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Sequential Extracorporeal Blood Purification Is Associated with Prolonged Survival among ICU Patients with COVID-19 and Confirmed Bacterial Superinfection

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Keywords

COVID-19 · Extracorporeal blood purification · Interleukin-6 · Intensive care unit · Sequential hemoperfusion · SOFA score · Survival

Abstract

Introduction: This study investigates the impact of sequential extracorporeal treatments with oXiris® or CytoSorb® plus Seraph-100® on the clinical and laboratory parameters of critically ill COVID-19 patients with bacterial superinfection. ***Methods:*** Patients admitted to the intensive care unit with COVID-19, bacterial superinfection, and undergoing blood purification (BP) were enrolled in this prospective, single-center, observational study. "standard BP" with oXiris® or CytoSorb® were used in 35 COVID-19 patients with bacterial infection. Seraph-100® was added in 33 patients when available serially in the same oXiris® circuit or as sequential treatment with CytoSorb® as a sequential BP. ***Results:*** A significant reduction in SOFA score 3 days after treatment was observed in patients undergoing sequential BP (11.3 vs. 8.17, $p < 0.01$) compared to those undergoing "standard BP" (11.0 vs. 10.3, $p > 0.05$). The difference between the observed and expected mortality rate based on APACHE IV was greater in the sequential BP group (42.4% vs. 81.7%, $p < 0.001$) than the "standard BP" (74.2% vs. 81.7%, $p > 0.05$). Patients treated with sequential BP had a longer survival than those treated with "standard BP" (22.4 vs. 18.7 months; $p < 0.001$). ***Conclusions:*** The sequential approach may enhance the positive effect of BP on organ dysfunction among critically ill patients with COVID-19 and bacterial superinfection.

Trial registration: ClinicalTrials.gov: NCT05470907. Registered July 21, 2022. Retrospectively registered.

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Introduction

The progression of SARS-CoV-2 infection to severe pneumonia, acute respiratory distress syndrome (ARDS), and ultimately, multiple organ dysfunctions are associated with prolonged ICU length of stay, resulting in the higher risk of developing secondary and opportunistic infections and increased mortality rate [1–4]. Accordingly, studies have reported high incidences of bacterial coinfections and secondary bacterial infections among COVID-19 patients with prolonged hospitalization, ranging from 3.5 to 49.6%, respectively, which further increase the overall mortality rate [5–11].

In critically ill COVID-19 patients, extracorporeal blood purification (EBP) therapies, hemodiafiltration with oXiris® or hemadsorption with CytoSorb®, have emerged as novel treatments in multiple organ dysfunctions [12–17]. Multiple EBPs are used contemporaneously or as sequential therapy to counteract multiple pathophysiological mechanisms associated with acute kidney injury (AKI) and systemic inflammation. Sequential EBPs may therefore be more efficacious than single EBPs in immunomodulating and supporting organ function in critically ill patients. The Seraph-100® Microbind Affinity Blood Filter (Seraph-100; Exthera Medical Corporation, Martinez, CA, USA) is an extracorporeal hemadsorption device with a broad-spectrum sorbent, capable of binding bacteria, viruses, and fungi in the blood, including SARS-CoV-2 [18–21]. This study investigates the impact of sequential EBP with oXiris® or CytoSorb® plus Seraph-100® on the clinical and laboratory parameters of critically ill COVID-19 patients with bacterial superinfection.

Methods

All patients with COVID-19 admitted to the ICU from January 2021 to February 2022 and with bacterial superinfection and undergoing BP were considered enrolled in this prospective, single-center, observational study. The SARS-CoV-2 infection was diagnosed by real-time positive reverse transcriptase polymerase chain reaction on nasal/oral swabs. Bacterial superinfection was diagnosed with a positive blood or airway culture, routinely performed for all ICU patients, either on admission or during the ICU stay. In accordance with local institutional guidelines, BPs were performed with oXiris®(Baxter, IL, USA) or CytoSorb®(CytoSorbent, Manmouth Junction, USA) for non-selective cytokine adsorption in every COVID-19 patient with evidence of systemic inflammation (IL-6 >25 pg/mL and/or leukocytes >15 × 10^9/L and/or CRP >40 mg/L and/or procalcitonin >0.9 mg/L) and organ dysfunction (SOFA score >5 or a diagnosis between (AKI), hemodynamic instability requiring vasoactive support, and ARDS). KDIGO criteria were used to diagnose AKI [22], while Berlin criteria [23] were used to define ARDS. All patients were treated with antimicrobials; the corticosteroids were given at the same time-point with similar doses and therapy periods, while none of the patients received IL-6 receptor blockers. Patients with AKI requiring continuous renal replacement therapy were treated only with oXiris®. The blood flow rate was set to 200–250 mL/min for both treatments. Continuous renal replacement therapy with oXiris® was performed in continuous veno-venous hemodiafiltration. Treatments with oXiris® and CytoSorb® were prescribed for 72 h or for shorter period if death occurred during the procedures, with the extracorporeal circuit being replaced every 24 h. In addition to treatments with oXiris® or CytoSorb®, defined for this study as "standard BP", Seraph-100® was used when available as sequential treatment. Seraph-100® treatments were prescribed for 4–6 h and only once per patient. In this observational study, we compared clinical and biochemical variables between patients undergoing "standard BP" and those undergoing sequential BP (SBP group). The control group was identified considering patients undergoing "standard BP" and using a propensity score analysis conducted on the covariates of APACHE IV score, SOFA score at baseline, AKI diagnosis, and use of CytoSorb® or oXiris® using a 1:1 ratio matching method. A cut-off of 3 days after admission to the ICU was chosen to define early and late onset of BP.

The patient's clinical parameters were extracted from ICU charts. The severity of organ dysfunction was assessed by APACHE IV and SOFA scores [24]. For each patient, complete clinical and laboratory examinations were performed on admission to the ICU, at baseline, 24-h after the first BP procedure, and 3 days after all BP procedures. The follow-up lasted until the last enrolled patient reached 28 days, after first BP procedure, in the ICU or died. The protocol was approved by the hospital's ethics committee (UHC Zagreb, Croatia) according to the Helsinki Declaration, and its subsequent modifications and data were managed in accordance with the patients' written informed consent by themselves at hospital admission or by the next of kin at admission to ICU.

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., USA). Considering a 2-sided *t*-test, a difference in ΔSOFA at 48 h between groups at least of 1.5, a standard deviation of ΔSOFA at 48 h in each group of 2 (estimated according to Wan et al. [25] from Villa et al. [16]) and a first-type error of 5%, 29 patients per group are needed to guarantee a power of 80%. In order to avoid the possibility of missing values, 35 patients per group were enrolled. Nearest neighbor matching with a propensity score caliper distance of 0.1 was employed to select patients treated with standard care to be included in the control group. A matching method with a 1:1 ratio was used. An optimal quality match was defined as a standardized mean difference ≤0.1 per matching variable between the study and control group patients. Paired t-Student and Wilcoxon tests were used for comparing the over-time trends of variables within the same group. Boxplots were drawn to describe different laboratory parameter variations with a good inter-observance agreement. Survival analysis was performed with Kaplan-Meier curves, while hazard ratios were estimated with Cox proportional hazards regression.

Results

During this period, a total of 68 patients were enrolled in this study. Thirty-three patients were treated with Seraph-100® in combination with "standard BP" (SBP group). A group of 35 patients treated only with

"standard BP" and with APACHE IV and SOFA scores at baseline, AKI diagnosis and treatment with CytoSorb® or oXiris® similar to that of the SBP group was selected as control group (BP group). The patients were admitted to the ICU for respiratory failure; 49 (71.0%) were already undergoing invasive or non-invasive mechanical ventilation at the time of admission to the ICU. Twenty-eight patients (40.6%) required vasoactive drugs on admission to the ICU due to hemodynamic instability. Renal replacement therapy was required in 21 patients (30.98%). The characteristics at the time of ICU admission are shown for all patients and for the SBP and BP subgroups in Table 1.

All of the patients enrolled in this study had positive supervisory cultures, either from blood or respiratory tract cultures, before start of BP. Ac. baumanii, Ps. aeruginosa, Kl. pneumomiae/oxytoca, and Staph. aureus MRSA were isolated in 38.3%, 33.8%, 17.6%, and 10.3% of patients, respectively.

No treatment-specific complications such as severe bleeding, thromboembolism, or electrolyte disorders were observed. The overtime variation of clinical and laboratory data observed for the BP and SBP groups before and after the extracorporeal treatments are presented in Table 2.

Differences in Clinical Variables and Laboratory Data between Patients Treated with SBP and BP

We have found a significantly fewer patients on vasopressors and a significant improvement in oxygenation in the SBP-treated group 3 days after all BP procedures (Table 2). We found at 3 days after all BP procedures a significant decrease in SOFA score in the SBP group (11.3 vs. 8.17, $p < 0.01$) compared to the BP group (11.0 vs. 10.3, $p > 0.05$) and in the APACHE IV (shown in Fig. 1a–c; Table 2).

In the SBP group, we have found a significant decrease in white blood count, ferritin, LDH, and IL-6 levels and an increase in lymphocytes after the procedure. We have not found any significant difference in laboratory parameters within the SBP and BP groups, between patients treated with oXiris® and those treated with CytoSorb®.

Differences in Clinical Variables and Laboratory Data between Survived and Deceased Patients Treated with SBP

Deceased patients treated with SBP had longer duration of symptoms before admission to the ICU and longer duration before the start of BP than survived patients (all $p < 0.05$). We found no differences in the number of patients on vasopressors or mechanical ventilation or in levels of inflammatory markers, while the deceased patients had significantly higher APACHE IV and SOFA scores at baseline.

Survival of Patients Treated with BP

The difference between the observed and the expected mortality rate according to APACHE IV was greater in the SBP group (42.4% vs. 81.7%, $p < 0.001$) than in the BP group (74.2% vs. 81.7%, $p > 0.05$). The mortality rate of patients in the SBP group treated early was lower than that of patients treated late (22.2% vs. 66.6%, $p < 0.001$) and that of the BP group (60.0% vs. 85.0%, $p < 0.05$).

Variables Associated with Survival of ICU Patients

A higher SOFA score at baseline and delayed start of BP were associated with higher mortality in the whole group (HR 1.26 [1.04, 1.51] and HR 3.22 [1.47, 7.01], respectively) (Table 3). Forty-one patients (60.3%) died before 28-days of follow-up, 15 (45.5%) in the SBP group, 26 (74.3%) in the BP group. The mean survival time was longer in the SBP group than in the BP group (22.4 [95% CI 19.8, 24.9] vs 18.7 [95% CI 16.1, 21.3] days; $p < 0.001$) (shown in Fig. 2) and in patients treated early with BP (22.6 [95% CI 19.8, 25.3] vs 18.0 [95% CI 15.6, 20.4] days; $p < 0.001$) (shown in Fig. 3).

Discussion

The main finding of this study was that sequential therapy, combining Seraph® with oXiris® or CytoSorb®, prolongs the survival of ICU patients with COVID-19 and confirmed bacterial superinfection. Sequential therapy is also associated with an improvement in respiratory function, a decrease in the dose and number of ICU patients on vasoactive therapy, and a reduction of the SOFA score severity. Sequential therapy, including Seraph® in the BP strategy, was superior in reducing inflammatory markers such as IL-6, ferritin, and C-reactive protein compared to "standard BP."

This is the first prospective study in this number of patients that analyzed the impact of sequential therapy with the Seraph® filter in COVID-19 ICU patients with bacterial superinfection. CytoSorb® (CytoSorbents Corporation, Monmouth Junction, NJ, USA) is a cytokine adsorber approved for infectious and non-infectious conditions and was used in patients with COVID-19 as well [17–24, 26–28]. The oXiris® membrane (Baxter, IL, USA) is a hemodiafilter, mainly used in septic patients with AKI and has also been used in COVID-19 patients [16, 29–32]. A major limitation of our study is that we

Table 1. Differences between patients treated with SBP and BP at admission to ICU

	All patients (*N* = 68)	SBP (*N* = 33)	BP (*N* = 35)	*p* value
Demographic parameters				
Age, years	62.7±11.3	61.2±11.9	64.5±11.9	0.24
Sex (males), *N* (%)	48 (69.5)	23 (69.5)	25 (69.5)	0.87*
BMI	29.1±6.4	28.6±6.3	29.7±6.5	0.30
Days of symptoms before admission to ICU	10.4±1.8	10.2±1.7	10.8±1.9	0.81
Patients hospitalized before ICU, *N* (%)	26 (38.2)	11 (33.3)	15 (42.8)	0.65*
Days of hospitalization before admission to ICU	3.2±0.2	3.4±0.3	3.0±0.2	0.45
Comorbidities, *N* (%)				
Chronic kidney disease	3 (4.0)	2 (6.1)	1 (2.9)	0.41*
Diabetes	16 (32.6)	10 (30.3)	6 (17.1)	0.20*
Hypertension	38 (55.1)	15 (45.5)	23 (65.7)	0.15*
Hematological disease	11 (15.9)	4 (12.1)	7 (20.0)	0.37*
Prior organ transplant	5 (7.2)	3 (9.1)	2 (5.7)	0.59*
Prior cardiovascular event	20 (28.9)	11 (33.3)	9 (25.7)	0.43*
Heart failure	11 (15.9)	5 (15.1)	6 (17.1)	0.82*
Obesity	38 (55.1)	16 (48.5)	22 (62.8)	0.23*
Pulmonary embolism	7 (10.1)	2 (6.1)	5 (14.3)	0.26*
Charlson comorbidity index	5.8±0.4	4.7±0.5	6.8±0.6	0.02
Days in ICU before starting with BP	5.02±0.7	4.39±0.6	5.69±0.9	0.27
Type of hemadsorber/filter (yes), *N* (%)				
oXiris	39 (57.3)	19 (57.6)	20 (57.1)	0.83*
CytoSorb	29 (42.7)	14 (42.4)	15 (42.9)	
CRRT+BP (yes), *N* (%)	21 (30.9)	8 (24.2)	13 (37.1)	0.24*
ECMO+BP (yes), *N* (%)	4 (5.9)	2 (6.1)	2 (5.7)	0.94*
Clinical data				
Heart rate, cp/min	90 (50–130)	88 (50–121)	91 (51–134)	0.59
Systolic blood pressure, mm Hg	123 (80–180)	127 (85–183)	121 (77–177)	0.26
Diastolic blood pressure, mm Hg	72 (40–100)	74 (43–105)	70 (39–98)	0.20
Mean arterial pressure, mm Hg	66 (38–123)	65 (36–121)	68 (40–129)	0.83
Glasgow coma score	12.2±1.5	12.1±1.5	12.2±1.5	0.89
Vasoactive therapy (yes), *N* (%)	28 (40.6)	12 (36.4)	16 (45.7)	0.43*
Vasoactive therapy dose, μg/kg/min	0.5±0.01	0.5±0.01	0.4±0.01	0.77
Urinary output, mL/h	118±25.4	102±23.2	120±25.9	0.38
Acute kidney injury (yes), *N* (%)	18 (26.1)	9 (27.3)	9 (25.7)	0.88*
Mechanical ventilation (yes), *N* (%)	49 (71.0)	26 (78.7)	23 (65.7)	0.23*
NIV	27 (55.1)	13 (50.0)	14 (60.9)	0.44*
Endotracheal intubation	22 (44.9)	13 (50.0)	9 (39.1)	
Respiratory rate, breaths/min	21 (10–40)	19 (8–36)	21 (10–40)	0.25
PEEP, cm H_2O	13.7±1.3	13.6±1.3	13.7±1.3	0.93
FiO_2, %	73.3±12.6	71.2±12.2	75.4±12.9	0.44
PaO_2, kPa	7.5±0.8	7.9±0.9	7.2±0.7	0.33
$PaCO_2$, kPa	6.4±0.3	6.7±0.5	6.2±0.2	0.35
PaO_2/FiO_2	76.7±13.1	77.1±13.2	76.6±13.1	0.51
SaO_2, %	91 (57–99)	91 (57–98)	91 (56–99)	0.98
Lactates, mmol/L	2.38±0.2	1.90±0.1	2.82±0.5	0.06
ARDS difficulty (yes), *N* (%)				
Mild	4 (5.8)	1 (3.0)	3 (8.6)	
Moderate	42 (60.9)	20 (60.6)	22 (62.8)	0.54*
Severe	23 (33.3)	12 (36.4)	10 (28.6)	
APACHE IV	163.7±35.5	171.1±35.9	154.5±34.3	0.13
SOFA score	9.26±1.5	9.71±1.9	8.74±1.3	0.25
Laboratory data				
Sodium, mmol/L	136.6±27.2	137.1±27.3	136.8±27.2	0.44
Potassium, mmol/L	4.4±0.8	4.3±0.8	4.4±0.8	0.48

Table 1 (continued)

	All patients (*N* = 68)	SBP (*N* = 33)	BP (*N* = 35)	*p* value
White blood count, $\times 10^9$/L	14.5±1.1	14.3±1.1	14.8±1.1	0.84
Hematocrit, %	32.9±7.7	32.3±7.7	33.1±7.8	0.72
Lymphocytes, %	9.4±0.8	7.9±0.4	11.0±1.3	0.07
Creatinine, µmol/L	184.3±29.5	197.3±29.9	173.2±29.1	0.70
GFR, mL/min/1.73 m^2	32 (14–54)	30 (12–51)	36 (17–58)	0.37
BUN, µmol/L	13.9±1.3	14.0±1.3	13.6±1.2	0.88
Bilirubin, µmol/L	17 (9–26)	15 (9–23)	17 (9–27)	0.69
LDH, U/L	677.1±83.7	681.2±83.9	676.2±83.5	0.97
Platelets, $\times 10^9$/L	231.9±43.1	241.2±43.0	224.7±42.8	0.53
INR	1.17±0.06	1.18±0.06	1.15±0.05	0.84
D-dimers, mg/L	9.2±1.6	9.2±1.6	9.2±1.6	0.99
Procalcitonin, mg/L	7.4±1.3	5.4±1.1	9.4±1.8	0.13
C-reactive protein, mg/L	148.9±21.2	144.6±21.1	153.5±21.7	0.70
Ferritin, µg/L	2,125 (233–12,312)	2,036 (201–12,102)	2,215 (296–12,572)	0.63
Interleukin-6, pg/mL	86.1±19.5	99.4±19.9	45.8±18.3	0.49

Results are shown as mean ± SD or median (interquartile range). SBP, sequential blood purification group; BP, standard blood purification group; BP, blood purification; ICU, intensive care unit; BMI, body mass index; NIV, non-invasive mechanical ventilation; ARDS, acute respiratory distress syndrome; GFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; INR, international normalized ratio. *Chi square.

used hemadsorption (CytoSorb®) or hemodiafiltration (oXiris®) in both patient subgroups to reduce cytokine levels. Some might argue that there are significant differences in the mode of action between these two, although we found no differences in clinical or laboratory parameters between CytoSorb® and oXiris® in both subgroups of patients with SBP and BP.

During admission to the ICU, COVID-19 patients were susceptible to bacterial superinfection due to the prolonged stay in the ICU and mechanical ventilation with higher mortality rates than in previous viral syndromes [33–35]. Acinetobacter, Klebsiella, and Pseudomonas were the most detected bacteria in this group of patients, which is like our results [11, 36, 37]. The systemic spread of the virus can be enhanced by bacterial superinfection and bacterial endotoxins, which further increases the risk of systemic inflammatory response and sepsis [38–41]. Another limitation of our study is that we did not measure any decrease of endotoxin levels by endotoxin activity assays in our COVID-19 ICU patients with bacterial superinfection. The Seraph-100® Microbind Affinity Blood Filter (ExThera, Martinez, CA, USA), which we used in our study, was previously granted a Europene Mark of Conformity under by the Food and Drug Administration (FDA) with a broad indication for the treatment of severe COVID-19. Recent studies have shown that Seraph® removes bacteria and other pathogens from the blood like SARS-CoV-2 nucleocapsid protein in severely ill COVID-19 patients [19, 20, 42, 43]. The first study with a larger number of COVID-19 ICU patients, the COSA registry, showed that earlier initiation of the filter, i.e., within 60 h of admission to the ICU, reduced mortality in these patients, which is in agreement with the results of our study [44].

The inability to measure bacterial and viral load before and after treatment with the Seraph® filter is another limitation of the study, which would potentially add further value to our results. The association of endotoxemia with cytokine hyperproduction has been previously reported in some patients [45, 46]. In this case, non-selective hemadsorption with CytoSorb® or hemodiafiltration with oXiris® and selective hemadsorption with polymyxin-bound membranes (Toraymyxin®) may be insufficient [47], which is in agreement with the results of our study. The concept of sequential EBP, endotoxin, and cytokine hemadsorbtion, has been described in papers preceding the COVID-19 pandemic but was applied in highly selective patients [48–51]. Ronco et al. proposed the same treatment modality for patients with COVID-19 [13]. As discussed above, the superiority of sequential hemadsorption over non-selective hemadsorption in these patients is probably based on the fact that cytokine hyper-production is not only based on the hyper-immune response to COVID-19 virus but also on

Table 2. Inter-group differences between SBP and BP patients and intra-group overtime variation of the same variables

	SBP			BP		
	day before EBP	day after EBP	3 days after all EBP	day before EBP	day after EBP	3 days after all EBP
SOFA score	11.30±1.4	10.27±1.5	**8.17±1.6**$^{*,\#}$	11.00±1.4	10.97±1.5	10.34±1.7
Vasoactive therapy, *N* (%)	17 (51.5)	18 (54.5)	**14 (46.6)***	21 (60.0)	23 (65.7)	23 (79.3)
Vasoactive dose, µg/kg/min	0.52±0.01	**0.42±0.01***	0.45±0.01	0.53±0.01	0.62±0.01	0.52±0.01
Lactates, mmol/L	2.21±0.3	1.85±0.3	**1.30±0.2**$^{\#}$	2.60±0.4	2.26±0.4	2.04±0.4
Mechanical ventilation, *N* (%)	26 (78.8)	29 (78.8)	27 (90.0)	30 (85.7)	35 (100.0)	26 (89.6)
NIV	9 (34.6)	8 (27.6)	6 (34.6)	6 (20.0)	6 (17.1)	1 (20.0)
Endotracheal intubation	17 (65.4)	21 (72.4)	21 (65.4)	24 (80.0)	29 (82.9)	25 (80.0)
Respiratory rate, breaths/min	21 (10–40)	**17 (6–34)***	**15 (5–32)**$^{*,\#}$	21 (10–39)	21 (10–39)	20 (9–37)
PEEP, cm H_2O	14.3±1.6	14.5±1.9	**12.7±1.6**$^{\#}$	13.7±1.5	14.1±1.8	13.6±1.9
PaO_2, kPa	8.2±0.2	9.4±0.3	9.6±0.5	8.6±0.3	9.6±0.5	9.2±0.4
FiO_2, %	72.8±13.3	60.1±14.4	**54.9±13.8**$^{\#}$	71.0±13.7	68.6±13.8	62.2±14.1
PaO_2/FiO_2	84.3±13.9	117.5±16.2	**131.8±16.9**$^{\#}$	90.8±14.3	104.4±15.7	112.9±15.1
$PaCO_2$, kPa	6.6±0.4	6.6±0.4	6.3±0.3	6.4±0.3	6.3±0.3	6.1±0.5
ARDS difficulty (yes), *N* (%)						
Mild	0 (0)	2 (6.1)	4 (13.3)	0 (0)	1 (2.8)	2 (6.9)
Moderate	20 (57.1)	18 (54.5)	19 (63.3)	16 (45.7)	14 (40.0)	11 (37.9)
Severe	13 (42.9)	13 (39.4)	**7 (23.3)**$^{*,\#}$	19 (54.3)	20 (57.2)	16 (55.2)
Creatinine, µmol/L	140.9±27.2	123.9±26.3	131.2±26.8	178.2±29.1	158.1±28.2	155.3±28.3
Bilirubin, µmol/L	16 (8–24)	16 (8–24)	18 (8–28)	15 (7–23)	20 (10–31)	18 (9–29)
LDH, U/L	672.1±82.0	547.3±73.7	**513.5±69.1***	486.7±60.2	614.6±81.2	429.6±58.4
Platelets, $\times10^9$/L	208.4±49.3	178.9±47.0	166.6±41.7	226.8±48.5	201.9±49.6	175.2±41.6
D-dimers, mg/L	9.2±2.5	5.0±1.4	**2.7±0.5**$^{\#}$	9.4±2.3	5.4±1.4	**3.5±0.6**$^{\#}$
White blood count, $\times10^9$/L	15.3±1.5	12.0±1.1	**9.9±1.0***	14.2±1.0	12.8±1.5	11.3±1.5
Hematocrit, %	38.0±2.9	35.0±2.1	33.0±2.0	35.1±2.1	35.0±2.0	32.9±2.0
Lymphocytes, %	6.8±1.0	10.8±1.0	**14.7±2.2**$^{\#}$	11.8±1.0	11.8±1.0	11.9±1.5
Procalcitonin, mg/L	6.6±1.6	4.3±1.7	**4.5±1.0**$^{\#}$	10.2±1.8	4.9±1.3	**4.7±1.8**$^{\#}$
C-reactive protein, mg/L	184.8±26.5	114.2±26.1	**72.4±24.6***	172.2±25.0	129.3±24.0	**111.4±25.8***
Ferritin, µg/L	2,242 (332–12,672)	1,402 (188–10,312)	**783 (102–8,312)**$^{*,\#}$	2,676 (385–12,802)	1,868 (209–11,654)	1,034 (156–9,981)
Interleukin-6, pg/mL	170.7±14.3	68.1±9.1	**10.7±3.2**$^{\#}$	87.9±9.6	58.3±9.0	28.6±4.3

Results are shown as mean ± SD or median (interquartile range). SBP, sequential blood purification; BP, standard blood purification; BP, blood purification; ICU, intensive care unit; BMI-body mass index; NIV, non-invasive mechanical ventilation; ARDS, acute respiratory distress syndrome; GFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; INR, international normalized ratio. $^{*}p < 0.05$ for inter-group difference. $^{\#}p < 0.05$ for intra-group variation.

endotoxins from bacteria contracted during the ICU stay or the migration of endotoxins from the gut and the enhancement of viral infectivity with circulating endotoxins. This is the most likely reason why we did not find a significant decrease of IL-6 levels after non-selective hemadsorption compared to sequential hemadsorption. The main reasons for the significant association of better survival with the SBP mode were a significant improvement in respiratory status, a decrease in vasoactive support, cytokine levels, and other inflammatory parameters and a significant decrease in APACHE IV and SOFA scores. One could debate why sequential hemadsorption achieved these improvements in our patients. In our opinion, cytokine reduction was not the only answer.

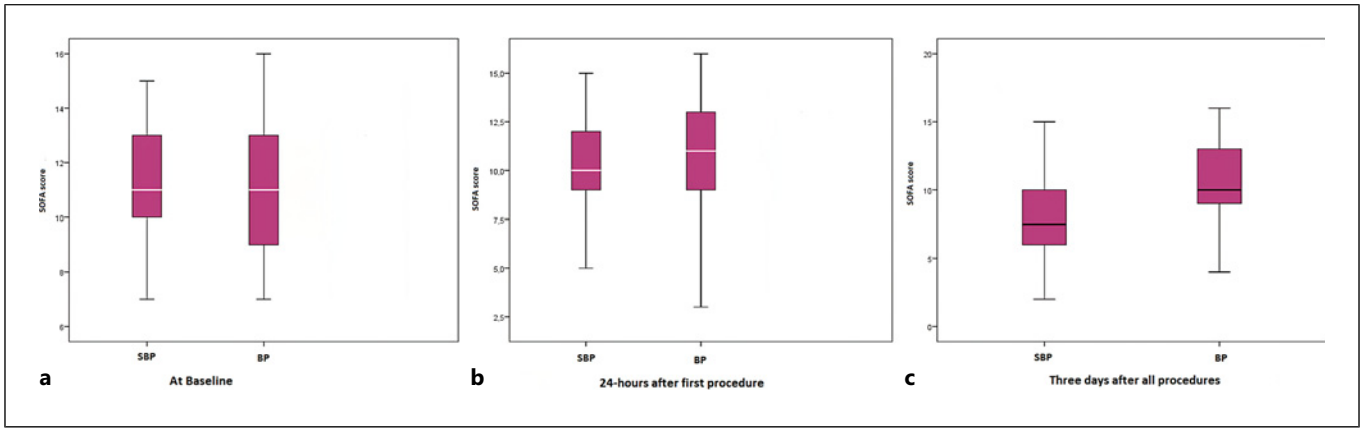

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Fig. 1. a–c SOFA score variations between SBP and BP groups. BP, "standard" blood purification; SBP, sequential blood purification.

Table 3. Factors associated with mortality

	Cox regression analysis	*p* value
	adjusted HR	
Age	1.00	0.99
Charlson comorbidity index	1.01	0.73
Days of symptoms before admission to ICU	0.98	0.61
Glasgow coma score	1.02	0.69
AKI at baseline (yes)	0.55	0.18
Severe ARDS at baseline (yes)	0.79	0.61
SOFA score at baseline	1.26	**0.02**
Late start of BP (yes)	3.22	<**0.01**
Vasopressors at baseline (yes)	0.84	0.73
Mechanical ventilation at baseline (yes)	0.81	0.71

ICU, intensive care unit; AKI, acute kidney injury; BP, blood purification. $p < 0.05$ was considered significant.

Reducing viral and bacterial load with the Seraph® filter and, consequently, directly reducing endotoxin levels was the most likely reason.

The mortality in our group of patients treated with sequential hemadsorption was significantly lower than the mortality of patients in the COSA registry with COVID-19 and bacterial superinfection treated with the Seraph® filter alone (42.4% vs 61.3%) and was even lower than those in other studies that analyzed the impact of hemadsorbers on survival in patients without confirmed bacterial superinfection [16, 44]. Although we are experiencing decline in incidence and severity of COVID-19, the results of this study could be relevant for other viral infections, especially upper respiratory tract infections which are often complicated with bacterial superinfections. Additional limitations are inherent to the study design, and further RCTs or case-control studies are needed before the wider use of sequential hemadsorption.

Conclusions

Critically ill patients with COVID-19 and bacterial superinfection treated with sequential hemadsorption survived significantly longer than ICU patients with COVID-19 treated with non-selective hemadsorption. BP treatment with the Seraph® filter leads to a significant improvement in respiratory status and a decrease in vasoactive support and reduces the severity of the SOFA score. Our results may suggest that COVID-19 ICU patients with bacterial superinfection are

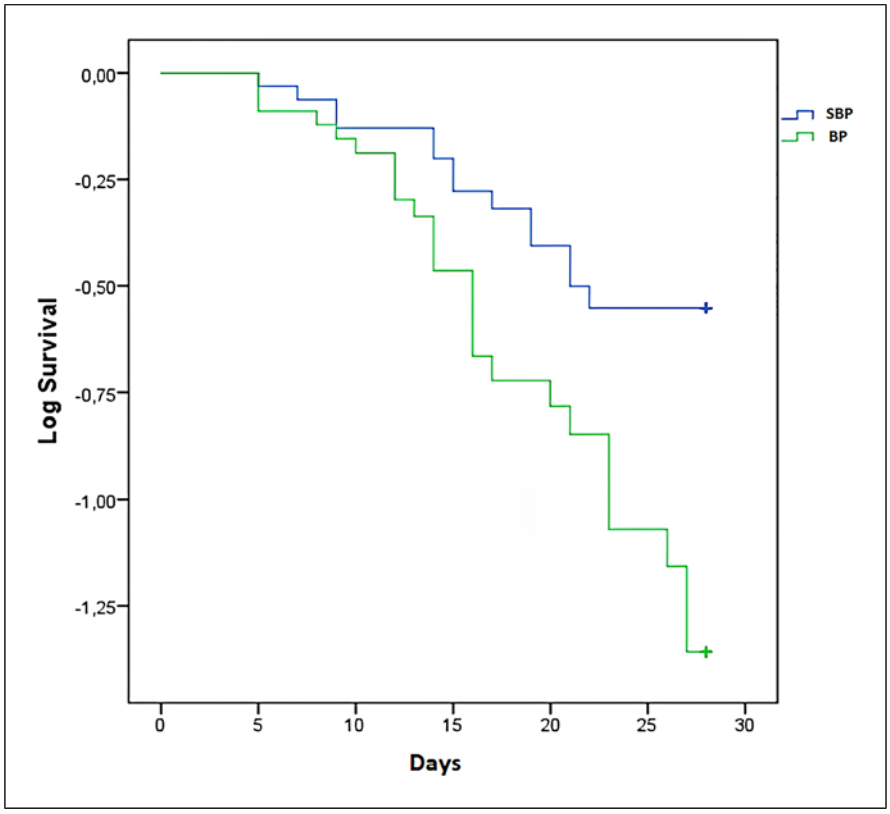

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Fig. 2. Kaplan-Meier analysis of survival probability according to SBP versus BP. BP, "standard" blood purification; SBP, sequential blood purification.

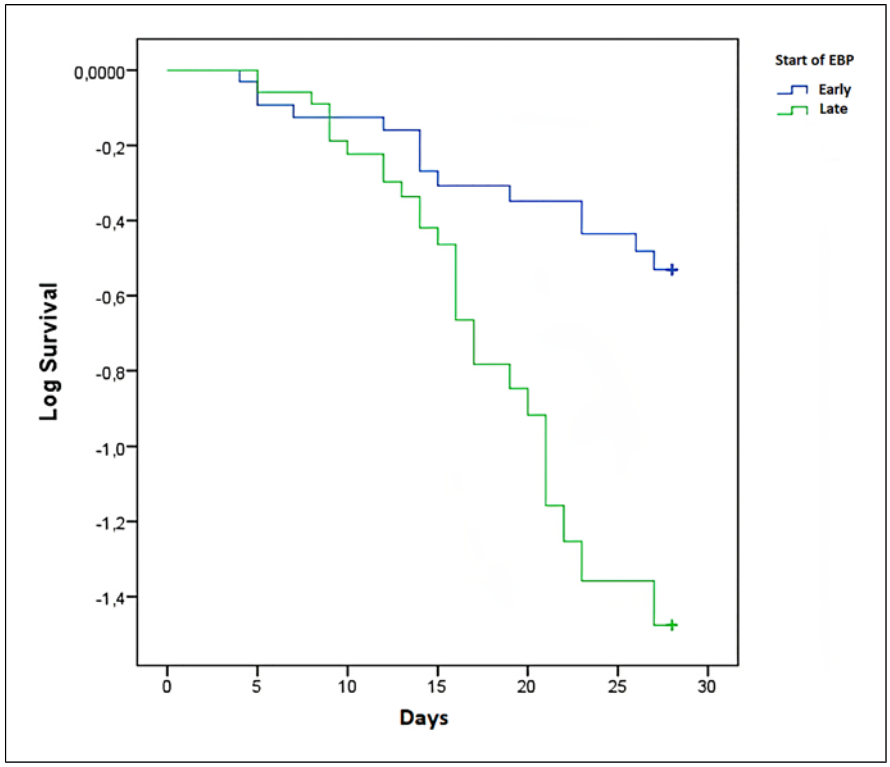

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Fig. 3. Kaplan-Meier analysis of survival probability according to early versus late start of EBP. EBP, extracorporeal blood purification.

potentially a target group for initiation of sequential hemadsorption, which should be confirmed in future randomized trials.

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Statement of Ethics

This study protocol was reviewed and approved by the hospital ethics committee (UHC Zagreb, Croatia-number:02/21-JG) following the Helsinki Declaration and its later amendments. Written informed consent to participate in the study was obtained from all participants.

Conflict of Interest Statement

The authors declare there is no conflict of interest related to the present manuscript and provide the following disclosures: Gianluca Villa has received support for travel expenses, hotel accommodations, and registration to meetings from Baxter. Claudio Ronco has received support for acting as an advisory board member for ASAHI, Baxter, GE, Jafron, and Medtronic, and speaker fees from Astute, bioMérieux, B. Braun, Cytosorbents, ESTOR, FMC, and Toray, all unrelated to this manuscript.

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Author Contributions

V.P. is the corresponding author and has contributed to the preparation of the paper (study concept, study design, data collection, data interpretation, writing, editing of text, approval of the final manuscript, all the above). I.S. has contributed to study design, data collection, data interpretation, writing, and approval of the final manuscript. D.L. has contributed to the study concept, data interpretation, and approval of the final manuscript. A.E. has contributed to data collection, data interpretation, writing, and approval of the final manuscript. D.K. has contributed to data collection, data interpretation, writing, and approval of the final manuscript. M.M. (Mate Mogus) has contributed to data collection, data interpretation, writing, and approval of the final manuscript. M.J. has contributed to data collection, data interpretation, and approval of the final manuscript. V.N. has contributed to data collection, data interpretation, and approval of the final manuscript. M.M. (Mirabel Mazar) has contributed to study design, data interpretation, editing of text, and approval of the final manuscript. S.M. has contributed to study design, data interpretation, editing of text, and approval of the final manuscript. G.V. has contributed to study design, data interpretation, writing, editing of text, and approval of the final manuscript. C.R. has contributed to data interpretation, writing, and approval of the final manuscript. The authors read and approved the final manuscript.

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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