Effect of Hemadsorption Therapy in Critically Ill Patients with COVID-19 (CYTOCOV-19): A Prospective Randomized Controlled Pilot Trial

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Keywords
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Abstract
Introduction: Immunomodulatory therapies have shown beneficial effects in patients with severe COVID-19. Patients with hypercytokinemia might benefit from the removal of inflammatory mediators via hemadsorption. Methods: Single-center prospective randomized trial at the University Medical Center Hamburg-Eppendorf (Germany). Patients with confirmed COVID-19, refractory shock (norepinephrine ≥0.2 µg/kg/min to maintain a mean arterial pressure ≥65 mm Hg), interleukin-6 (IL-6) ≥500 ng/L, and an indication for renal replacement therapy or extracorporeal membrane oxygenation were included. Patients received either hemadsorption therapy (HT) or standard medical therapy (SMT). For HT, a CytoSorb® adsorber was used for up to 5 days and was replaced every 18–24 h. The primary endpoint was sustained hemodynamic improvement (norepinephrine ≤0.05 µg/kg/min ≥24 h). Results: Of 242 screened patients, 24 were randomized and assigned to either HT (N = 12) or SMT (N = 12). Both groups had similar severity as assessed by SAPS II (median 75 points HT group vs. 79 SMT group, p = 0.590) and SOFA (17 vs. 16, p = 0.551). Median IL-6 levels were 2,269 (IQR 948–3,679) and 3,747 (1,301–5,415) ng/L in the HT and SMT groups at baseline, respectively (p = 0.378). Shock resolution (primary endpoint) was reached in 33% (4/12) versus 17% (2/12) in the HT and SMT groups, respectively (p = 0.640). Twenty-eight-day mortality was 58% (7/12) in the HT compared to 67% (8/12) in the SMT group (p = 1.0). During the treatment period of 5 days, 6/12 (50%) of the SMT patients died, in contrast to 1/12 (8%) in the HT group. Conclusion: HT was associated with a non-significant trend toward clinical improvement within the intervention period. In selected patients, HT might be an option for stabilization before transfer and further therapeutic decisions. This finding warrants further investigation in larger trials.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in 2019 and caused a global healthcare emergency [1–3]. Up to 20% of patients with coronavirus disease 2019 (COVID-19) were hospitalized and about 5% required intensive care treatment including mechanical ventilation due to severe acute respiratory failure [4–6]. Mortality rates in critically ill patients with COVID-19 remain unacceptably high [6–9].

In severe COVID-19, a dysregulated systemic immune overactivation causes the elevation of inflammatory cytokines [10, 11]. High interleukin-6 (IL-6) levels were associated with multiorgan failure and mortality [12–14]. Similar to septic shock caused by bacteria, SARS-CoV-2-associated hyperinflammation can also initiate a proinflammatory feedback loop, triggering hypercytokinemia and leading to hemodynamic instability or even shock [15]. Immunomodulatory therapies, including corticosteroids and IL-6 antagonists, have recently shown beneficial effects [16–18]. Removal of circulating inflammatory mediators by cytokine adsorption might represent a biologically plausible method to achieve a less proinflammatory cytokine milieu, thus conferring significant clinical improvement in severe COVID-19. Hemadsorption using CytoSorb® (CytoSorbents Corporation, Monmouth Junction, NJ, USA) is approved in Europe and has previously been shown to attenuate an excessive systemic inflammatory response [19]. By eliminating various mediators (e.g., IL-1/6/8/10), bacterial toxins, and danger-associated molecular patterns (DAMPs), the treatment may contribute to the hemodynamic stabilization of patients with septic shock [20]. The adsorber consists of porous polystyrene with an effective surface area of >40,000 m², thus allowing permanent binding of molecules in the range of 5–60 kDa in a concentration-dependent manner [21]. The device can be inserted into a renal replacement therapy (RRT) circuit or an extracorporeal membrane oxygenation (ECMO) system [20, 22, 23]. Because of its potentially beneficial effect on critically ill patients with COVID-19, CytoSorb® received emergency use authorization in the US by the FDA [24]. The purpose of this randomized controlled trial was to evaluate the effect of cytokine elimination by hemadsorption on hemodynamics and disease severity in critically ill patients with COVID-19 with proven hypercytokinemia.

Materials and Methods

Trial Design

The CYTOCOV-19 trial was an investigator-initiated, open-label, prospective, randomized, controlled study in critically ill patients with COVID-19 admitted to the ICUs of the Department of Intensive Care Medicine at the University Medical Center Hamburg-Eppendorf (Germany). The study protocol was approved by the Ethics Committee of the Hamburg Chamber of Physicians (No.: PV7314) and complies with the Declaration of Helsinki.

Patients, Inclusion and Exclusion Criteria

All critically ill patients with confirmed COVID-19 were screened for eligibility. Patients were included when they presented with confirmed COVID-19 and refractory shock with the need for norepinephrine ≥0.2 μg/kg/min to maintain a mean arterial pressure (MAP) ≥65 mm Hg, IL-6 ≥500 ng/L and a need for RRT and/or ECMO. Exclusion criteria were diagnosis of advanced liver cirrhosis (Child-Pugh C), do-not-resuscitate order, moribund condition, expected survival of less than 14 days due to comorbidities, pregnancy or breastfeeding, or participation in another interventional trial.

Randomization

Eligible patients were randomly assigned in a 1:1 ratio to standard medical therapy (SMT) plus hemadsorption therapy (HT) or SMT alone. The randomization sequence was generated using permuted blocks with a size of 4 and was not stratified. Medical staff involved in patient care was aware of group assignment since use of a hemadsorption device in addition to standard therapy could not be blinded with reasonable effort.

Trial Intervention

In the intervention group, a hemadsorption device was incorporated into either the RRT or the ECMO system, respectively. For HT, a CytoSorb® adsorber (total volume 300 mL, priming volume 120 mL, filled with sterile normal saline) was used and placed in a pre-filter position within the RRT circuit. The device was replaced every 18–24 h. Treatment duration was five consecutive days, and treatment was stopped early when shock reversal was observed for at least 24 h (primary endpoint). Flow rates through the hemadsorption device were above 150 mL/min. Early replacement was indicated when blood flow decreased below 100 mL/min or complications like line clotting were observed. For RRT, the multiFiltratePRO Ci-Ca system was used throughout for pre-dilution CVVHD with the Ultraflux AV 600 polysulfone capillary hemofilter (both Fresenius Medical Care, Bad Homburg, Germany).

Blood samples were taken routinely before the initiation of HT and on each subsequent day until day 10. Clinical laboratory parameters included differential blood count, serum electrolytes, kidney and liver function parameters, coagulation, IL-6, mid-regional pro-adrenomedullin (MR-pro-ADM), and procalcitonin (PCT). The reference timepoint was the time of randomization. Patient follow-up was performed for at least 28 days after randomization.

Primary and Secondary Endpoints

The primary endpoint was shock reversal defined as hemodynamic stabilization with a significant reduction of norepi-
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Study Definitions and Patient Management

Confirmed COVID-19 was defined as at least one positive result of reverse transcriptase-polymerase chain reaction (rt-PCR) for SARS-CoV-2 obtained from naso-pharyngeal swabs and/or bronchial secretions or blood. Acute respiratory distress syndrome (ARDS) was defined according to the Berlin definition, using the PaO$_2$/FiO$_2$ ratio (Horowitz index) [25]. Severity of illness was evaluated by SOFA and simplified acute physiology (SAPS II) scores [26, 27]. A Charlson Comorbidity Index (CCI) was calculated for all patients [28]. Medical treatment was performed following national and international recommendations. Norepinephrine was infused to obtain a MAP above 65 mm Hg [29–31]. ECMO was evaluated in patients with severe refractory hypoxemia (PaO$_2$/FiO$_2$ ratio <80) not responding to conservative ARDS management. RRT was started in patients with severe metabolic acidosis, anuria unresponsive to fluids, hyperkalaemia, and/or uremic complications, according to the most recent Austrian/German recommendations [32, 33]. IL-6 was measured by an electrochemiluminescence assay (Atellica IM Analyzer; Siemens Healthcare GmbH, Erlangen, Germany).

Statistical Analysis

Data are presented as absolute and relative frequency for categorical variables and as median and interquartile range for continuous variables. Categorical variables were compared with χ²-tests or Fisher’s exact tests. Continuous variables were compared using the Mann-Whitney U test. Within-group and between-group comparisons of IL-6 levels were Bonferroni corrected for multiple comparisons. Survival function estimates were calculated using the Kaplan-Meier method and were compared using the log-rank test. Statistical tests were two-sided with a 5% significance level and with nominal p values reported for description outside the primary analysis. Statistical analyses were performed using IBM SPSS Statistics Version 24.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). The study was prepared in accordance with the Consolidated Standards of Reporting Trials recommendations.

Results

A total of 242 patients were assessed for eligibility, and 24 patients underwent randomization. Of these, 12 patients were assigned to either the HT group or SMT. The last day of follow-up was May 1, 2021. The flow diagram displaying screening, randomization, and outcomes is depicted in Figure 1.

Characteristics of the Study Population

The characteristics of the study population are shown in Table 1. Thirteen (54%) patients were referred from other hospitals for further intensive care management. Before randomization, patients had been treated in the ICU for a median time of 6.3 (2.5–10.7) days (HT: 5.9 [2.4–10.7] vs. SMT: 6.3 [3.3–9.5], p = 0.799). At time of inclusion, 22 (92%) and 11 (46%) patients of the whole cohort were on RRT and vvECMO, respectively. The initial RRT mode was continuous veno-venous hemodialysis (CVVHD) in 22 (92%) and continuous veno-venous hemofiltration (CVVH) in 2 (8%) patients. Indications for RRT were metabolic acidosis in 16 (67%) patients, fluid overload in 11 (46%), and hyperkalemia unresponsive to conservative management in 3 (13%); 7 (29%) patients had more than one indication for RRT. Two patients (8%) were on chronic dialysis. The median Horowitz index was 102 (73–181) in the HT and 105 (88–126) in the SMT group at the time of study inclusion. Patients in the HT group received a median dose of 0.399 (0.252–0.791) μg/kg/min norepinephrine (p = 0.128). Median IL-6 levels were 2,269 (948–3,679) and 3,747 (1,301–5,415) ng/L in the HT and SMT groups at baseline, respectively (p = 0.378).

Hemadsorption

Details regarding hemadsorption treatment are shown in Table 2. Time from randomization to the start of hemadsorption was 0.9 (0.5–2.3) h. The hemadsorption device was added to the RRT circuit in 11 (92%) and to the ECMO system in 1 (8%) patient, respectively. All patients were on continuous RRT; anticoagulation was performed using systemic heparin in 1 (8%) patient and regional anticoagulation with citrate-calcium in 11 (92%) patients assigned to the HT group. Overall, 74 hemadsorption devices were used and patients received 6 (5.8–6.3) hemadsorption treatments during the intervention period. Duration of treatment was 22.9 (17.4–24.7) h per adsorber. Overall, 9 (12%) hemadsorption treatments had to be terminated early because of circuit clotting. In addition, treatment duration below 18 h was observed in 5 (7%) treatment sessions which was due to logistical problems. Due to technical difficulties when exchanging the hemadsorption device within the ECMO circuit, one treatment was prolonged to 46.6 h. No other device-related complications were observed during the intervention period. Two (16%) patients reached the primary trial endpoint before day 5, as predefined in the study protocol, and HT was discontinued at the next planned hemadsorption de-
vice exchange. We did not observe device-related adverse or serious adverse events.

**Laboratory Changes**

During the first 5 days of treatment, IL-6 levels decreased. In particular, IL-6 concentration fell to 478 (240–841) ng/L (HT, \( p = 0.012 \)) and 597 (488–2,436) ng/L (SMT, \( p = 0.657 \)) after 24 h, 254 (73–1,381) ng/L (HT, \( p = 0.012 \)) and 390 (163–599) ng/L (SMT, \( p = 0.086 \)) after 48 h, 116 (60–755) ng/L (HT, \( p = 0.002 \)) and 293 (145–1,786) ng/L (SMT, \( p = 0.093 \)) after 72 h, 147 (23–1,457) ng/L (HT, \( p = 0.006 \)) and 189 (125–972) ng/L (SMT, \( p = 0.028 \)) after 4 days and to 287 (22–1,457) ng/L (HT, \( p = 0.012 \)) and 211 (101–376) ng/L (SMT, \( p = 0.028 \)) after 5 days in the HT and SMT group respectively (\( p \) indicates comparison for each timepoint with baseline values of each group; \( p = 0.05/5 = 0.01 \) was considered statistically significant). Serum IL-6 reduction in the first 24 h of
treatment compared between HT and SMT groups was 79% versus 85% (p = 0.335). Serum PCT values were similar at baseline (HT: 4.69 [1.67–8.75] µg/L, SMT: 4.21 [1.80–17.61] µg/L) and showed a persistent increase in the SMT group (>3 µg/L) throughout the intervention period (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000526446), whereas PCT levels decreased and remained lower in the HT group.

Table 1. Characteristics of randomized patients at time of inclusion who were assigned to HT or SMT group

| Parameters                        | HT (n = 12)     | SMT (n = 12)     | p value |
|-----------------------------------|----------------|-----------------|---------|
| **Demographics**                  |                |                 |         |
| Age, years                        | 60 (56–63)     | 69 (58–76)      | 0.114   |
| Male gender                       | 9 (75)         | 9 (75)          | 1.0     |
| Weight, kg                        | 93 (70–95)     | 103 (84–123)    | 0.178   |
| Height, cm                        | 178 (174–180)  | 176 (172–183)   | 0.887   |
| **Comorbidities**                 |                |                 |         |
| Charlson comorbidity index (pts.)| 2 (1–3)        | 2 (1–3)         | 0.843   |
| Any comorbidity                    | 10 (83)        | 11 (92)         | 1.0     |
| Arterial hypertension              | 6 (50)         | 10 (83)         | 0.193   |
| Diabetes mellitus                  | 5 (42)         | 3 (25)          | 0.667   |
| Coronary heart disease             | 2 (17)         | 4 (33)          | 0.640   |
| Congestive heart disease           | 1 (8)          | 0 (0)           | 1.0     |
| Chronic kidney disease             | 2 (17)         | 3 (25)          | 1.0     |
| Chronic respiratory disease        | 3 (25)         | 3 (25)          | 1.0     |
| Liver disease                      | 0 (0)          | 0 (0)           | 1.0     |
| Malignant condition                | 1 (8)          | 1 (8)           | 1.0     |
| Lymphoma                           | 0 (0)          | 0 (0)           | 1.0     |
| Solid organ tumor                  | 3 (25)         | 3 (25)          | 1.0     |
| History of smoking                 | 1 (8)          | 3 (25)          | 0.590   |
| **Disease severity (baseline)**    |                |                 |         |
| SAPS II (pts.)                     | 75 (72–83)     | 79 (74–84)      | 0.590   |
| SOFA (pts.)                        | 17 (15–18)     | 16 (15.75–18)   | 0.551   |
| APACHE II (pts.)                   | 33 (29–41)     | 38 (36–41)      | 0.198   |
| **ICU characteristics (baseline)** |                |                 |         |
| Mean arterial pressure, mm Hg      | 74 (66–80)     | 67 (64–72)      | 0.178   |
| Norepinephrine, dose, µg/kg/min    | 0.399 (0.252–0.791) | 0.792 (0.457–1.195) | 0.128 |
| RRT                                | 11 (92)        | 11 (92)         | 1.0     |
| PaO2/FiO2 – ratio                  | 102 (73–181)   | 105 (88–126)    | 0.178   |
| vvECMO                             | 6 (50)         | 5 (42)          | 1.0     |
| **Blood gas analysis**             |                |                 |         |
| paO2, mm Hg                        | 77 (70–81)     | 74 (68–81)      | 0.932   |
| paCO2, mm Hg                       | 46 (40–61)     | 54 (46–64)      | 0.378   |
| pH, level                          | 7.31 (7.27–7.38) | 7.25 (7.21–7.30) | 0.033   |
| HCO3, mmol/L                       | 24.2 (20.7–27.8) | 21.9 (19.4–23.4) | 0.178   |
| Lactate, mmol/L                    | 2.5 (1.4–3.1)  | 2.8 (2.2–3.5)   | 0.478   |
| **Laboratory values**              |                |                 |         |
| Leukocytes, G/L                    | 11.1 (5.6–18.9) | 12.9 (11.0–21.7) | 0.319   |
| Thrombocytes, G/L                  | 157 (97–246)   | 272 (163–312)   | 0.378   |
| D-dimers, mg/L                     | 8.64 (4.01–10.70) | 7.05 (2.37–14.29) | 0.630   |
| IL-6, ng/mL                        | 2.269 (948–3,679) | 3.747 (1,301–5,415) | 0.378   |
| pro-ADM, nmol/L                    | 6.25 (4.03–7.26) | 10.01 (4.74–12.24) | 0.089   |
| PCT, µg/L                          | 4.69 (1.67–8.75) | 4.21 (1.80–17.61) | 0.932   |
| CRP, mg/L                          | 290 (208–319)  | 179 (208–298)   | 0.887   |

Data are expressed as n (%) or median (interquartile range). ARDS, acute respiratory distress syndrome; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; pts., points; vvECMO, veno-venous extracorporeal membrane oxygenation; IL, interleukin; PCT, procalcitonin; CRP, C-reactive protein; pro-ADM, pro-adrenomedullin.
Table 2. Intensive care unit characteristics of patients who were assigned to the HT group or SMT

| Parameters | HT (n = 12) | SMT (n = 12) | p value |
|------------|-------------|--------------|---------|
| **HT details** | | | |
| Treatment mode | | | |
| RRT | 11 (92) | – | – |
| ECMO | 1 (8) | – | – |
| Randomization to start of hemadsorption, h | 0.9 (0.5–2.3) | – | – |
| Total duration of hemadsorption, h | 131.7 (121.3–143.8) | – | – |
| Duration of hemadsorption per session | 22.9 (17.4–24.7) | – | – |
| Number of adsorbers per patient | 6 (5.8–6.3) | – | – |
| **ICU – characteristics & management** | | | |
| Acute respiratory distress syndrome | | | |
| No ARDS | 0 (0) | 1 (8) | 1.0 |
| Mild | 1 (8) | 0 (0) | |
| Moderate | 1 (8) | 1 (8) | |
| Severe | 10 (83) | 10 (83) | |
| **ARDS – management** | | | |
| Prone positioning | 9 (75) | 10 (83) | 1.0 |
| Neuromuscular blockade | 7 (58) | 4 (33) | 0.414 |
| Inhaled NO | 9 (75) | 3 (25) | 0.039 |
| Glucocorticoid therapy | 11 (92) | 11 (92) | 1.0 |
| vvECMO | 7 (58) | 5 (42) | 0.684 |
| RRT | 12 (100) | 12 (100) | – |
| Tracheostomy | 5 (42) | 6 (50) | 1.0 |
| Dexamethasone | 8 (67) | 5 (42) | 0.414 |
| Remdesivir | 3 (25) | 3 (25) | 1.0 |
| Tocilizumab | 1 (8) | 0 (0) | 1.0 |

Data are expressed as n (%) or median (interquartile range). ARDS, acute respiratory distress syndrome; RRT, renal replacement therapy; vvECMO, veno-venous extracorporeal membrane oxygenation; h, hours.

Table 3. Primary and secondary endpoints and outcomes of patients who were assigned to HT or SMT

| Parameters | HT (n = 12) | SMT (n = 12) | p value |
|------------|-------------|--------------|---------|
| **Primary endpoint** | | | |
| Shock reversal within 10 days | 4 (33) | 2 (17) | 0.640 |
| **Secondary endpoints** | | | |
| Change in SOFA Score (points) | 1 (0.8–1.5) | 1 (0–2.3) | 0.843 |
| Lactate clearance <2 mmol/L | 6 (50) | 6 (50) | 1.0 |
| Length of RRT, days | 14.4 (7.2–24.8) | 7.93 (1.3–23.3) | 0.242 |
| Length of vvECMO, days | 25.5 (12.6–33) | 18.4 (2.4–20.5) | 0.149 |
| Time to shock reversal, days | 6.3 (3.7–10) | 9.2 (5.1–15.9) | 0.110 |
| Length of mechanical ventilation, days | 15.3 (7.5–25.6) | 11.9 (2.0–35.5) | 0.378 |
| Reduction (≥20%) of | | | |
| IL-6 | 11 (92) | 8 (67) | 0.317 |
| PCT | 9 (75) | 6 (50) | 0.400 |
| D-Dimers | 0 (0) | 1 (8) | 0.478 |
| **Outcome** | | | |
| 28-day mortality | 7 (58) | 8 (67) | 1.0 |

Data are expressed as n (%) or median (interquartile range). SOFA, sequential organ failure assessment; RRT, renal replacement therapy; vvECMO, veno-venous extracorporeal membrane oxygenation; PCT, procalcitonin; IL-6, interleukin-6.
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Analysis of Endpoints and Outcomes

The primary endpoint of shock reversal within 10 days of randomization was reached by 4 patients (33%) in the HT group and 2 patients (17%) in the SMT group ($p = 0.640$). The time to shock reversal was 6.3 (3.7–10.0) days in the HT and 9.2 (5.1–15.9) days ($p = 0.110$) in the SMT group. We observed a 28-day mortality of 58% ($n = 7$) in the HT group and of 67% ($n = 8$) in the SMT group ($p = 0.382$, cf. Kaplan-Meier survival estimates (Fig. 2). Primary and secondary endpoints are shown in detail in Table 3.

Discussion

This is the first randomized controlled trial investigating HT for cytokine elimination in critically ill patients with COVID-19 with proven and profound hypercytokinemia. In this study, the primary endpoint of shock reversal was not reached for the intervention group, and we could not demonstrate a significant reduction of IL-6 by HT. However, HT may potentially be accompanied by early clinical stabilization of severely ill patients when compared to SMT.

The COVID-19 pandemic resulted in high hospitalization rates with up to 5% admitted to the ICU, mainly due to respiratory failure [1, 2, 6]. The interplay between direct viral damage to alveolar epithelial cells and excessive endothelial activation results in SARS-CoV-2 related lung injury accompanied by excessive cytokine production [19]. Extensive pulmonary and multiorgan endothelial lesions are largely described as a hallmark of severe respiratory failure [34]. Among others, high IL-6 levels were observed and strongly associated with multiorgan failure and mortality in critically ill patients with COVID-19 [12, 13]. Hemadsorption techniques targeting circulating inflammatory mediators may lead to a re-balancing of the internal cytokine milieu. Several case series and small studies in patients with COVID-19 or septic shock have shown promising results using hemadsorption [20, 22, 35, 36]. Although initial reports suggested an uncontrolled cytokine response in patients with COVID-19, cytokine levels have been reported to be not as high as compared to other causes of ARDS [10, 11, 37, 38]. However, some patients exhibit uncontrolled hyperinflammatory cytokine release, which in many cases entails multiple organ dysfunction and death. Therefore, we sought to specifically target the population, which might benefit most from hemadsorption treatment by including only severely ill patients with cytokinemia defined as IL-6 $\geq$500 ng/L accompanied by refractory shock. Recently, a small randomized controlled trial by Supady et al. [39] using HT in COVID-19 patients with ARDS requiring ECMO therapy could not show beneficial effects. The primary endpoint was IL-6 serum concentration 72 h after randomization. However, median baseline IL-6 levels in the intervention group were low (357 ng/L), compared to 2,269 ng/L in our study. However, we observed a significant decrease in IL-6 levels both in the intervention and the control group within the first 24 h. We further observed a significant and sustained decrease in PCT (see online suppl. Fig. 1), which supports the effectiveness of HT to reduce PCT as shown earlier [40]. We hypothesize that initiation of hemadsorption should probably not be solely based on the clinical condition and acute respiratory failure, as recently shown by Supady et al. [39] As depicted in the flow diagram (Fig. 1), we had a 100% recruitment of suitable patients in the present study (based on clinical/predefined inclusion criteria). We defined a suitable target population that, in contrast to the work of Supady et al. [39], did not show any conspicuous mortality during therapy. Notably, our cohort consisted of severely ill patients, which is demonstrated by high SOFA and SAPS II scores, usually associated with a mortality rate of above 80% [26, 27].

Observational data suggest improvement of hemodynamics and a trend toward improved mortality with the use of hemadsorption in critically ill patients with septic shock. One study by Friesecke et al. [20] showed that hemoperfusion was associated with decreased vasopressor requirement and shock reversal in 65% of treated patients, and that this was accompanied by a significant reduction of IL-6 and

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Fig. 2. Kaplan-Meier survival estimates: shown are Kaplan-Meier estimates of the probability of survival for patients assigned to HT or SMT. The shaded area indicates the intervention period. Log-rank: $p = 0.382$. 

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lactate levels. In the present study, we observed a higher rate of shock reversal within 10 days after randomization in patients of the HT (33%) than in the SMT group (17%); however, this did not reach statistical significance. The survival curve in our study shows that the treatment group (HT) had a survival advantage, which was, however, limited to the intervention period (Fig. 2). If this survival advantage is attributable to the pre-randomization differences is unclear. Further larger studies have to clarify the finding. We neither observed nor expected differences in 28-day mortality between the two groups. This is in line with a previous RCT of hemadsorption in patients with septic shock which did not result in improved survival [41, 42]; but again, in this trial, initial IL-6 levels were substantially lower in both groups (median 357 vs. 289 ng/L) compared with those in our study. In a recent retrospective study with propensity score matching analysis, no difference could be demonstrated in terms of hemodynamic stabilization between cytokine adsorption and SMT. However, this was an uncontrolled short-term (<24 h) intervention in a mixed population with sepsis, septic shock and hyperinflammation due to a variety of causes [43].

Of particular interest is our observation that patients in the HT group could be stabilized during the intervention period compared to patients in the SMT group. We can only speculate if extended treatment duration or targeting only patients with sustained hyperinflammation would result in beneficial and clinically meaningful effects of hemadsorption. However, addressing this question would require a different study design. To date, specific therapies for severe COVID-19 are scarce. Early stabilization of severely affected patients with proven hypercytokinemia to allow referral to a tertiary care center or to bridge to further interventions might be a reasonable indication for the use of hemadsorption. For this reason, our findings warrant further investigation in larger trials.

This study has important limitations which should be mentioned. We are reporting a small randomized single-center open-label trial. Owing to the small sample size, we observed important differences regarding age and norepinephrine dose at baseline between both groups. Although these differences did not reach statistical significance, they could have influenced the primary outcome. Methodologically, trials involving rather complex medical devices are inherently difficult to double-blind, so that bias cannot be ruled out. Further, even though the flow chart (Fig. 1) shows that we comprehensively enrolled all available patients after screening for eligibility, this study may still be subject to selection bias, and external validity of our results may be limited. Although statistically non-significant, there was a noticeable imbalance in noradrenalin dose, age, and arterial pH to the disadvantage of the control group. Before randomization, our patients had been treated in the ICU for a median time of 6.3 days, and more than half of the cohort were referrals from other hospitals. It is conceivable that an earlier initiation of HT might have resulted in more beneficial effects. Lastly, the duration of hemadsorption was pre-specified and limited to 5 days. Whether an extended use of hemadsorption beyond 5 days would result in an improved outcome remains unclear.

This study also has some strengths. Our study is consistent with previous findings in patients with septic shock. To our knowledge, this is the first study evaluating efficacy and outcome of HT in critically ill COVID-19 patients with hypercytokinemia, severe systemic inflammation, and multiple organ dysfunction. Screening more than 200 ICU patients only yielded inclusion of 24 patients, which confirms previous findings that uncontrolled hypercytokinemia is only present in some patients, and those might require a tailored and personalized therapeutic approach based on biological plausibility.

**Conclusion**

Uncontrolled hypercytokinemia accompanied by severe systemic inflammation and multiple organ dysfunction occurs in a subgroup of critically ill patients with COVID-19. There were no effects on IL-6 levels or 28-day mortality. Early mitigation of organ dysfunction leading to clinical stabilization was observed in the HT group. HT in patients with severe COVID-19 was feasible and safe and might be used for stabilization before transfer to a tertiary care center or for decision of further interventions. Whether longer duration or an earlier start of HT would prove beneficial should be elucidated and warrants further clinical investigations.

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**Statement of Ethics**

This clinical study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Hamburg Chamber of Physicians on March 30, 2020 (No.: PV7314). Written consent
informed consent was obtained from all patients or their legal representatives. If this was not possible in time before enrollment, the ethics committee had approved a deferred consent procedure in which trial participation is initiated following the presumed will of the patient in the context of the existing emergency situation. As soon as the patient’s legal representative was available, written informed consent was obtained immediately.

**Conflict of Interest Statement**

Dominik Jarczak has received lecture honoraria and travel reimbursement from ADVITOS and CytoSorbents Europe GmbH. Marlene Fischer receives research support from the External Research Program, Medtronic, Minneapolis, MA. Stefan Kluge received research support by Ambu, E.T.View Ltd., Fisher & Paykel, Pfizer, and Xenios, lecture honoraria from ArjoHuntleigh, Astellas, Astra, Basilea, Bard, Baxter, Biotest, CSL Behring, CytoSorbents, Fresenius, Gilead, MSD, Orion, Pfizer, Philips, Sedana, Sorin, Xenis, and Zoll, and consultant honorarium from AMODEM, Astellas, Baxter, Bayer, Fresenius, Gilead, MSD, Pfizer, and Xenios. Axel Nierhaus has received lecture honoraria and travel reimbursement from ThermoFisher Scientific GmbH, Fresenius AG, CytoSorbents Europe GmbH and Biotest AG, Germany over the past 5 years. Daniel Peter Frings reports lecture honoraria within the last 5 years from Xenios AG. Kevin Roedl, Geraldine de Heer, Christoph Burdelski, Barbara Sensen, Olaf Boenisch, and Pishtaz Adel Tariparast do not report any conflicts of interest. No other potential conflict of interest relevant to this article was reported.

*References*

1 Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1,591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA*. 2020 Apr 6;323(16):1574–81.

2 Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 57,000 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020 May 26;323(20):2052–9.

3 WHO. World Map: COVID-19. 2021.

4 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–20.

5 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.

6 Roedl K, Jarczak D, Thasler L, Bachmann M, Schulte F, Bein B, et al. Mechanical ventilation and mortality among 223 critically ill patients with COVID-19: a multicentric study in Germany. *Aust Crit Care*. 2021;32(2):167–75.

7 Karagiannidis C, Mostert C, Hentschker C, Voshaar T, Malzahn J, Schilling G, et al. Case characteristics, resource use, and outcomes of 10,021 patients with COVID-19 admitted to 920 German hospitals: an observational study. *Lancet Respir Med*. 2020;8(9):853–62.

8 Richards-Belle A, Orzechowska I, Gould DW, Thomas K, Dodge JC, Mouncey PR, et al. COVID-19 in critical care: epidemiology of the first epidemic wave across England, Wales and Northern Ireland. *Intensive Care Med*. 2020;46(11):2035–47.

9 COVID-ICU Group on behalf of the REVAC Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med*. 2021 Jan;47(1):60–73.

10 McElvany OJ, McEvoy NL, McElvany OF, Carroll TF, Murphy MP, Dunlea DM, et al. Characterization of the inflammatory response to severe COVID-19 illness. *Am J Respir Crit Care Med*. 2020 Sep 15;202(6):812–21.

11 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020 Mar 28;395(10129):1033–4.

12 Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020 Mar 3;46(5):846–8.

13 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–62.

14 Kaur S, Bansal R, Kollimuttathuillum S, Gowda AM, Singh B, Mehta D, et al. The looming storm: blood and cytokines in COVID-19. *Blood Rev*. 2021 Mar;46:100743.

15 Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. *Am J Pathol*. 2021 Jan;191(1):4–17.

16 Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19: preliminary report. *N Engl J Med*. 2021;384(8):693–704.

17 Salama C, Han J, Yao L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. *N Engl J Med*. 2021;384(1):20–30.

18 Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P, et al. Effect of tocilizumab vs usual care in adults hospitalized with covid-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):32–40.

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**Author Contributions**

Dominik Jarczak, Kevin Roedl, and Axel Nierhaus conceived and designed the study. Kevin Roedl, Dominik Jarczak, Geraldine de Heer, Christoph Burdelski, Daniel Peter Frings, Barbara Sensen, Olaf Boenisch, Pishtaz Tariparast, and Axel Nierhaus were involved in data acquisition. Marlene Fischer, Kevin Roedl, Dominik Jarczak and Axel Nierhaus analyzed and interpreted the data. Kevin Roedl drafted the manuscript. Dominik Jarczak, Marlene Fischer, Stefan Kluge and Axel Nierhaus critically revised the manuscript for important intellectual content. All the authors read and approved the final manuscript.

**Data Availability Statement**

Due to local ethical and federal data privacy rules the complete dataset is available upon written request directed to the corresponding author.
23 Kogelmann K, Scheller M, Drüner M, Jarczak D, Scheller I, Paal M, Winkels M, Irlbeck M, Rimmelé T, Schneider AG. Hemoadsorption with CytoSorb®. Intensive Care Med. 2019 Feb;45(2):236–9.

24 FDA. CytoSorb® emergency use authorization for use in patients with COVID-19 infection. 2020.

25 Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: the Berlin definition. JAMA. 2012 Jun 20;307(23):2526–33.

26 Le Gall JR, Lemeshow S, Gross S, Felix SB, Ni-erhaus A. Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. J Artif Organs. 2017 Sep;20(3):252–9.

27 Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. Intensive Care Med. 1996 Jun;22(7):707–10.

28 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–83.

29 Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus disease 2019 (COVID-19). Intensive Care Med. 2020 May; 46(5):854–87.

30 Kluge S, Janssens U, Welte T, Weber-Carstens S, Marx G, Karagiannidis C. German recommendations for critically ill patients with COVID-19. Med Klin Intensivmed Notfmed. 2020 Dec;115(Suppl 3):111–4.

31 Alhazzani W, Evans L, Abhamsi F, Møller MH, Ostermann M, Prescott HC, et al. Surviving sepsis campaign guidelines on the management of adults with coronavirus disease 2019 (COVID-19) in the ICU: first update. Crit Care Med. 2021 Mar;49(3):e219–34.

32 RENAL Replacement Therapy Study Investigators; Bellomo R, Cass A, Cole L, Finfer S, Gallagher M, et al. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med. 2009;361(17):1627–38.

33 Joannidis M, John S. Acute kidney injury and renal-replacement therapy in critically ill patients: 2018: recommendations from the renal section of the DGIIN, OGIAIN and DIVI. Med Klin Intensivmed Notfmed. 2018 Jun;113(5):356–7.

34 Dupont T, Caillat-Zucman S, Fremeaux-Bacchi V, Morin F, Lengliné E, Darmon M, et al. Identification of distinct immunophenotypes in critically ill coronavirus disease 2019 patients. Chest. 2021 May;159(5):1884–93.

35 Villa G, Romagnoli S, De Rosa S, Greco M, Resta M, Pomarè Montin D, et al. Blood purification therapy with a hemodialfiltrer featuring enhanced adsorptive properties for cytokine removal in patients presenting COVID-19: a pilot study. Crit Care. 2020 Oct 12;24(1):605.

36 AIjharry A, Faqghi F, Memish ZA, Balhammar A, Nasim N, Shahzad A, et al. Continuous renal replacement therapy with the addition of CytoSorb cartridge in critically ill patients with COVID-19 plus acute kidney injury: a case-series. Artif Organs. 2021 May;45(5):E101–12.

37 Kox M, Waalders NJB, Kooistra EJ, Gerritsen J, Pickkers P. Cytokine levels in critically ill patients with COVID-19 and other conditions. JAMA. 2020 Sep 3;324(15):1565–7.

38 Sinha P, Cafée CS, Cherian S, Brealley D, Cutler S, King C, et al. Prevalence of phenotypes of acute respiratory distress syndrome in critically ill patients with COVID-19: a prospective observational study. Lancet Respir Med. 2020 Dec;8(12):1209–18.

39 Supady A, Weber E, Rieder M, Lother A, Niklaus T, Zahn T, et al. Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): a single centre, open-label, randomised, controlled trial. Lancet Respir Med. 2021 Jul;9(7):755–62.

40 Hawchar F, Laszlo I, Oveges N, Traisy D, On-drik Z, Molnar Z. Extracorporeal cytokine adsorption in septic shock: a proof of concept randomized, controlled pilot study. J Crit Care. 2019 Feb;49:172–8.

41 Schädler D, Pausch C, Heise D, Meier-Hellmann A, Brederla J, Weiler N, et al. The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: a randomized controlled trial. PLoS One. 2017;12(10):e0187015.

42 Lebrerton G, Dorgamk HMAC, Quentric P, Combes A, Gorochov G, Schmidt M. Longitudinal Cytokine Profiling in Patients with Severe COVID-19 on Extracorporeal Membrane Oxygenation and Hemoadsorption. Am J Respir Crit Care Med. 2021 Jun 1;203(11):1433–5.

43 Scharf C, Schroeder I, Paal M, Winkels M, Irbeck M, Zoller M, et al. Can the cytokine adsorber CytoSorb® help to mitigate cytokine storm and reduce mortality in critically ill patients? A propensity score matching analysis. Ann Intensive Care. 2021 Jul 22;11(1):115.

44 Jarczak D, Roedl K, Fischer M, de Heer G, Burdelski C, Frings DP, et al. Effect of hemadsorption therapy in critically ill patients with COVID-19 (CYTOCOV-19): a prospective randomized controlled pilot trial, version 1 [Preprint]. Research Square; 2021.