CRP), reduction of chest X-ray infiltration, and improvement of arterial hypoxemia (increased PaO_2/FiO_2 ratio) without statistical difference. We also found a higher incidence of nosocomial infection after treatment in the control group than the hemoadsorption 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 hemoadsorption group compared with the control group.

The difference in mortality outcomes between our previous study [8], demonstrating a 96.7% reduction, and this current study, showing a 74% benefit, can be attributed to various factors. These include differences in the studied populations, focusing on distinct SARS-CoV-2 variants, varied study designs (randomized control trial vs. prospective), the implementation of a new tocilizumab administration protocol upon clinical deterioration, and a longer time from severe pneumonia onset to hemoadsorption in the current study compared to the previous one (28.9 h vs. 24 h). Hemoadsorption can remove inflammatory markers and consequently reduce plasma cytokine levels through hemoadsorption into either charcoal or

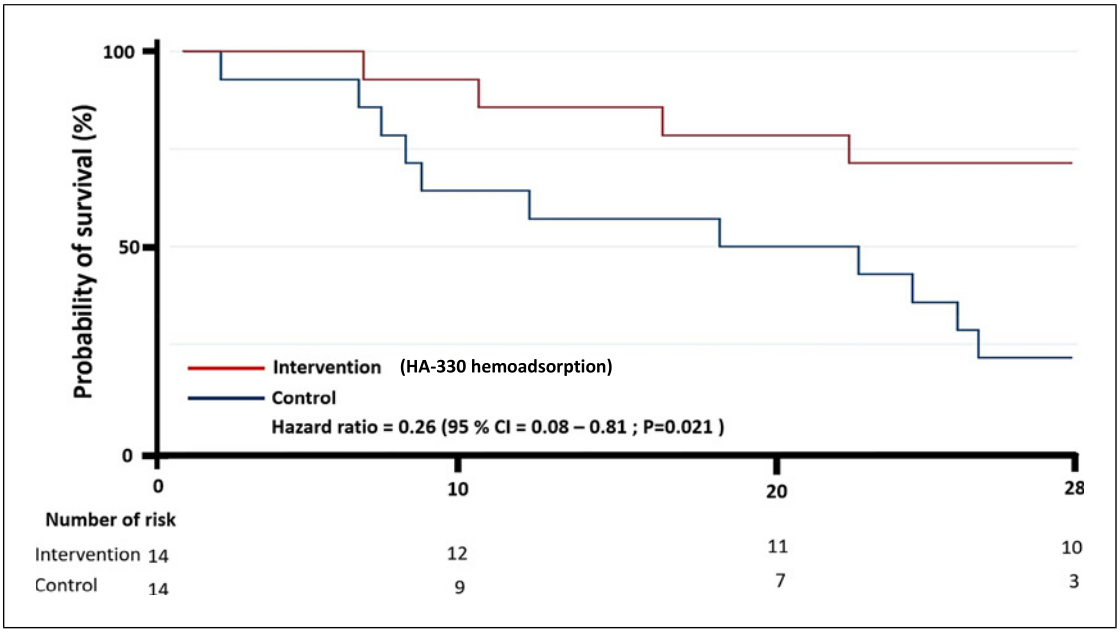

Fig. 3. Kaplan-Meier curves for survival in the intervention (hemoadsorption) group and control group.

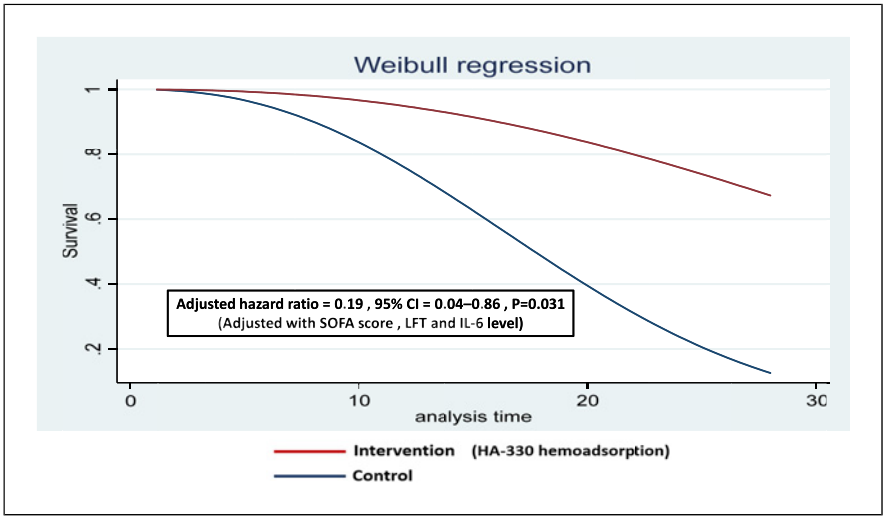

Fig. 4. Cox proportional hazard model for adjusting the factors that may associated with the 28-day mortality.

resin beads contained in an adsorbent cartridge. This technique can be used in selected patients with systemic inflammatory syndrome, such as refractory septic shock orsevere COVID-19 [14, 15]. 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 [16]. In our previous study [8], the early use of HA-330 hemoadsorption 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. [17], which studied the efficacy of hemoadsorption 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 Hemoadsorption at the time of initiation. Moreover, in the current study, 64.3% of patients in the

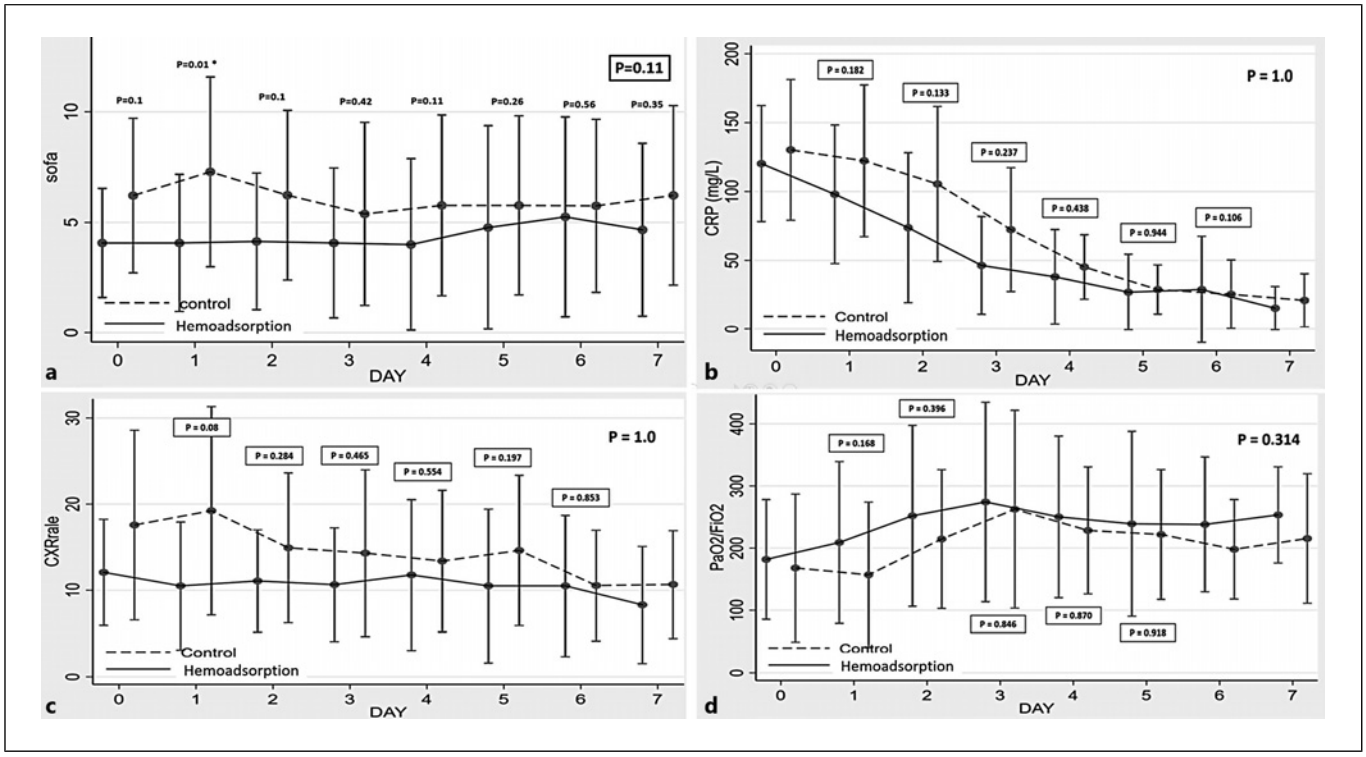

Fig. 5. Longitudinal outcomes in both groups (solid line = intervention group, dash line = control group). **a–d** SOFA score, CRP, CXR-RALE score, PaO_2/FiO_2 from day 1 to day 7 after randomization, respectively.

control group received intravenous Tocilizumab, in contrast to the hemoadsorption group that did not receive it. This was due to deterioration occurring 24–48 h after randomization. Therefore, hemoadsorption therapy may help mitigate the inflammation process and reduce the need for anti-inflammatory treatment. Thus, it is reasonable to assume that considering the timing of Hemoadsorption 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 several limitations which need to be addressed. 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 [17]. 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 rather small. We admitted that this study may be under power, hence there was a high chance that the observed results turned out by chance, rather than a clear signal. Therefore, we decided to present this study as the pilot study and still need large RCT to confirm our finding. Fourth, only one type of hemoadsorption 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 hemoadsorption. The mean time from severe pneumonia diagnosis to tocilizumab initiation was approximately an 8-h delay compared to the hemoadsorption group, which may have affected this study's outcome.

Conclusion

Based on our pilot randomized trial, the early application of HA-330 hemoadsorption in patients with severe forms of COVID-19 may establish a favorable outcome in terms of mortality. These data provide the initial proof of concept for feasibility of conducting a large-scale study in the future.

Statement of Ethics

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

K.S. and N.S. helped in conceptualization and writing – original draft preparation and contributed to methodology and writing – review and editing. K.S. conducted study and data collection and contributed to data analysis. N.S. helped in supervision. All authors read and approved the final manuscript.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (N.S.) on reasonable request.

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