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

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Research

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Abstract

Purpose: Immunomodulatory therapies have shown beneficial effects in patients with severe COVID-19. Patients with hypercytokinemia might benefit from 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 mmHg), IL-6≥500 ng/l and an indication for renal replacement therapy (RRT) or extracorporeal membrane oxygenation (ECMO) 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 hours. The primary endpoint was sustained hemodynamic improvement (norepinephrine ≤0.05 µg/kg/min≥24h). Secondary endpoints included 28-day mortality, SOFA, and reduction of IL-6, PCT, and MR-proADM.

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). At randomization, 22 (92%) patients were on RRT and 11 (46%) had vv-ECMO. Median IL-6 levels were 2269 (IQR 948–3679) and 3747 (1301–5415) ng/l in the HT and SMT group at baseline, respectively (p=0.378). Serum IL-6 reduction in the first 24h of treatment compared between both groups was 83% vs. 46% (p=0.235). Shock resolution (primary endpoint) was reached in 33% (4/12) vs. 17% (2/12) in the HT and SMT group, respectively (p=0.640). 28-day mortality was 58% (7/12) in the HT compared to 67% (8/12) in the SMT group (p=1.0).

Conclusion: HT was associated with a non-significant trend towards clinical improvement within the intervention period including reduction of IL-6 levels and shock resolution. In selected patients, HT might therefore be an option for stabilization and bridge to transfer and decision. (*Trial registration:* ClinicalTrials.gov: NCT04344080, https://clinicaltrials.gov/ct2/show/NCT04344080, trial registration date 04/14/2020)

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Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged 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 (4, 7–9).

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 multi-organ failure

and mortality (12–14). Immunomodulatory therapies, including corticosteroids and IL-6 antagonists, have recently shown beneficial effects (15–17).

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 [33]. By eliminating various mediators (e.g., IL-1/6/8/10), bacterial toxins and danger-associated molecular patterns (DAMPS), the treatment may contribute to hemodynamic stabilization of patients with septic shock (18). 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 (19). The device can be inserted into a renal replacement therapy (RRT) circuit or an extracorporeal membrane oxygenation (ECMO) system (18, 20, 21). Because of its potentially beneficial effect in critically ill patients with COVID-19, CytoSorb® received emergency use authorization in the US by the FDA (22).

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.

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 mmHg, Interleukin-6 ≥ 500 ng/l and need for RRT 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 plus hemadsorption therapy (HT) or standard medical therapy (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 in either the RRT or the ECMO system, respectively. For hemadsorption therapy 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 hours. Treatment duration was five consecutive days, and treatment was stopped early when shock reversal was observed for at least 24 hours (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.

Blood samples were taken routinely before initiation of hemadsorption therapy 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-proADM), and procalcitonin (PCT). The reference timepoint was 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 norepinephrine to a dose of 0.05 µg/kg/min or lower while maintaining MAP ≥ 65 mmHg for at least 24 hours. Secondary endpoints included improvement of organ dysfunction measured by sequential organ failure assessment (SOFA) score, lactate clearance, time on RRT, time on ECMO, duration of mechanical ventilation, time to shock reversal, length of ICU stay, total vasopressor dose, ICU and hospital mortality within 28 days. Further secondary endpoints included reduction (≥ 20%) of IL-6, PCT and MR-proADM within 10 days after randomization.

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) (23). Severity of illness was evaluated by SOFA (24) and simplified acute physiology (SAPS II) (25) scores. Charlson Comorbidity Index (CCI) (26) was calculated in all patients. Medical treatment was performed following national and international recommendations. Norepinephrine was infused to obtain MAP above 65 mmHg (27–29). 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 (30, 31). 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 Chi-square-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 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) 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 hemadsorption therapy (HT) group or standard medical therapy (SMT). Last day of follow-up was May 1, 2021. The flow diagram displaying screening, randomization and outcomes is depicted in Fig. 1.

Characteristics of the study population

The characteristics of the study population are shown in Table 1. Demographic, clinical and physiological characteristics were comparable and balanced between both groups. Thirteen (54%) patients were referred from other hospitals for further intensive care management. At time of inclusion 22 (92%) and 11 (46%) patients of the whole cohort were on RRT and vv-ECMO, respectively. 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%), hyperkalemia irresponsive to conservative management in 3 (13%); seven (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 time of study inclusion. Patients in the HT group received a median dose of 0.399 (0.252–0.791) and in the SMT group of 0.792 (0.457–1.195) µg/kg/min norepinephrine (p = 0.128). Median interleukin-6 levels were 2269 (948–3679) and 3747 (1301–5415) ng/l in the HT and SMT group at baseline, respectively (p = 0.378).

Table 1
Characteristics of randomized patients at time of inclusion who were assigned to hemadsorption therapy or standard medical therapy group

Parameters	*Hemadsorption therapy (n = 12)*	*Standard medical therapy (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

Data are expressed as n (%) or median (interquartile range)

Abbreviations: ARDS, acute respiratory distress syndrome; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; pts., points; ECMO, extracorporeal membrane oxygenation; IL, Interleukin; PCT, procalcitonin; CRP, c-reactive protein; pro-ADM, pro-adrenomedullin;

Parameters	*Hemadsorption therapy (n = 12)*	*Standard medical therapy (n = 12)*	*p-value*
ICU Characteristics (Baseline)			
Mean arterial pressure, mmHg	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
Renal replacement therapy	11 (92)	11 (92)	1.0
PaO_2/FiO_2 - Ratio	102 (73–181)	105 (88–126)	0.178
Extracorporeal membrane oxygenation	6 (50)	5 (42)	1.0
Blood gas analysis			
paO_2, *mmHg*	77 (70–81)	74 (68–81)	0.932
$paCO_2$, *mmHg*	46 (40–61)	54 (46–64)	0.378
pH, level	7.31 (7.27–7.38)	7.25 (7.21–7.30)	0.033
HCO_3^-, 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/l	2269 (948–3679)	3747 (1301–5415)	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)			
Abbreviations: ARDS, acute respiratory distress syndrome; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; pts., points; ECMO, extracorporeal membrane oxygenation; IL, Interleukin; PCT, procalcitonin; CRP, c-reactive protein; pro-ADM, pro-adrenomedullin;			

Hemadsorption

Details regarding hemadsorption treatment are shown in Table 2. Time from randomization to start of hemadsorption was 0.9 (0.5–2.3) hours. 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) hours per adsorber. Overall, 9 (12%) hemadsorption treatments had to be terminated early because of circuit clotting. In addition, treatment duration below 18 hours 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 hours. 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 device exchange. We did not observe device related adverse or serious adverse events.

Table 2
Intensive care unit characteristics of patients who were assigned to the hemadsorption therapy group or standard medical therapy

Parameters	*Hemadsorption therapy (n = 12)*	*Standard medical therapy (n = 12)*	*p-value*
Hemadsorption therapy details	11 (92)	-	-
Treatment mode	1 (8)	-	-
- RRT	0.9 (0.5–2.3)	-	-
- ECMO	131.7 (121.3–143.8)	-	-
Randomization to start of hemadsorption (h)	22.9 (17.4–24.7)	-	-
Total duration of hemadsorption (h)	6 (5.8–6.3)	-	-
Duration of hemadsorption per session		-	-
Number of adsorbers per patient			
ICU – Characteristics & Management			1.0
Acute respiratory distress syndrome	0 (0)	1 (8)	
No ARDS	1 (8)	0 (0)	
Mild	1 (8)	1 (8)	
Moderate	10 (83)	10 (83)	
Severe			

Data are expressed as n (%) or median (interquartile range)

Abbreviations: ARDS, acute respiratory distress syndrome; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; h, hours;

Parameters	*Hemadsorption therapy (n = 12)*	*Standard medical therapy (n = 12)*	*p-value*
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
ECMO	7 (58)	5 (42)	0.684
Renal Replacement Therapy	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)			
Abbreviations: ARDS, acute respiratory distress syndrome; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; h, hours;			

Laboratory changes

During the first 5 days of treatment, IL-6 levels decreased (see Suppl. Figure 1). In particular, IL-6 concentration fell to 478 (240–841) ng/l (HT, p = 0.012) and 597 (488–2436) ng/l (SMT, p = 0.657) after 24 hours, 254 (73–1381) ng/l (HT, p = 0.012) and 390 (163–599) ng/l (SMT, p = 0.086) after 48 hours, 116 (60–755) ng/l (HT, p = 0.002) and 293 (145–1786) ng/l (SMT, p = 0.093) after 72 hours, 147 (23–1457) ng/l (HT, p = 0.006) and 189 (125–972) ng/l (SMT, p = 0.028) after 4 days and to 287 (22–1457) 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; a $p = 0.05/5 = 0.01$ was considered statistically significant). Serum IL-6 reduction in the first 24h of treatment compared between HT and SMT group was delta (Δ) 83% vs. 46% (p = 0.235). 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 (cf. Suppl. Figure 2), whereas PCT levels decreased and remained lower in the HT group.

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 and Suppl. Figure 1.

Table 3
Primary and secondary endpoints and outcomes of patients who were assigned to hemadsorption therapy or standard medical therapy

Parameters	*Hemadsorption therapy (n = 12)*	*Standard medical therapy (n = 12)*	*p-value*
Primary endpoint	4 (33)	2 (17)	0.640
Shock reversal within 10 days			
Secondary endpoints			
Change in SOFA Score (points)	1 (0.8–1.5)	1 (0–2.3)	0.843
Lactate clearance < 2mmol/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 ECMO, days	25.5 (12.6–33)	18.4 (2.4–20.5)	0.149
Time to shock reversal	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	11 (92)	8 (67)	0.317
- IL-6	9 (75)	6 (50)	0.400
- PCT	0 (0)	1 (8)	0.478
- D-Dimers			
Outcome			
28d – Mortality	7 (58)	8 (67)	1.0
Data are expressed as n (%) or median (interquartile range)			
Abbreviations: SOFA, sequential organ failure assessment; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; PCT, procalcitonin; IL-6, interleukin 6; d, day;			

Discussion

This is the first randomized controlled trial investigating hemadsorption therapy for cytokine elimination in critically ill patients with COVID-19 with proven hypercytokinemia. This study demonstrates that hemadsorption could significantly reduce inflammatory cytokines accompanied by clinical stabilization of severely ill patients as compared to standard medical therapy.

The COVID-19 pandemic resulted in high hospitalization rates with up to 5% admitted to the ICU mainly due to respiratory failure (2–4). 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 (32). Extensive pulmonary and multiorgan endothelial lesions are largely described as a hallmark of severe respiratory failure (33). Among others, high IL-6 levels were observed and strongly associated with multi-organ 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 (18, 20, 34, 35). Although initial reports suggested 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, 36). 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. using HT in COVID-19 patients with ARDS requiring ECMO therapy could not show beneficial effects (37). The primary endpoint was IL-6 serum concentration 72h after randomization. However, median baseline IL-6 levels in the intervention group were low (357 ng/l), compared to 2269 ng/l in our study. In fact, we observed a significant decrease of IL-6 levels in the intervention group (83% vs. 46%) within the first 24h demonstrating the efficacy of hemadsorption in patients with excessive IL-6 values. In addition, we observed a significant and sustained decrease of PCT (see Supp. Figure 2), which supports the effectiveness of HT as shown earlier (38). These findings suggest that initiation of hemadsorption should probably not solely be based on the clinical condition and acute respiratory failure as recently shown by Supady et. al. 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., did not show any conspicuous mortality during therapy. Notably, our cohort consisted of severely ill patients which is demonstrated by high SOFA and SAPSII scores, usually associated with a mortality rate of above 80% (24, 25).

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. 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 lactate levels (18). 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 allows the assumption that the treatment group (HT) had a survival advantage, which was, however, limited to the intervention period (Fig. 2). 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 (39, 40), 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.

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 (Fig. 2). 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 limitations which should be mentioned. We are reporting a small randomized single center open-label trial. 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 comprehensibly 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 randomisation, our patients had been treated on 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 prespecified and limited to five days. Whether an extended use of hemadsorption beyond five days would result in improved outcome remains unclear.

This study also has several strengths. Despite the small sample size important baseline characteristics such as disease severity and comorbidities were generally comparable and balanced between both groups. 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 significant subgroup of critically ill patients with COVID-19. In our cohort of critically ill patients, we observed beneficial effects of HT during the intervention period. Short-term outcomes including mitigation of organ dysfunction leading to clinical stabilization was observed in the HT group. Although some beneficial effects were observed, 28-day mortality was not improved. HT might be used for stabilization before transfer to a tertiary care center or for decision of further interventions.

Whether longer duration or earlier start of HT would prove beneficial should be elucidated and warrants further clinical investigations.

Declarations

Ethics approval and consent to participate:
This clinical study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Hamburg Chamber of Physicians on 30 March 2020 (No.: PV7314). Written informed consent was obtained from all patients or their legal representatives. If this was not possible in time before enrolment, 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.

Consent for publication:
Not applicable

Availability of data and materials:
The full trial protocol and the datasets supporting the conclusions of this article are available upon reasonable request.

Competing Interest:
DJ has received lecture honoraria and travel reimbursement from ADVITOS and CytoSorbents Europe GmbH. MF receives research support from the External Research Program, Medtronic, Minneapolis, MA. SK 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, Xenios and Zoll, and consultant honorarium from AMOMED, Astellas, Baxter, Bayer, Fresenius, Gilead, MSD, Pfizer and Xenios. AN has received lecture honoraria and travel reimbursement from ThermoFisher Scientific GmbH, Fresenius AG, CytoSorbents Europe GmbH and Biotest AG, Germany over the past five years. D.F. reports lecture honoraria within the last 5 years from Xenios AG. KR, CB, GdH, OB, AT and BS do not report any conflicts of interest. No other potential conflict of interest relevant to this article was reported.

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Authors' contributions:
DJ, KR and AN conceived and designed the study. KR, DJ, CB, GH, DF, BS, OB, AT and AN were involved in data acquisition. MF, KR, DJ and AN analysed and interpreted the data. KR drafted the manuscript. DJ, MF, SK and AN critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

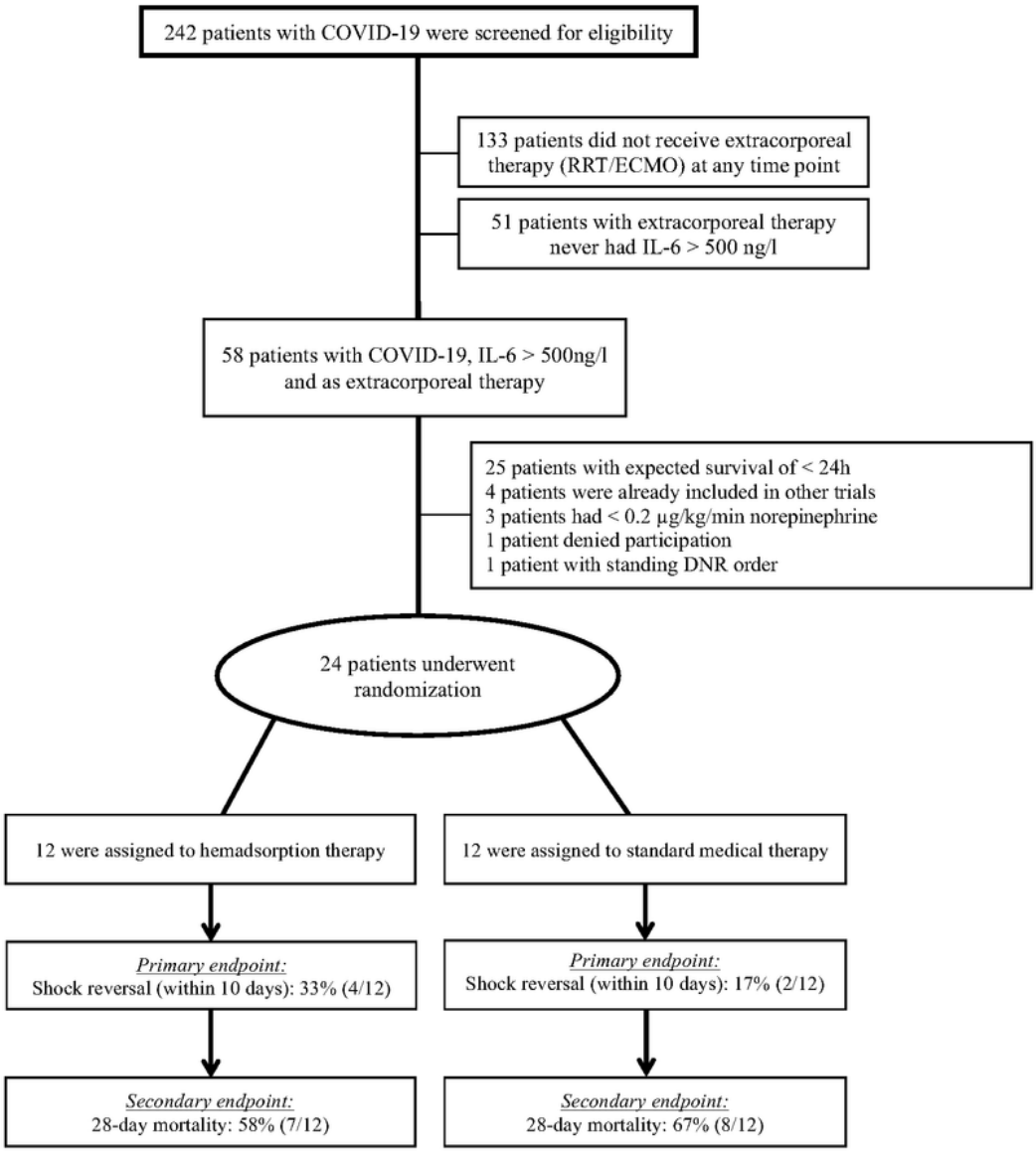

Figure 1

Flow-Diagram of the study

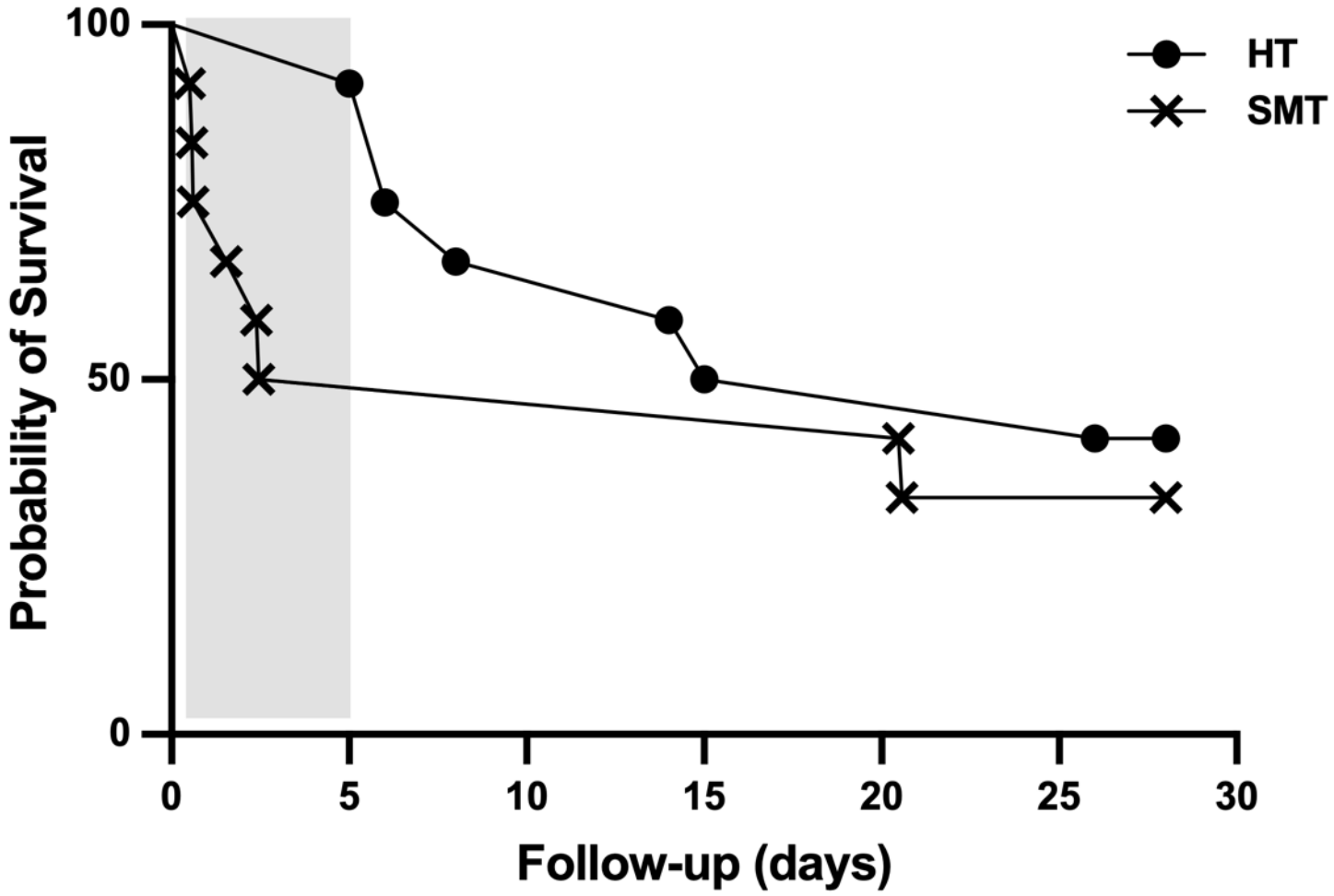

Figure 2

Kaplan-survival estimates

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