

# CytoSorb Rescue for COVID-19 Patients With Vasoplegic Shock and Multiple Organ Failure: A Prospective, Open-Label, Randomized Controlled Pilot Study\*

**OBJECTIVES:** To investigate the effect of extracorporeal cytokine reduction by CytoSorb (CytoSorbents, Monmouth Junction, NJ) on COVID-19-associated vasoplegic shock.

**DESIGN:** Prospective, randomized controlled pilot study.

**SETTING:** Eight ICUs at three sites of the tertiary-care university hospital Charité–Universitätsmedizin Berlin.

**PATIENTS:** COVID-19 patients with vasoplegic shock requiring norepinephrine greater than 0.2 µg/kg/min, C-reactive protein greater than 100 mg/L, and indication for hemodialysis.

**INTERVENTIONS:** Randomization of 1:1 to receive CytoSorb for 3–7 days or standard therapy. To account for inadvertent removal of antibiotics, patients in the treatment group received an additional dose at each adsorber change.

**MEASUREMENTS AND MAIN RESULTS:** The primary endpoint was time until resolution of vasoplegic shock, estimated by Cox-regression. Secondary endpoints included mortality, interleukin-6 concentrations, and catecholamine requirements. The study was registered in the German Registry of Clinical Trials (DRKS00021447). From November 2020 to March 2021, 50 patients were enrolled. Twenty-three patients were randomized to receive CytoSorb and 26 patients to receive standard of care. One patient randomized to cytokine adsorption was excluded due to withdrawal of informed consent. Resolution of vasoplegic shock was observed in 13 of 23 patients (56.5%) in the CytoSorb and 12 of 26 patients (46.2%) in the control group after a median of 5 days (interquartile range [IQR], 4–5 d) and 4 days (IQR, 3–5 d). The hazard ratio (HR) for the primary endpoint, adjusted for the predefined variables age, gender, extracorporeal membrane oxygenation-therapy, or time from shock onset to study inclusion was HR, 1.23 (95% CI, 0.54–2.79);  $p = 0.63$ . The mortality rate was 78% in the CytoSorb and 73% in the control group (unadjusted HR, 1.17 [95% CI, 0.61–2.23];  $p = 0.64$ ). The effects on inflammatory markers, catecholamine requirements, and the type and rates of adverse events were similar between the groups.

**CONCLUSIONS:** In severely ill COVID-19 patients, CytoSorb did not improve resolution of vasoplegic shock or predefined secondary endpoints.

**KEY WORDS:** acute respiratory distress syndrome; COVID-19; CytoSorb; extracorporeal cytokine elimination; hyperinflammation; vasoplegic shock

COVID-19 has become a major global health threat. Approximately 17% of patients hospitalized with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) require mechanical ventilation for COVID-19-associated pneumonia, which can progress to acute respiratory distress syndrome (ARDS) and multiple organ failure (1).

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In a considerable proportion of critically ill patients, acute disease progression has been attributed to a hyperinflammatory state as interleukin-6 (IL-6) levels correlate with COVID-19 severity (2), and elevated IL-6 levels have been associated with poor outcome in severe COVID-19 ARDS (3). Furthermore, only the use of dexamethasone and tocilizumab (anti-IL-6 receptor antibody) has so far been shown to improve outcome in critically ill COVID-19 patients (4, 5), suggesting a beneficial effect by reducing the cytokine-associated immune response. Extracorporeal treatment approaches include to improve virus elimination (6, 7), optimization of the von Willebrand factor/a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 ratio (8), or cytokine reduction. The CytoSorb adsorber (CytoSorbents, Monmouth Junction, NJ) contains hemocompatible porous polymer chains capable of reducing molecules of medium weight (5–55 kDa), such as cytokines, toxins, and therapeutic drugs from the blood (9). Although data on clinical effectiveness are inconsistent (10–12), CytoSorb is broadly used in sepsis patients (10, 13). The adsorber can easily be integrated in extracorporeal blood-circulation devices such as hemodialysis or extracorporeal membrane oxygenation (ECMO) and is considered safe (10, 11, 14). CytoSorb has been Conformité Européenne-certified in the European Union, and the Food and Drug Administration authorized its emergency use in COVID-19 patients (15), as potential beneficial effects have been described in case series (16, 17). However, a recent single-center randomized controlled trial (RCT) reported potentially harmful effects of CytoSorb in COVID-19 patients on ECMO therapy (18).

Our study aimed to investigate the effect of CytoSorb in COVID-19 patients with vasoplegic shock, hyperinflammation, and indication for continuous venovenous hemodialysis (CVVHD). We hypothesized that CytoSorb treatment might lead to a faster recovery from vasoplegic shock and improve outcomes compared with standard treatment.

## MATERIALS AND METHODS

### Study Design

CytoResc was a prospective, single-center, open-label, randomized controlled pilot study to investigate the effect of CytoSorb in COVID-19 patients with vasoplegic shock, laboratory signs of hyperinflammation, and

indication for CVVHD. CytoResc was conducted on eight ICUs at three sites of the Charité—Universitätsmedizin Berlin. The study protocol was published previously (19), but subsequently, three modifications were introduced (**Supplemental Methods**, Supplemental Digital Content 1, <http://links.lww.com/CCM/H51>). The original protocol and amendment were approved by the local ethics committee of the Charité (EA1/069/20). The study was registered in the German Registry of Clinical Trials (DRKS00021447) on April 27, 2020. The trial was conducted according to the Declaration of Helsinki. Written informed consent was obtained from patients or their legal representatives. After the inclusion of 10 patients per randomization group, the preliminary interim safety and efficacy data were reviewed by an independent data safety monitoring board and the local ethics committee, which approved study continuation.

### Patient Selection

All patients greater than or equal to 18 years persistently tested positive for SARS-CoV-2 via polymerase chain reaction and presenting with vasoplegic shock (defined as need for noradrenaline greater than 0.2 µg/kg/min to maintain a mean arterial pressure [MAP] greater than or equal to 65 mm Hg), a C-reactive protein (CRP) value greater than 100 mg/L, and indication for CVVHD were eligible for study inclusion. All patients had respiratory failure requiring invasive mechanical ventilation. Patients who received tocilizumab and pregnant women were excluded. The investigators performed the consecutive patient screening and enrollment. At inclusion, the attending physician was asked to confirm complete eligibility and that death within the next 24 hours was not considered imminent.

### Randomization and Masking

Randomization was performed by the Clinical Study Center of the Charité using a computer-generated 4 × 4 block regime stratified for the participating ICUs with 1:1 treatment allocation to standard of care or additional CytoSorb treatment. Therapy was applied open-label.

### Procedures

Outside the trial interventions, all patients received standard intensive care treatment according to

ARDS and sepsis guidelines (20, 21). More information concerning volume management, catecholamine therapy, the hemodialysis protocol, and antimicrobial therapy can be found in the Supplemental Methods (Supplemental Digital Content 1, <http://links.lww.com/CCM/H51>). CytoSorb-treatment was initiated right after fulfilling the inclusion criteria and conducted for 3–7 days according to the discretion of the treating physicians. The CytoSorb adsorber was incorporated in the CVVHD circuit before the dialysis filter and changed every 24 hours. The control group had no device incorporated in the CVVHD circuit. To account for inadvertent removal of antibiotics (22), patients in the treatment group received an additional dose at each adsorber change. Prespecified laboratory parameters, outcome variables, and adverse events within 30 days were documented in the electronic clinical research file.

## Outcomes

The primary outcome was time until resolution of vasoplegic shock (defined as no need for vasopressors for at least 8 hr to sustain an MAP greater than or equal to 65 mm Hg). Secondary endpoints were 7-day mortality after fulfilling the inclusion criteria, 30-day mortality, mortality until ICU and hospital discharge, measurements of IL-6 on day 1 and 3 of intervention, duration of mechanical ventilation, duration of ICU-stay, catecholamine dose on day 1, 2, 3, 7, and 30 after start of CytoSorb. The combined vasopressor dose (norepinephrine, epinephrine, and vasopressin) was calculated according to Lambden et al (23).

## Statistical Analysis

In cooperation with the Charité Institute of Biometry and Clinical Epidemiology, this study was conducted as an investigator-initiated pilot study to explore the feasibility of the intervention and the treatment effect. Due to its exploratory nature (unprecedented disease course in a new viral disease, and heterogeneous and sparse data on the efficacy of CytoSorb in COVID-19 patients) and inestimable recruitment variables (patient flow and condition), no specific assumptions could be made regarding the effect size of the intervention. The analyses are, therefore, explorative; *p* values should be interpreted as such; and no adjustment for multiple testing was performed.

The effect of the CytoSorb-treatment on the primary endpoint was estimated and tested by a Cox proportional hazards regression model with time until resolution of vasoplegic shock as outcome variable censored at the time of death. The analysis was done unadjusted and adjusted for the following variables: age, sex, ECMO-therapy, and binary variable for time from beginning of shock until study inclusion smaller or larger than 24 hours. For sensitivity analysis, we added an interaction term for intervention group and beginning of shock. Results are presented as hazard ratios (HRs) with 95% CI. In addition, the time until resolution of vasoplegic shock in the intervention and control group was depicted in Kaplan-Meier curves.

Secondary endpoints were reported descriptively as median with interquartile range (IQR). To explore differences between the treatment groups, we used Cox proportional hazards regressions for time-to-event endpoints, Chi-square tests for nominal endpoints, and Wilcoxon-Mann-Whitney tests for continuous variables. ICU-mortality was analyzed by Cox-regression and Kaplan-Meier analyses. Associations between catecholamine use and prespecified laboratory outcomes were depicted as boxplots and analyzed by Wilcoxon-Mann-Whitney tests. No imputation was performed for missing data points. Descriptive statistics and boxplots were performed using R 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). Cox-models, and Chi-square tests and Wilcoxon-Mann-Whitney were performed using Statistical Package for the Social Sciences (SPSS) Version 25 (IBM Corp, Armonk, NY).

## RESULTS

From November 11, 2020, to March 15, 2021, all ICU patients tested positive for SARS-CoV-2 ( $n = 907$ ) were screened for eligibility, and 50 patients were enrolled in the trial. Twenty-three patients (46.9%) were randomized to receive CytoSorb-treatment and 26 (53.1%) to receive standard treatment. One patient primarily randomized to the CytoSorb-group was excluded due to withdrawal of informed consent before start of the intervention (**Supplemental Fig. 1**, Supplemental Digital Content 2, <http://links.lww.com/CCM/H52>). **Table 1** shows the baseline patient characteristics. Comorbidities and indicators for disease severity were balanced between both groups. Median norepinephrine dose at inclusion was 0.32  $\mu\text{g}/\text{kg}/\text{min}$  (IQR, 0.3–0.4  $\mu\text{g}/\text{kg}/\text{min}$ ) in the CytoSorb and 0.3  $\mu\text{g}/\text{kg}/\text{min}$  (IQR,

**TABLE 1.**  
**Baseline Characteristics of the Study Cohort**

Characteristic	CytoSorb (n = 23)	Control (n = 26)
Age, median (IQR), yr	61 (58–65)	66 (60–71)
Male sex, no. of patients (%)	21 (91.3)	20 (76.9)
Body mass index, median (IQR), kg/m <sup>2</sup>	29 (25–36)	29 (25–34)
Comorbidities		
Hypertension, no. of patients (%)	15 (65.2)	17 (65.4)
Diabetes, no. of patients (%)	3 (13.0)	11 (42.3)
Chronic kidney disease (stage II–IV), no. of patients (%)	6 (30)	7 (30.4)
Coronary artery disease, no. of patients (%)	2 (8.7)	3 (11.5)
Chronic obstructive pulmonary disease, no. of patients (%)	2 (8.7)	4 (15.4)
Malignancy, no. of patients (%)	1 (4.3)	4 (15.4)
Immunosuppressive therapy, no. of patients (%)	5 (21.7)	4 (15.4)
Any comorbidity, no. of patients (%)	19 (82.6)	15 (57.7)
Clinical characteristics at study inclusion		
Sequential Organ Failure Assessment score, median (IQR)	14 (13–15)	14 (13–16)
Time since hospital admission, median (IQR), d	17 (9–23)	12 (9–23)
Time since admission to ICU, median (IQR), d	15 (7–19)	10 (9–20)
Time since beginning of shock, <sup>a</sup> median (IQR), d	1 (0–1)	1 (0–1)
Antimicrobial therapy at inclusion, no. of patients (%)	22 (95.7)	25 (96.2)
Horowitz index (Pao <sub>2</sub> /Fio <sub>2</sub> ), median (IQR), mm Hg <sup>b</sup>	133 (106–182)	142 (128–172)
Extracorporeal membrane oxygenation (ECMO) therapy at study inclusion, no. of patients (%)	9 (39.1)	7 (26.9)
Time on ECMO before study inclusion, median (IQR), d	3 (0–8)	4 (3–13)
ECMO blood flow at study inclusion, median (IQR), L/min	4.3 (3.4–5.25)	3.8 (3.5–5.1)
ECMO gas flow at study inclusion, median (IQR), L/min	3.5 (2–4.5)	4 (2–9.5)
Catecholamine therapy at inclusion		
Number of catecholamines, median (IQR)	1 (1–1.5)	1 (1–1)
Patients on norepinephrine (%)	23 (100)	26 (100)
Norepinephrine dose, median (IQR), µg/kg/min	0.32 (0.3–0.4)	0.3 (0.2–0.3)
Patients on epinephrine (%)	1 (4.3)	2 (7.7)
Epinephrine dose, median (IQR), µg/kg/min	0.08 (0.08–0.08)	0.1 (0.04–0.1)
Patients on vasopressin (%)	6 (26.1)	2 (7.7)
Vasopressin dose, median (IQR), international units/hr	1.25 (1–1.9)	2 (2–2)
Patients on dobutamine (%)	0 (0)	1 (3.8)
Dobutamine dose, median (IQR), µg/kg/min	–	3 (3–3)
Inflammatory parameters at study inclusion		
Leucocyte count, median (IQR), count/nL	13.7 (9.4–18.1)	14.19 (9.7–22.6)
C-reactive protein, median (IQR), mg/dL	260.3 (171.4–307.5)	237.2 (169–327.9)
Procalcitonin, median (IQR), µg/L	3.95 (1.6–6.2)	4.55 (2.8–13.5)
Interleukin-6, median (IQR), ng/L, no. of patients (%)	591.0 (23.9–1,852.8), 22 (95)	552.5 (299.5–1,787.5), 22 (85)

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.

<sup>a</sup>Defined as norepinephrine > 0.2 µg/kg/min.

<sup>b</sup>Pao<sub>2</sub>/Fio<sub>2</sub> is displayed only for patients without ECMO therapy.

0.2–0.3 µg/kg/min) in the control group. Both groups demonstrated markedly elevated CRP levels with 260.3 mg/dL (IQR, 171.4–307.5 mg/dL) and 237.2 mg/dL (IQR, 169–327.9 mg/dL) and serum IL-6 levels with 591.0 ng/L (IQR, 23.9–1,852.8 ng/L) and 552.5 ng/L (IQR, 299.5–1,787.5 ng/L) in the CytoSorb and control groups, respectively. In the CytoSorb-group, six of 23 patients (26.1%) and three of 26 patients (11.5%) in the control group had positive blood cultures. An additional 10/23 patients (43.5%) in the CytoSorb-group and 10/26 patients (38.5%) in the control group had a pathogen detected in a sample other than blood cultures (**Supplemental Table 1**, Supplemental Digital Content 3, <http://links.lww.com/CCM/H53>; **Supplemental Table 2**, Supplemental Digital Content 4, <http://links.lww.com/CCM/H54>). All patients were mechanically ventilated and received steroids according to the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial (4). The majority received hydrocortisone for vasoplegic shock (CytoSorb: 69.6%; control: 80.8%) (Supplemental Table 1, Supplemental Digital Content 3, <http://links.lww.com/CCM/H53>). Nine patients in the CytoSorb-group (39.1%) and seven patients (26.9%) in the control

group received ECMO therapy at inclusion (Table 1). Patients randomized to the CytoSorb-group received treatment for 3 days (IQR, 3–4 d) (**Table 2**). For additional baseline characteristics at ICU admission, see **Supplemental Table 3** (Supplemental Digital Content 5, <http://links.lww.com/CCM/H55>).

### Primary Outcome

The primary outcome, time until resolution of vasoplegic shock, was similar between the groups with 5 days (IQR, 4–5 d) in the CytoSorb and 4 days (IQR, 3–5 d) in the control group. Resolution of shock was reached in 13 of 23 patients (56.5%) in the CytoSorb-group and 12 of 26 patients (46.2%) in the control group (Table 2). The unadjusted HR for the primary endpoint was 1.23 (95% CI, 0.56–2.71;  $p = 0.60$ ) for the CytoSorb-group. Adjustment for age, gender, ECMO therapy, and duration of shock less than 24 hours until inclusion demonstrated similar results (HR, 1.23 [95% CI, 0.54–2.79];  $p = 0.63$ ) (Table 3). **Figure 1A** shows the Kaplan-Meier curve for resolution of vasoplegic shock censored for death.

**TABLE 2.**  
**Outcomes of the Study Cohort**

Outcome	CytoSorb (n = 23)	Control (n = 26)	p
Resolution of vasoplegic shock, no. of patients (%)	13 (56.5)	12 (46.2)	–
Duration norepinephrine > 0.2 µg/kg/min, median (IQR), d	2 (1–2)	1 (0–2)	–
Time until resolution of vasoplegic shock, median (IQR), d	5 (4–5)	4 (3–5)	–
Overall mortality on ICU, no. of patients (%)	18 (78.3)	19 (73.1)	–
7-d mortality, no. of patients (%)	6 (26.1)	9 (34.6)	0.52 <sup>a</sup>
30-d mortality, no. of patients (%)	17 (73.9)	15 (57.7)	0.23 <sup>a</sup>
Discharged from ICU, no. of patients (%)	5 (21.7)	7 (26.9)	0.67 <sup>a</sup>
Duration of stay in ICU in surviving patients, median (IQR), d	66 (33–77)	62 (56–68)	1.00 <sup>b</sup>
Duration of stay in hospital in all surviving patients, median (IQR), d	53 (29.5–66)	65 (60–69)	0.32 <sup>b</sup>
Patients free from mechanical ventilation at ICU discharge in surviving patients (%)	5 (100)	6 (85.7)	–
Duration of mechanical ventilation in ICU-surviving patients, median (IQR), d <sup>c,d</sup>	41 (31.5–62.5)	52 (40–60)	0.76 <sup>b</sup>
Duration of ECMO-therapy, median (IQR), d	11 (4.8–22.2)	8 (5–21)	0.92 <sup>b</sup>
Overall patients on ECMO therapy, no. of patients (%)	12 (52.2)	10 (38.5)	0.34 <sup>b</sup>
Patients free from hemodialysis at ICU discharge (%)	4 (80)	6 (85.7)	–

(Continued)

**TABLE 2. (Continued).**  
**Outcomes of the Study Cohort**

Outcome	CytoSorb (n = 23)	Control (n = 26)	p
Duration of hemodialysis in ICU-surviving patients, median (IQR), d <sup>c,d</sup>	35 (16–72.5)	36 (32–55)	0.88 <sup>b</sup>
Catecholamine dose, median (IQR), (µg/kg/min) at day 1 <sup>e</sup>	0.49 (0.25–0.81)	0.31 (0.2–0.55)	0.06 <sup>b</sup>
No. of patients (%)	22 (95.7)	23 (88.5)	
Catecholamine dose, median (IQR), (µg/kg/min) at day 2 <sup>e</sup>	0.26 (0.16–0.53)	0.2 (0.15–0.43)	0.43 <sup>b</sup>
No. of patients (%)	17 (73.9)	19 (73.1)	
Catecholamine dose, median (IQR), (µg/kg/min) at day 3 <sup>e</sup>	0.17 (0.13–0.26)	0.17 (0.13–0.36)	0.70 <sup>b</sup>
No. of patients (%)	14 (60.9)	14 (53.8)	
Catecholamine dose, median (IQR), (µg/kg/min) at day 7 <sup>e</sup>	0.12 (0.05–0.38)	0.13 (0.08–0.4)	0.84 <sup>b</sup>
No. of patients (%)	6 (26.1)	7 (26.9)	
Cumulative fluid balance, study inclusion until day 1, median (IQR), mL	4,338 (2,624.5–6,720)	3,427 (2,217–5,806)	0.37 <sup>b</sup>
Cumulative fluid balance, study inclusion until day 3, median (IQR), mL	4,687 (2,751–7,623)	2,193 (–425 to 4,604)	0.12 <sup>b</sup>
No. of patients (%)	17 (73.9)	21 (80.8)	
Cumulative fluid balance, study inclusion until day 7, median (IQR), mL	4,486 (1,515–8,284)	1,583 (815–5,559)	0.34 <sup>b</sup>
No. of patients (%)	17 (73.9)	17 (65.4)	
Cumulative fluid balance study, inclusion until norepinephrine < 0.2 µg/kg/min, median (IQR), mL	3,745 (1,012–7,409)	2,925 (1,666–3,655.5)	0.30 <sup>b</sup>
No. of patients (%)	17 (73.9)	19 (73.1)	
Cumulative fluid balance, study inclusion until resolution of shock, median (IQR), mL	5,865 (3,609–7,134)	2,415 (1,057–4,011.2)	0.43 <sup>b</sup>
No. of patients (%)	13 (56.5)	12 (46.2)	
Interleukin-6 at day 3, median (IQR), ng/L	66.3 (35–422)	103 (30–295)	0.78 <sup>b</sup>
No. of patients (%)	15 (65.2)	19 (73.1)	
Interleukin-6 at day 7, median (IQR), ng/L	69.3 (44.7–445)	120 (43.7–925.5)	0.56 <sup>b</sup>
No. of patients (%)	16 (69.6)	17 (65.4)	
Sequential Organ Failure Assessment score at day 7, median (IQR)	12 (9.5–15.5)	12 (10.5–14.5)	0.61 <sup>b</sup>
Duration CytoSorb therapy, median (IQR), d	3 (3–4)	0 (0)	–

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range.

<sup>a</sup> Chi-squared test.

<sup>b</sup> Wilcoxon-Mann-Whitney *U* test.

<sup>c</sup> Time since study inclusion.

<sup>d</sup> Time for end of mechanical ventilation and hemodialysis was censored at ICU-discharge.

<sup>e</sup> Calculation of the combined catecholamine dose was performed according to Lambden et al (23).

As sensitivity analysis, an additional Cox-regression with an interaction term for shock duration and CytoSorb-treatment was done. It revealed no advantage for early implementation of CytoSorb less than or equal to 24 hours for resolution of vasoplegic shock (HR, 1.35 [95% CI, 0.42–4.35]; *p* = 0.62) or

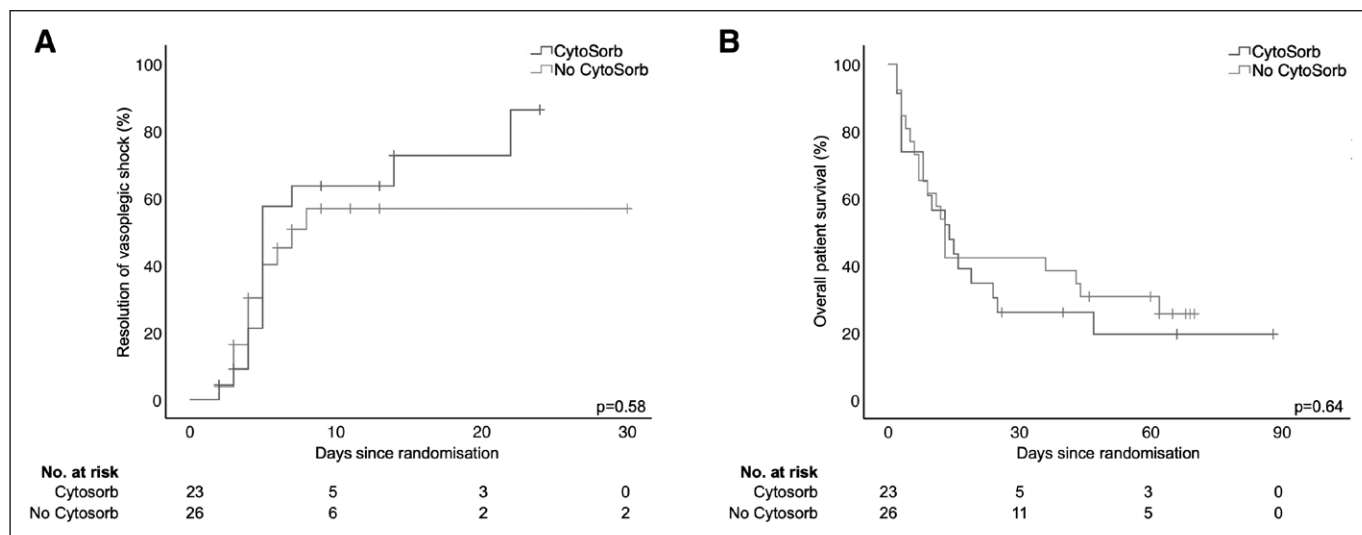
**TABLE 3.**  
**Cox-Regression for Time Until Resolution of Vasoplegic Shock and Time Until Death in the ICU**

Variables	Hazard Ratio (95% CI)	p
Resolution of vasoplegic shock		
Unadjusted analysis		
CytoSorb treatment	1.23 (0.56–2.71)	0.60
Adjusted analysis		
CytoSorb treatment	1.23 (0.54–2.79)	0.63
Age per year	1.02 (0.97–1.07)	0.52
Sex, female	1.21 (0.39–3.82)	0.74
ECMO therapy	1.10 (0.34–3.54)	0.88
Shock duration ≤ 24 hr prior to inclusion	2.19 (0.90–5.30)	0.08
ICU mortality		
Unadjusted analysis		
CytoSorb treatment	1.17 (0.61–2.23)	0.64
Adjusted analysis		
CytoSorb treatment	0.91 (0.46–1.81)	0.79
Age per year	1.01 (0.97–1.05)	0.68
Sex, female	0.66 (0.27–1.65)	0.37
ECMO therapy	2.80 (1.31–6.02)	0.01
Shock duration ≤ 24 hr prior to inclusion	1.47 (0.73–2.98)	0.29

ECMO = extracorporeal membrane oxygenation.

Resolution of vasoplegic shock: Cox-regression for time until resolution of vasoplegic shock. A hazard ratio > 1 indicates a better chance for shock resolution compared with the reference group.

ICU mortality: Cox-regression for time until death in the ICU. Hazard ratio > 1 indicates a higher risk of death during the ICU stay.



**Figure 1.** Kaplan-Meier curves for resolution of vasoplegic shock and patient survival. **A**, Kaplan-Meier curves for the primary endpoint—resolution of vasoplegic shock censored for death. **B**, Kaplan-Meier curves for patient survival censored for discharge from ICU.

ICU-mortality (HR, 0.95 [95% CI, 0.34–2.63];  $p = 0.92$ ) (**Supplemental Table 4**, Supplemental Digital Content 6, <http://links.lww.com/CCM/H56>; **Supplemental Table 5**, Supplemental Digital Content 7, <http://links.lww.com/CCM/H57>).

## Secondary Outcomes

Secondary endpoints did not differ between both groups (Table 2). Death in the ICU occurred in 18/23 patients (78%) in the CytoSorb and in 19/26 patients (73%) in the control group (Table 2; **Fig. 1B**; **Supplemental Table 6**, Supplemental Digital Content 8, <http://links.lww.com/CCM/H58>). The unadjusted HR for ICU-mortality was 1.17 (95% CI, 0.61–2.23;  $p = 0.64$ ). Adjustment for age, gender, ECMO-therapy, and shock duration less than 24 hours prior to inclusion did not relevantly change the results (HR, 0.91 [95% CI, 0.46–1.81;  $p = 0.79$ ]) (Table 3). Of note, the higher mortality of patients receiving ECMO therapy at inclusion with seven of seven (100%) in the control versus seven of nine (78%) in the CytoSorb-group had a pronounced effect on the adjusted analysis.

The median catecholamine use during the first 7 days is displayed in **Figure 2, A and B**. No obvious differences were detected between the CytoSorb and the control group after 3 and 7 days (norepinephrine: 3 d,  $p = 0.37$ ; norepinephrine: 7 d,  $p = 0.60$ ; combined vasopressor dose: 3 d;  $p = 0.70$  and 7 d;  $p = 0.84$ ) (Fig. 2, A and B; Table 2). For individual courses of catecholamine use for each patient, see **Supplemental Figure 2** (Supplemental Digital Content 9, <http://links.lww.com/CCM/H59>). Due to the increased vasopressin use in the CytoSorb-group, we performed an additional COX-regression. The use of vasopressin did not affect the resolution of shock but was associated with higher mortality (**Supplemental Table 7**, Supplemental Digital Content 10, <http://links.lww.com/CCM/H60>). The cumulative fluid balance over the first 7 days after study inclusion was comparable, although patients in the CytoSorb-group tended to require numerically higher fluid volumes (Table 2; **Supplemental Fig. 3**, Supplemental Digital Content 11, <http://links.lww.com/CCM/H61>).

**Figure 2, C and D**, shows boxplots of IL-6 and CRP over time. Median values of inflammatory parameters decreased without difference between the groups (IL-6 day 3;  $p = 0.78$ , IL-6 day 7;  $p = 0.56$ , CRP day 3;  $p = 0.92$ , CRP day 7;  $p = 0.56$ ). See **Supplemental Figure 4**

(Supplemental Digital Content 12, <http://links.lww.com/CCM/H62>) for individual patient data on IL-6 concentrations over time. To account for secondary infections at study inclusion, we performed a COX-regression including microbiologic findings, which resulted in no relevant changes in resolution of shock and mortality (**Supplemental Table 8**, Supplemental Digital Content 13, <http://links.lww.com/CCM/H63>).

## Adverse Events

During the trial, 49 adverse events occurred in 21 of 23 patients (91.3%) in the CytoSorb-group, and 47 adverse events occurred in 23 of 26 patients (88.5%) in the control group (**Supplemental Table 9**, Supplemental Digital Content 14, <http://links.lww.com/CCM/H64>). Arrhythmias, severe infectious complications, and bleeding were the most common adverse events. The types and rates of adverse events were rather similar in both groups with exception of arrhythmias, which occurred more frequently in the CytoSorb-group.

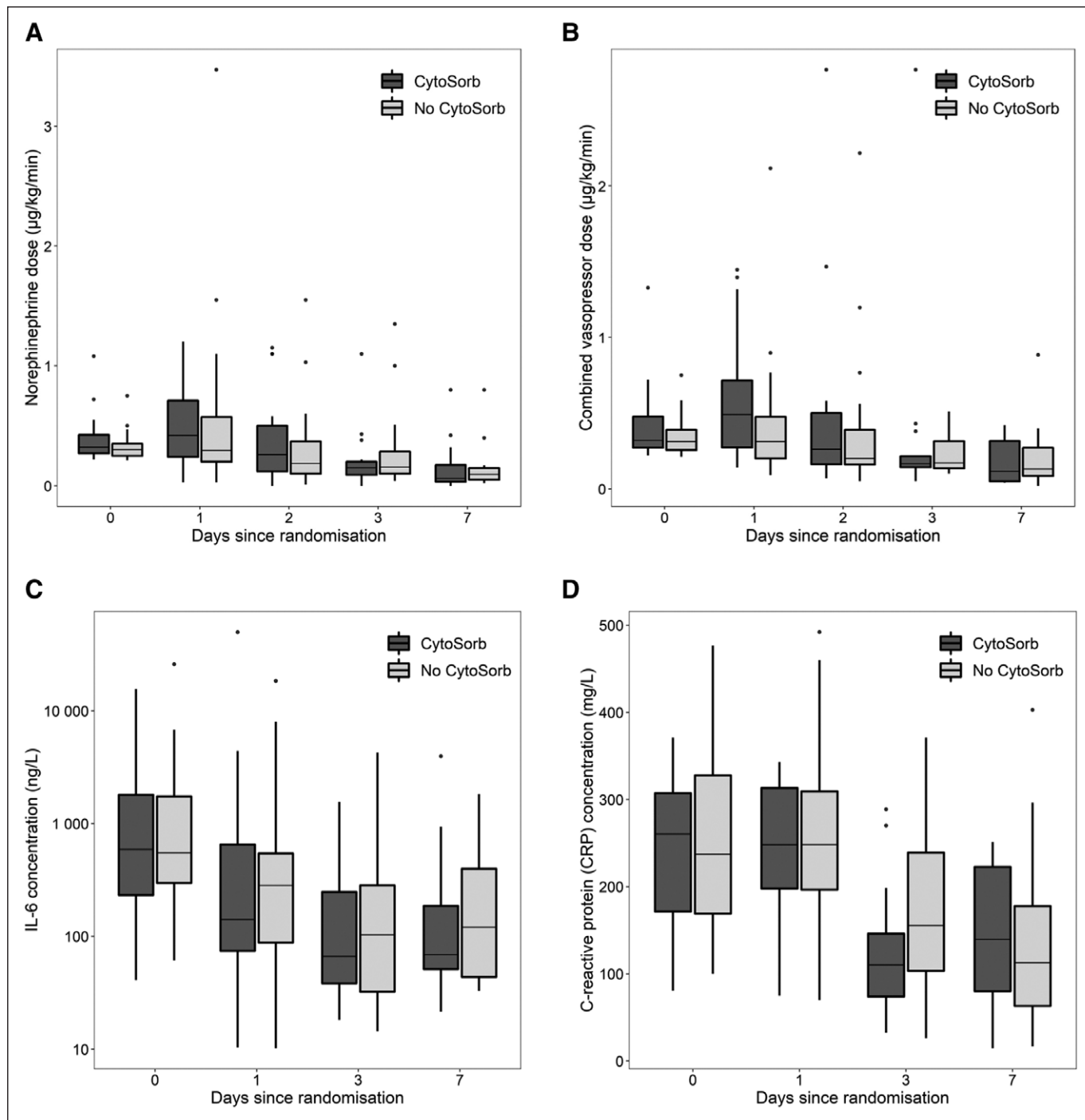
## DISCUSSION

In this randomized controlled pilot study of COVID-19 patients with vasoplegic shock, hyperinflammation, and indication for CVVHD, CytoSorb adsorption did not improve resolution of shock compared with patients treated with standard therapy. Although the Kaplan-Maier curve for the CytoSorb-group visually separated from the control group, this effect was driven by low remaining case numbers. Mortality rates showed no marked difference between the groups. There were no obvious differences in catecholamine requirements or the kinetics of inflammatory parameters (e.g., IL-6 and CRP).

Data on clinical effectiveness of CytoSorb are inconsistent. Although register data, single-center, and retrospective studies implied a possible advantage of CytoSorb-therapy (10, 14, 24), two RCTs, one in sepsis patients and one in cardiac-surgery patients, did not find a decrease in cytokines or improved clinical outcome with CytoSorb-treatment (11, 12). However, this may have been a consequence of the heterogeneous causes and clinical presentations in septic patients and the rather low cytokine levels in surgical patients.

In critically ill COVID-19 patients, several observations indicate a hyperinflammatory state (25, 26). Although evidence indicates lower IL-6 concentrations





**Figure 2.** Catecholamine use and inflammatory parameters over time. Boxplots plotted over time. Outliers are displayed as *dots*. **A**, Median norepinephrine dose over time: No relevant differences were detected between the CytoSorb group and control group after 3 d ( $p = 0.37$ ) and 7 d ( $p = 0.60$ ). **B**, Median combined vasopressor dose over time: No relevant differences were detected between the CytoSorb group and control group after 3 d ( $p = 0.70$ ) and 7 d ( $p = 0.84$ ). **C**, Serum interleukin-6 (IL-6) concentrations shown as logarithmic scale. No relevant differences were detected between the CytoSorb group and control group after 3 d ( $p = 0.78$ ) and 7 d ( $p = 0.56$ ) of treatment. **D**, Total C-reactive protein (CRP) levels. No relevant differences were detected between the CytoSorb group and control after 3 d ( $p = 0.92$ ) and 7 d ( $p = 0.56$ ) of treatment.

in COVID-19 patients compared with other ARDS cohorts and the pathophysiological mechanisms of a dysregulated immune response remain a matter of debate (27, 28), the observation that immunomodulating

agents such as dexamethasone and tocilizumab improve outcomes in COVID-19 patients requiring organ support provides a rationale for strategies to reduce cytokine load (4, 5). In our study, all patients received

steroids according to the RECOVERY trial (4). As the beneficial effects of tocilizumab were not known at the time of study conduction (5), patients receiving tocilizumab were excluded to avoid masking the effect of extracorporeal cytokine adsorption.

To date, there is one RCT investigating the effect of CytoSorb in COVID-19 patients (18). Supady et al (18) found a significantly higher mortality in 14 of 17 COVID-19 patients (82%) with indication for ECMO therapy treated with CytoSorb compared with four of 17 ECMO patients (24%) treated without cytokine adsorption, calling for a very careful application of CytoSorb in COVID-19 patients requiring ECMO. However, only approximately 7% of mechanically ventilated COVID-19 patients receive ECMO-therapy (1). The results might, therefore, not be applicable to a broader patient population. Furthermore, patient inclusion was conducted independent of inflammatory markers or signs of vasoplegic shock.

In contrast, we studied the effect of CytoSorb in COVID-19 patients with vasoplegic shock, hyperinflammation, and indication for CVVHD given the urgent need for rapid shock reversal in this patient group. Compared with the results of Supady et al (18), we did not observe excess mortality in the CytoSorb-group. Nonetheless, mortality rates in our study were very high in both the CytoSorb (78%) and the control (73%) group. At study inclusion, nine and seven patients received ECMO-therapy in the CytoSorb and the control group, respectively, of which seven of nine (78%) in the CytoSorb and all seven (100%) in the control group died. Although, the higher mortality rate in ECMO patients in the control group had a pronounced effect on the adjusted COX-regression for ICU-mortality, this did not relevantly change the results. Although mortality rates up to 48% have been reported in critically ill COVID-19 patients (29), mortality increases significantly in patients with acute kidney injury reaching up to 57–70% in patients requiring dialysis (1, 30, 31). This might explain our results since exclusively patients with shock and indication for CVVHD were included.

Given the severity of disease with vasoplegic shock and multiple organ failure, it is possible that our intervention was applied too late during the disease course. In fact, a recent study showed the safe application of early extracorporeal cytokine adsorption (less than 24 hr) in septic shock as stand-alone therapy without

dialysis with significant reductions of norepinephrine requirements and procalcitonin (PCT) levels compared with controls (32). As the optimal timing of cytokine adsorption is still unknown, we performed an additional Cox-regression with an interaction term for shock duration less than or equal to 24 hours prior to inclusion and treatment groups. Although limited by the overall number of cases, this analysis did not reveal an advantage for early implementation of CytoSorb less than or equal to 24 hours. Another implication for the optimal timing of CytoSorb-treatment is the discrimination between hyperinflammation and secondary infection. Readily available biomarkers such as CRP, PCT, IL-6, or ferritin are imperfect discriminators between these entities. In our cohort, all patients had markedly elevated inflammatory markers, but half of the patients also had positive microbiological findings around study inclusion. Although including microbiological findings in the COX-regression did not relevantly change the results, it remains unclear to what extent the vasoplegic shock can be attributed to COVID-19-driven hyperinflammation or to sepsis due to secondary superinfection. Further, adequately powered trials might address CytoSorb as stand-alone therapy in the early hours of ICU admission or use an adaptive study design in the absence of biomarkers that are able to distinguish hyperinflammation and infectious syndromes.

Some studies and register data have shown a prominent decrease in inflammatory markers such as IL-6, CRP, or PCT during the first 24–48 hours of CytoSorb-treatment (10, 16, 32). However, consistent with the results of Supady et al (18), we did not observe relevant differences in IL-6 and CRP even after 72 hours of CytoSorb-treatment. This is in line with other controlled studies in non-COVID patients (11, 33). In addition, significant reductions in catecholamine requirements have been reported previously (10, 14, 32). In our study, the decrease in catecholamine requirement was similar in both groups. Possible reasons for this inhomogeneity of results may include different study types and sample sizes, as well as the concentration of the inflammatory markers at the beginning of treatment, since clearance efficacy of the adsorber is concentration-dependent (34). However, given that most controlled trials did not find meaningful differences between groups, we agree with the notion that the observed beneficial effects on cytokine

lowering and hemodynamic stabilization may in part be explained by adjunctive therapy or the natural disease course rather than by cytokine adsorption (18, 33). Furthermore, the immune response in COVID-19-associated ARDS and its association with clinical outcomes remain incompletely understood. Some authors in fact question the existence of a hyperinflammatory state in COVID-19 patients (27, 28). A recent study rather identified a dysregulation in hepatocyte growth factor and C-X-C motif chemokine ligand 13 both associated with lung tissue repair and pulmonary fibrosis as best predictor for ICU-admission and death (35). Therefore, the rationale for a relatively unspecific cytokine adsorption as therapeutic option for severe COVID-19 is debatable. Importantly, our study did not reveal distinct safety signals, as the types and rates of adverse events were similar in both groups and no unexpected or procedure-related adverse events occurred.

This study has strengths and limitations. To our knowledge, this is the largest RCT addressing CytoSorbuse in COVID-19 patients, delivering important data concerning an intervention that is broadly used in clinical practice despite a lack of high-level evidence. Our study comprises only patients with confirmed COVID-19 in the most critical state with vasoplegic shock and multiple organ failure. Disease severity and additional therapeutic measures were well balanced. Limitations include that as an exploratory pilot study it was planned without formal sample size calculation. Second, although initially planned as multicenter study, only one large study center included patients, albeit at three different campuses and in eight different ICUs. Third, since all patients in our cohort fulfilled criteria for multiple organ failure at randomization, we cannot fully exclude that implementation of CytoSorb at an earlier stage could have altered the results. Furthermore, the sometime-uncertain attribution of vasoplegic shock to COVID-19 driven hyperinflammation or to sepsis due to secondary superinfection might imply a potential hidden confounder.

## CONCLUSIONS

In this pilot trial in severely ill COVID-19 patients, CytoSorb-treatment did not improve resolution of vasoplegic shock compared with standard therapy. We did not find beneficial effects among the secondary endpoints, including mortality.

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