

High-dose CytoSorb hemoadsorption is associated with improved survival in patients with septic shock: A retrospective cohort study

Philipp Schultz

Ruhr-Universität Bochum Klinikum Herford

Elke Schwier

Ruhr-Universität Bochum Klinikum Herford

Claas Eickmeyer

Ruhr-Universität Bochum Klinikum Herford

Dietrich Henzler (✉ mail@d-henzler.de)

Ruhr-Universität Bochum Medizinische Fakultät <https://orcid.org/0000-0001-5511-6885>

Thomas Koehler

Ruhr-Universität Bochum Klinikum Herford

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Abstract

Background: Septic shock and SIRS are life-threatening diseases with persistent high mortality. Hemoadsorption with CytoSorb[®] offers a possible therapeutic approach, but the optimal timing, dosing and indications are still unclear.

Methods: Observational data from 70 patients with septic shock or SIRS, treated in a university hospital with hemoadsorption by CytoSorb[®] in addition to renal replacement therapy were analyzed retrospectively. Physiologic parameters and clinical outcomes were extracted from the electronic charts. The predicted mortality was calculated based on APACHE II and SOFA scores and compared with the actual 28-day survival. The total amount of blood purified was correlated with outcome.

Results: The main origins of septic shock were abdominal (n=29) or pulmonary (n=22). The mean age was 70.6±13.3 years. Hemoadsorption was applied for 85.6±53.8h with 3.2±1.7 cycles lasting 26.75±11.1h each. The severity was characterized by a mean APACHE II score of 30.2±6.3 and SOFA score of 13.8±3.5, which calculated to a predicted mortality of 73.3% and 62.1%, respectively. The observed mortality was significantly lower (35/70 patients (50%), p<0.05). Interleukin-6 levels at baseline were high (survivors: 7964±11242pg/ml; nonsurvivors: 8.755±15.800pg/ml, p=0.27) and decreased rapidly within 4-24h. Survival was independently associated with lower IL-6 levels and norepinephrine dosage after 24h. An increase in IL-6 after 48h was predictive of poor outcome.

The treatment duration and amount of blood purified was higher in survivors than in non-survivors (8.47±4.42 vs. 6.07±3.57l/kg BW, p=0.017). We identified 3 clusters of <6l/kg, 6-13l/kg and ≥13l/kg BW with a linear dose-response relation between blood purification volume and survival. Although the predicted mortality was comparable among the clusters (p=ns), survival was best in the highest volume cluster (16.7%; p=0.045).

Conclusions: The application of CytoSorb[®] seems to be safe and effective in various conditions of septic shock and SIRS, although the optimal duration and dosing remain unclear. In a cohort of severely ill patients the observed mortality rate was lower than predicted and decreased linearly with blood purification volumes exceeding 6l/kg BW. These results suggest that hemoadsorption with CytoSorb[®] improves survival in septic shock or SIRS, provided that the applied dose is high enough.

Background

Sepsis and septic shock are complex, life-threatening organ dysfunction caused by an inadequate, misdirected host response to infection [1] with persistent high mortality and morbidity [2, 3]. No single intervention or treatment bundle so far has significantly improved outcome, which may in part be contributed to the increasing age of the population [4] and the increase in anti-infective resistance [5–7].

An important determinant of multi-organ septic dysfunction is a generalized microcirculatory disorder induced by multiple humoral and cellular mechanisms. Cytokines are an important part of the

inflammatory reaction [8–12]. Pro-inflammatory cytokines Interleukin (IL)-6, IL-8, IL-18, tumor necrosis factor alpha (TNF- α) are necessary for the life-sustaining control of infection. The misregulated, excessive release of pro-inflammatory cytokines leads to a generalized inflammatory reaction with autodestructive potential (so-called cytokine storm). Up-regulation of anti-inflammatory cytokines (IL-10) is intended to prevent an overreaction of the immune system [13] which may lead to immune paralysis with secondary, potentially fatal infection [14–16].

Sepsis is the most common cause of acute kidney injury (AKI) in intensive care patients and an independent predictor of poor outcome [17]. Continuous renal replacement therapy (CRRT) is a standard to preserve hemodynamic stability. Other than shock-associated hypoperfusion/ischemia, the pathophysiological cause of septic AKI may be a dysregulated, excessive immune response. The Toll-like receptor 4 (TLR 4), the nuclear factor κ B (NF κ B) and TNF- α , IL-1, IL-6, and IL-8 play an important role in mediating this response which ultimately causes apoptosis [18].

Hemoadsorption using CytoSorb® offers a new therapeutic approach. Highly porous polymer beads bind a broad spectrum of different pro- and anti-inflammatory and endogenous substances (e.g. bilirubin, ammonia, bile acids, free hemoglobin dimer) [19, 20], myoglobin [21] or different drugs [22, 23]. Preferentially hydrophobic molecules with a molecular weight of up to 55 kDa are removed with a high clearance rate [24]. As this is a concentration-dependent process [23, 25], low (physiological) cytokine levels are not or only slightly influenced and imbalances may be compensated.

In contrast to therapeutic concepts that target specific pathways in the complex signal transduction of sepsis (e.g. specific antibodies), hemoadsorption just reduces the excess immune response. Individual pathways of the inflammatory reaction, which is regulated on many levels, will not be blocked. CytoSorb® efficiently removes a broad spectrum of toxic PAMPs and DAMPs from the blood [26, 27] *in-vitro*, which could alleviate the negative consequences, such as capillary leakage to improve microcirculation and organ function *in-vivo* [28, 29].

Indications, timing and duration of hemoadsorption in septic shock is being discussed controversially. A randomized controlled trial (RCT) could not prove a survival benefit with the use of CytoSorb® in patients with ARDS [30]. However, the duration of application was short and the severity of disease was significantly lower than otherwise reported [28, 31, 32]. More recently, the observed mortality of patients with septic shock treated with CytoSorb® was significantly reduced compared to the expected mortality [33].

In 2016 hemoadsorption with CytoSorb® was introduced as a new treatment in the author's institution for patients with septic shock and/or non-infectious SIRS. Hemoadsorption was administered in addition to standard therapy for those who received continuous veno-venous hemodialysis (CVVHD). The anticoagulation was performed by citrate, because there is no interaction with the adsorber [34].

The aim of this study was to review the first experience with the new treatment, to identify response parameters and to assess the effect on outcomes.

Methods

Study population

The retrospective identification of the patients was carried out via the hospital information system (SAP, Heidenheim, Germany). Patients with septic shock and/or non-infectious SIRS were searched, who received hemoadsorption with CytoSorb® in addition to standard therapy [1, 35]. No other hemoadsorption therapies were used in the investigated period. A targeted search was conducted for patients whose admission diagnosis or Diagnosed Related Groups (DRGs) contained the following International Code of Diseases-10 (ICD-10) numbers: A02.1 to A41.9 - sepsis of different etiology and R57.2 - septic shock. Subsequently, the OPS code 8-821.2 (extracorporeal adsorption of low and medium molecular weight hydrophobic substances) was used.

Between March 2016 and January 2019, 286 patients with septic shock were admitted to the intensive care unit with septic shock according to the sepsis-3 criteria [36], characterized by a serum lactate concentration > 2 mmol/l and vasopressor requirement despite fluid resuscitation for achieving a mean arterial pressure (MAP) of > 65 mmHg. 96 patients with acute renal failure AKI II [37] (serum creatinine with 2.0 to 2.9-fold increase of the initial value, urine production < 0.5 ml/kg/h for more than 12 h) were treated with CVVHD and additional hemoadsorption (change interval 24 h) [28, 33]. The CVVHD was operated at blood flow rates between 100–150 ml/min to achieve a dialysis dose of 20–30 ml/kg/h [28].

9 patients were excluded because treatment was not started as recommended [28, 33] within the first 24 hours after diagnosis of sepsis, 17 patients were excluded due to incomplete data sets. The data of the remaining 70 patients were extracted from the electronic records of the intensive care unit (Patient Data Management System ICM, Dräger, Lübeck, Germany) (Fig. 1).

Information on patient characteristics, diagnosis, physiological parameters and laboratory values were collected or calculated from the electronic records. Patient outcomes were collected from the hospital information system. The physiologic parameters 1 hour before and 4, 8, 24, 48, 72 and 96 hours after the start of hemoadsorption treatment were included into the analysis. Data (blood flow (ml/min) and dialysate flow (ml/h)) of continuous renal replacement and hemoadsorption therapy were collected at each time point. The duration of the CytoSorb® treatment (h) was determined.

A dose definition for hemoadsorption was calculated as the amount of blood purified (ABP) as follows:

$$ABP = (CD \times BF) / BW \times 0,001$$

ABP = Amount of Blood Purified (l/kg), CD = Duration of treatment with CytoSorb® (min), BF = Blood Flow (ml/min), BW = Body Weight (kg)

Definition of outcomes

The length of stay in intensive care (LOS) and hospital stay were determined. The APACHE II and SOFA scores were calculated and the predicted mortality was derived according to open source calculators (<https://clinicalcalc.com/>). Surviving patients (SURV) were compared with non-survivors (NSURV) for

baseline characteristics, treatment parameters and different treatment modalities (norepinephrine dose, fluid balance). The observed outcomes were compared with predicted mortality from APACHE II and SOFA scores

Statistical analysis

Data were tested for normality with KS-test. Groups were compared using t-Test or Wilcoxon-Test for not normally distributed values, respectively. The time course of IL-6, vasopressors or SOFA scores were analyzed by analysis of variance (ANOVA) for repeated measurements. Categorical data were analyzed by chi² test. P-values < 0.05 were considered significant (IBM SPSS Statistics Version 25, IBM Corporation, Armonk, New York, USA). Data are presented as mean ± standard deviation or median (interquartile range) as appropriate.

This study was approved by the institutional ethics committee of the Ruhr University Bochum (reference number: 2019 - 450_1, from February 2, 2019).

Results

70 patients were included in the final analysis (Fig. 1). All patients were mechanically ventilated and had developed acute renal failure AKI II receiving CVVHD before treatment with hemoadsorption (Table 1). Participants represented a cohort of the most severely sick patients characterized by APACHE II score of 30.2 ± 6.3 and a SOFA score of 13.8 ± 3.5 . The predicted mortality according to APACHE II and SOFA was $73.3 \pm 17\%$ and $62.1 \pm 23\%$, respectively. The observed 28-day mortality was 50% (Table 1).

Table 1 Comparison between survivors and non-survivors

Characteristics	Total number	Survivors	Non-Survivors	p-Value
Number of patients	70	35	35	
Age (years)	70.6 ±13.3	67.7 ±11.6	73.4 ±14.4	0.62
Sex (male/female), (n)	43/27	23/12	20/15	
Weight (kg)	83.2 ±18.9	83.5 ±20.4	83 ±17.5	0.56
Body surface area (m ²)	1.97 ± 0.35	2 ±0.27	1.9 ±0.41	0.46
Height (cm)	173.5 ± 8.5	175.1 ±8.2	171.7 ±8.6	0.55
BMI (kg/m ²)	27.5 ± 5.6	27 ±5.2	28.1 ±6	0.54
APACHE II	30.2 ± 6.3	28.5 ±6.3	31.8 ±5.9	0.96
SOFA	13.8 ±3.5	13.2 ±3.5	14.4 ±3.3	0.61
Predicted mortality APACHE II (%)	73.3 ±17	69.4 ±19.2	77.2 ±13.6	0.34
Predicted mortality SOFA (%)	62.1 ±23	57.8 ±22.7	66.5 ±23	0.16
Duration of CytoSorb [®] application (h)	85.6 ±53.8	102 ±51.2	68.1 ±51.2	0.009*
Number of CytoSorb [®] -Adsorbers/Patient	3.2 ±1.7	3.63 ±1.77	2.77 ±1.52	0.72
Use life per CytoSorb [®] -Adsorber (h)	26.75 ±11.1	29.1 ±9.1	24.4 ±12.5	0.96
Observed 28-d mortality (%)	50	0	100	
LOS in ICU (days)	23.9 ±22.6	36.6 ±24.2	11.1 ±10.8	0.0001*
Site of infection (n)				
abdominal	29	13	16	
pulmonary	22	14	8	
other focus	7	3	4	
Non-infectious SIRS (n)	12	5	7	

Demographic and clinical characteristics for all patients, survivors and non survivors at baseline (*statistical significance)

The origin of septic shock were abdominal (n = 29), pulmonary (n = 22) or of different origin (n = 7). In 12 cases no infectious focus was detected and a systemic inflammatory response syndrome (SIRS) of non-infectious origin was diagnosed stemming from pancreatitis, severe brain injury or veno-venous extracorporeal membrane oxygenation (VV-ECMO). There were no significant differences between SURV and NSURV in baseline characteristics (Table 1).

The total hemoadsorption treatment duration was 85.6 ± 53.8 h and was significantly longer in survivors ($p = 0.009$). On average, 3.2 ± 1.7 cartridges were used, which amounted to 26.75 ± 11.1 h per cartridge. The mean useful life of a single adsorber was 29.1 ± 9.1 h (SURV) and 24.4 ± 12.5 h (NSURV), respectively ($p = 0.96$).

The course of IL-6 levels, lactate and vasopressor dose over the first 96 h were lower in SURV than NSURV (Table 2). Baseline IL-6 levels were high compared to previous studies, but not significantly different between survivors and non-survivors ($p = 0.27$). After 24 h, IL-6 levels had decreased more in SURV compared to NSURV ($p = 0.001$). In NSURV, IL-6 concentrations started to increase again after 48 h (Table 2).

After start of treatment, the maximum required dose of norepinephrine was consistently lower in the SURV than in the NSURV ($0.39 \mu\text{g}/\text{kg}/\text{min}$ vs. $0.62 \mu\text{g}/\text{kg}/\text{min}$ $p = 0.02$), but exhibited no difference at baseline (Table 2). The need for vasopressors in the SURV group decreased continuously over the course of treatment and was significantly lower than in the NSURV group after 4 h already and continued to decrease 24 h after the start of treatment. The mean arterial pressure (MAP) was in the target range of 65 mmHg and not different between SURV and NSURV. The oxygenation index was comparable between SURV and NSURV. The serum lactate levels in the SURV group decreased continuously over the course of treatment and differed significantly from the NSURV group at each time point (Table 2).

Table 2. Comparison between survivors and non-survivors

Characteristics	Total number	Survivors	Non-Survivors	p-Value
Amount of blood purified -ABP- (l/kgBW)	7.3 ±4.2	8.47 ±4.42	6.07 ±3.57	0.017
Interleukin-6 (pg/ml)	8360 ±13612	7964 ±11242	8755 ±15800	0.27
1. Before	3644 ±7599	2157 ±3423	5310 ±10318	0.06
	3549 ±9130	2044 ±3991	4960 ±12036	0.07
	2713 ±5803	1299 ±2783	4221 ±7616	0.001*
2. 4 h	2867 ±8586	614 ±780	5571 ±12295	0.001*
	1355 ±5062	280 ±261	3428 ±8467	0.001*
	1822 ±6547	698 ±1908	4194 ±11275	0.01*
3. 8 h				
4. 24 h				
5. 48 h				
6. 72				
7. 96 h				
Leukocyte count (Gpt/l)	17.3 ±6.30	14.6 ±9.6	17.9 ±12.7	0.81
1. Before	21.0 ±16.0	16.8 ±12.5	24.5 ±18.1	0.38
	19.8 ±11.5	18.2 ± 10.3	21.2 ±12.5	0.37
	16.8 ±9.90	14.5 ±9.1	19.6 ±10.3	0.44
2. 4 h	16.0 ±10.6	13.1 ±7.7	19.8 ±12.7	0.11
	16.0 ±10.5	12.1 ±6.2	24.1 ±13.0	0.01*
	15.0 ±9.00	11.1 ±4.9	24.0 ±10.1	0.03*
3. 8 h				
4. 24 h				
5. 48 h				
6. 72				
7. 96 h				
Lactate (mmol/l)	4.77 ±4.35	3.24 ±2.56	7.75 ±4.11	0.01*
1. Before	4.40 ±3.49	2.95 ±2.18	5.85 ±3.97	0.001*
	4.51 ±4.05	2.57 ±1.64	6.50 ±4.77	0.001*
	3.97 ±4.06	2.13 ±1.38	5.98 ±5.00	0.001*
2. 4 h	3.11 ±3.35	1.66 ±1.14	5.00 ±4.26	0.001*
	2.11 ±2.35	1.44 ±1.24	3.53 ±3.39	0.001*
	2.17 ±3.16	1.19 ±0.44	4.62 ±5.25	0.001*

3. 8 h				
4. 24 h				
5. 48 h				
6. 72				
7. 96 h				
Norepinephrine dose ($\mu\text{g}/\text{kg}/\text{min}$)				
1. Before	0.42 \pm 0.37 0.51 \pm 0.48 0.47 \pm 0.43 0.40 \pm 0.40 0.30 \pm 0.33	0.38 \pm 0.71 0.39 \pm 0.30 0.35 \pm 0.26 0.23 \pm 0.20 0.15 \pm 0.16	0.46 \pm 0.37 0.62 \pm 0.60 0.59 \pm 0.53 0.58 \pm 0.49 0.49 \pm 0.39	0.53 0.02* 0.09 0.001* 0.001*
2. 4 h	0.20 \pm 0.23 0.19 \pm 0.27	0.12 \pm 0.14 0.10 \pm 0.15	0.37 \pm 0.30 0.41 \pm 0.38	0.001* 0.001*
3. 8 h				
4. 24 h				
5. 48 h				
6. 72				
7. 96 h				
MAP (mmHg)				
1. Before	67 \pm 19 64 \pm 18 69 \pm 20 68 \pm 21	71 \pm 21 68 \pm 18 71 \pm 22 72 \pm 22	63 \pm 17 60 \pm 17 67 \pm 18 64 \pm 19	0.24 0.82 0.58 0.75
2. 4 h	69 \pm 16 71 \pm 17 71 \pm 15	70 \pm 16 75 \pm 17 74 \pm 14	67 \pm 16 64 \pm 14 65 \pm 16	0.88 0.57 0.87
3. 8 h				
4. 24 h				
5. 48 h				
6. 72				
7. 96 h				

Oxygenation index (PaO ₂ /FiO ₂)				
1. Before	224 ±115	235 ±122	213 ±107	0.52
	254 ±107	267 ±111	242 ±104	0.76
2. 4 h	266 ±103	286 ±136	246 ±125	0.35
	247 ±100	251 ±107	243 ±94,0	0.52
3. 8 h	256 ±103	282 ±107	225 ±90,0	0.47
	273 ±112	294 ±113	232 ±102	0.86
4. 24 h	261 ±093	275 ±081	230 ±113	0.37
5. 48 h				
6. 72				
7. 96 h				

Biological and physiological parameters before and 4h, 8h, 24h, 48h, 72h and 96h after start of hemoadsorption treatment with CytoSorb[®] for all patients, survivors and non survivors.

(*statistical significance); MAP-mean arterial pressure (mmHg)

Amount of blood purified (ABP)

The distribution of ABP ranged from 0.73 l/kg to 20.57 l/kg BW. The ABP was higher in SURV (8.47 l/kg ± 4.42) than in NSURV (6.07 l/kg ± 3.57, p = 0.017) (Table 2). After plotting against observed mortality (supplemental Fig. Suppl. 1) we identified three clusters:

A – low ABP < 6 l/kg (n = 29)

B – intermediate ABP 6–13 l/kg (n = 35)

C – high ABP ≥ 13 l/kg (n = 6).

No differences were detected in age, height and body surface area between clusters. The patients in cluster C were significantly lighter and had a lower body mass index (BMI). APACHE II and SOFA scores did not differ among clusters (Table 3). We observed a linear reverse correlation of ABP clusters and outcome, although the disease severity and the predicted mortality were not different at baseline. In the high ABP cluster the observed 28-d mortality was significantly lower (16.7%) than in intermediate (42.9%) and low ABP clusters (65.5%) (p = 0.045) (Table 3). Survival curves started to separate after 48 h of treatment (Fig. 2). Patients in cluster C received more adsorbers (p = 0.0001) and a longer treatment (p = 0.001), (Table 3).

Table 3 Comparison between the different clusters of amount of blood purified (ABP)

Characteristics	Amount of blood purified -ABP- (l/kgBW)			p-Value
	< 6	6-13	≥13	
Cluster	A	B	C	
Number of patients	29	35	6	
Age (years)	74.17 ±12.1	67.66 ±14.1	70.33 ±11.6	0.15
Sex (male/female), (n)	19/10	22/13	2/4	
Weight (kg)	88.70 ±20.9	81.1 ±16.5	69.5 ±13.70	0.05*
Body surface area (m ²)	2.10 ±0.26	01.92 ±0.40	1.81 ±0.20	0.16
Height (cm)	173.10 ±8.30	174.3 ±8.60	170.2 ±9.30	0.50
BMI (kg/m ²)	29.60 ±6.80	26.5 ±4.10	23.8 ±3.10	0.02*
APACHE II	28.97 ±7.00	30.91 ±5.60	31.50 ±5.80	0.40
SOFA	13.28 ±4.20	14.03 ±2.90	15.00 ±1.10	0.47
Predicted mortality APACHE II (%)	69.40 ±22.30	75.56 ±11.70	78.78 ±10.10	0.26
Predicted mortality SOFA (%)	59.80 ±27.70	62.1 ±19.70	73.30 ±14.70	0.43
Duration of CytoSorb [®] application (h)	48.70 ±22.9	102.4 ±48.4	159.3 ±66.40	0.001*
Number of CytoSorb [®] absorbers / Patient	2.04 ±0.91	3.71 ±1.25	5.83 ±2.48	0.0001*
Use life per CytoSorb [®] adsorber (h)	24.40 ±8.5	28.6 ±13.5	27.1 ± 3.9	0.32
Survivor (n)	10	20	5	
Observed 28-d mortality (%)	65.5	42.9	16.7	0.045*
Site of infection (n)				
abdominal	15	10	4	
pulmonary	6	15	1	
other focus	5	2	0	
Non-infectious SIRS	3	8	1	

No differences were found between clusters for IL-6, vasopressor doses, MAP, lactate, leukocyte count and oxygenation index (Table 4). In all clusters the IL-6 serum concentrations decreased and reached comparable values after only 4 h (Fig. 3).

Table 4 Comparison between the different clusters of amount of blood purified (ABP) (l/kg BW)

Characteristics	Amount of blood purified -ABP- (l/kg BW)			p-Value
	< 6	6-13	≥13	
Cluster	A	B	C	
Interleukin-6 (pg/ml)				
1. Pre-	10836 ±15007	4578 ±7218	16969 ±25585	0.05*
	3409 ±4783	4032 ±9812	2537 ±2772	0.91
	3773 ±9730	3191 ±9150	4369 ±7493	0.95
	3415 ±6822	2431 ±5502	1411 ±2039	0.70
2. 4 h	3534 ±11308	2810 ±7226	542 ±471	0.79
	153 ±180	1881 ±6085	337 ±360	0.63
	104 ±84	1918 ±7412	2607 ±3956	0.88
3. 8 h				
4. 24 h				
5. 48 h				
6. 72 h				
7. 96 h				
Leukocyte count (Gpt/l)				
1. Before	16.7 ±11.4	15.3 ±9.10	19.1 ±7.9	0.74
	28.6 ±22.9	15.9 ±8.40	18.3 ±5.4	0.09
	21.6 ±15.0	18.9 ±9.70	18.1 ±5.6	0.70
	18.5 ±11.9	16.0 ±10.6	15.0 ±6.2	0.60
	15.9 ±12.1	16.4 ±10.6	14.4 ±5.2	0.91
2. 4 h	12.1 ±5.70	18.1 ±12.0	11.0 ±2.0	0.12
	8.3 ±4.10	17.1 ±9.50	10.5 ±3.6	0.05
3. 8 h				
4. 24 h				
5. 48 h				
6. 72				
7. 96 h				

Characteristics	Amount of blood purified -ABP- (l/kg BW)			p-Value
Lactate (mmol/l)				
1. Before	3.79 ±3.11	4.11 ±3.92	4.21 ±2.65	0.93
	4.57 ±3.44	4.30 ±3.65	4.15 ±3.35	0.94
	4.95 ±4.72	4.07 ±3.45	5.01 ±4.25	0.66
	4.92 ±5.30	3.25 ±3.01	4.07 ±2.62	0.29
2. 4 h	3.57 ±4.10	2.81 ±3.06	3.20 ±2.17	0.73
	1.09 ±0.41	2.46 ±2.77	2.06 ±1.36	0.25
	1.03 ±0.37	2.48 ±3.69	1.75 ±0.66	0.57
3. 8 h				
4. 24 h				
5. 48 h				
6. 72				
7. 96 h				
Norepinephrine dose (µg/kg/min)				
1. Before	0.36 ±0.30	0.44 ±0.35	0.63 ±0.67	0.27
	0.54 ±0.60	0.45 ±0.35	0.72 ±0.57	0.41
	0.57 ±0.59	0.37 ±0.26	0.60 ±0.26	0.13
	0.54 ±0.54	0.32 ±0.27	0.31 ±0.22	0.11
2. 4 h	0.39 ±0.43	0.26 ±0.27	0.22 ±0.21	0.30
	0.12 ±0.19	0.23 ±0.25	0.19 ±0.18	0.41
	0.03 ±0.02	0.20 ±0.29	0.31 ±0.22	0.19
3. 8 h				
4. 24 h				
5. 48 h				
6. 72				
7. 96 h				

Characteristics	Amount of blood purified -ABP- (l/kg BW)			p-Value
MAP (mmHG)				
1. Before	68 ±16	70 ±22	51 ±12	0.08
	61 ±17	68 ±20	58 ±08	0.23
2. 4 h	66 ±20	71 ±21	65 ±16	0.52
	65 ±18	71 ±22	69 ±24	0.53
3. 8 h	69 ±15	68 ±17	74 ±12	0.69
	63 ±12	71 ±18	86 ±09	0.02
4. 24 h	83 ±10	68 ±15	77 ±16	0.27
5. 48 h				
6. 72				
7. 96 h				
Oxygenation index (PaO ₂ /FiO ₂)				
1. Before	243 ±121	213 ±113	192 ±086	0.49
	257 ±096	253 ±120	241 ±100	0.97
2. 4 h	264 ±117	263 ±131	293 ±220	0.89
	258 ±100	237 ±106	261 ±071	0.71
3. 8 h	247 ±128	260 ±093	268 ±059	0.88
	323 ±157	247 ±093	321 ±054	0.09
4. 24 h	243 ±085	260 ±100	289 ±052	0.73
5. 48 h				
6. 72				
96 h				

Biological and physiological parameters before and 4h, 8h, 24h, 48h, 72h and 96h after start of hemoadsorption treatment with CytoSorb[®] for the different clusters of amount of blood purified (ABP)(l/kg BW) (*statistical significance).

Discussion

In this retrospective, investigator initiated study we analyzed the course of treatment in 70 surgical intensive care patients who received hemoadsorption with the CytoSorb[®] adsorber in septic shock or

non-infectious SIRS in addition to standard therapy [1, 38]. No possible side effects occurred during the course of the hemoadsorption treatment which suggests that the therapy is well tolerated and does not pose added risks to the patient. The mortality rate of 50% was clearly lower than predicted by APACHE-II (73.3%) and SOFA score (62.1%).

A main goal of our study was to identify parameters of response and predictors of survival associated with the treatment. As a major predictor we found an association of the applied dose with survival (Fig. 2 and Fig. 4). So far, no dose-response relationship had been described. We calculated the dose as the amount of blood purified (ABP) by the adsorber as a function of blood flow and duration in relation to body weight. Differences in ABP were caused by 3 mechanisms:

First, the blood flow through the CVVHD was set according to standard protocols for CRRT with citrate anticoagulation, resulting in blood flows from 100–150 ml/min. The blood flow was adjusted for CVVHD needs but was not targeted in respect to ABP. As a result, smaller patients received higher doses of hemoadsorption. *Second*, for the lack of data on when to end treatment, hemoadsorption was stopped at the discretion of the treating intensivist, e.g. after hemodynamic stabilisation, resulting in different treatment periods. *Third*, some patients with a foudroyant course of the disease had died early before the planned end of hemoadsorption treatment.

The duration of hemoadsorption treatment in our cohort (85.6 h) was longer than previously described, which ranged from 50 h [31], 56 h [33] up to 63 h [28]. Since no exact data on blood flow were reported, we can only speculate that ABP was higher in our cohort. Compared to data from the international CytoSorb® registry [31] the disease severity (APACHE II 29.8 vs. 28.97) and the predicted mortality (70.4% vs. 69.4%) were similar, but we observed a much lower mortality (50% vs. 66.2%). The number of adsorbers used was 3.2 on average in our cohort, but was much lower in the registry in a range of 1–5 adsorbers per patient [31]. These patients received a mean hemoadsorption treatment of 50 h, which is comparable to the low ABP cluster of < 6 ml/kg BW (48.9 h) in our cohort with a quite similar mortality of 65%. If a dose of ≥ 13 l/kg BW were targeted, the only way this could be achieved within 50 h with a blood flow of at least 303 ml/min, assuming a body weight of 70 kg. In reality, very few dialysis machines are able to deliver such blood flows, especially with the use of citrate anticoagulation. Other authors recommend lower blood flow rates [28]. We conclude that an ABP of ≥ 13 l/kg BW was not achieved in any of the previous investigations.

As a clinical consequence we have started targeting an ABP of ≥ 13 l/kg BW for standard application. To calculate the desired dose we have provided an Excel (Microsoft Corp. Redmont, WA. U.S.A.) based tool in the online supplements. Additionally, we have to consider the saturation kinetics of the adsorber over time [23, 25]. It is possible that the effect on the observed reduction in mortality may also be depending on the change intervals and useful life of the cartridge. Whether reducing the recommended change interval from 24 h to 12 h or even 8 h in the acute phase of massive hyperinflammation has an additional effect on outcome, should be investigated in further studies.

IL-6 levels at baseline were substantially higher in our cohort than in other previously published studies targeting the same disease population [29–31, 39, 40] and were considerably higher than recommended entry levels [41] (Fig. 5). A possible explanation may be the early and frequent monitoring of IL-6 levels leading to detection of high IL-6 levels that occur early in septic shock and rapidly decrease in the further course of the disease [42]. The course of decreasing levels of IL-6 is concordant with the concentration dependent adsorption kinetics of the adsorber cartridge [23, 25] and explains the visible approximation of the IL-6 levels after only four hours (Fig. 5). However, contrary to previous data [39, 43], the IL-6 levels were not directly related to mortality. Instead, the time course of IL-6 and the ABP were predictive of outcome suggesting that the ability to efficiently remove IL-6 faster than new cytokines are released by the organism is crucial for survival. In consequence, persistent high or increasing levels of IL-6 during the treatment phase were associated with worse outcome and may represent important prognosis factors.

We have not observed any differences in MAP between survivors and non-survivors or between the three ABP clusters. We assume that this is mainly the result of an effective vasopressor regime that targets the standard MAP values. Among survivors, vasopressor use decreased to 31.6% after 72 hours and to 26.3% after 96 hours compared to baseline. In accordance with previous studies [28, 29, 32, 40, 44] a rapid shock reversal was achieved (Fig. 5).

There was a trend, though not statistically significant, to lower MAP in the highest ABP cluster (C) at the start of hemoadsorption which corresponds to the high IL-6 levels at baseline. Presumably, these patients had sepsis-induced volume deficit [1, 45], insufficient norepinephrine doses or a decrease in cardiac output [46]. It is possible that an individual adjustment of the MAP target has been made [47]. Non-survivors exhibited higher norepinephrine (Fig. 5) and lactate levels, probably due to impaired microcirculation [48] and more vasoplegia, which means a higher risk of death. Elevated lactate levels are considered an independent risk factor for death in septic shock [33]. These differences were not observed between ABP clusters.

IL-6 has been reported to be associated with sepsis severity, end organ damage [49, 50] and increased mortality in septic patients [42, 49]. Frencken and colleagues observed that high levels of IL-6 and IL-10 are both associated with increased mortality. Of note, the ratio of the pro-inflammatory (IL-6) to the anti-inflammatory (IL-10) cytokine had no influence on mortality [51]. However, a better understanding of the „double-edged sword“ of pro- and anti-inflammatory cytokines and their interaction in a temporal context is crucial for the creation of new therapeutic approaches [9]. In respect to cytokine load, patients with high ABP had exhibited a specifically severe pro-inflammatory situation (cytokine storm) with the highest IL-6 values of all clusters (Table 3, Fig. 3). The fact that those patients actually did well implies differences in pathophysiology at baseline. We conclude that patients with extreme hyperinflammation may be the greatest beneficiaries from a therapeutic approach that specifically targets removal of pro-inflammatory substances, although the initial IL-6 levels were not directly related to mortality.

Previous studies in patients in septic shock with hemoadsorption had identified a pneumogenic focus as an independent risk factor for death [33]. In contrast, we could not establish such a correlation for any

infectious focus, however all patients were surgical patients and pneumonia was postoperative. Likewise, a non-infectious SIRS was not relevant for mortality.

Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), which first appeared in December 2019 in China, has spread rapidly around the world. Some patients develop a severe cytokine release syndrome (CRS), a cytokine storm, in response to the virus. Subsequent organ failure can potentially lead to death [52–56]. Such hyperinflammatory state can lead to impairment or destruction of the lungs and other organs. As an extreme increase in various pro- and anti-inflammatory cytokines such as IL-1, IL-2, IL-7, IL-10, G-CSF, MCP-1, MIP-1 α , INF- γ and TNF- α [41] has been postulated some authors have advocated for the use of hemoadsorption in treating COVID-19-associated cytokine storm syndrome [56–59]. As a consequence, in April 2020, the CytoSorb[®] was temporarily approved by the U.S. Food and Drug Administration (FDA) for emergency use in patients with CRS under certain conditions [60].

Limitations:

The present study has several limitations. As in every retrospective design treatment effects may be overestimated, side effects may be underestimated and confounders may not be adequately represented. We have also included some patients who presented similarly from a biological perspective with initial high accumulation of different cytokines from the IL-6 family [42] but did not have an-infectious cause of SIRS. Even so, the phenotype was quite similar to septic patients with proven infection. Our cohort of patients received a new intervention with standardized indication and was comparable by physiologic means to other published data. We used a stepwise backward design to identify factors associated with improved outcome and found an association between the amount of blood purified and survival. These results are for hypothesis generating and should be used for adequately powered prospective trials.

Conclusions

The application of CytoSorb[®] hemoadsorption appears to be safe and effective in various conditions of septic shock and SIRS, although the optimal duration and dosing remain unclear. By a novel approach considering the amount of blood purified we could demonstrate that there is a possible relationship between the administered dose of hemoadsorption and survival in septic shock. In a cohort of severely ill patients the observed mortality rate was lower than predicted and decreased further with blood purification volumes exceeding 6l/kg BW. These results suggest that hemoadsorption with CytoSorb[®] possibly reduces mortality in septic shock or severe CRS, provided that the applied dose is high enough. Further dose-finding studies and RCT's are necessary to verify these results.

Abbreviations

ABP: amount of blood purified; AKI: Acute Kidney Injury; ANOVA: analysis of variance; APACHE: Acute and chronic health evaluation; ARDS: Adult respiratory distress syndrome; BF: Blood Flow; BMI: Body Mass

Index; BW: Body Weight; CD: Duration of treatment with CytoSorb®; COVID-19: Coronavirus Disease 2019; CRRT: Continuous renal replacement therapy; CVVHD: continuous venovenous hemodialysis; CRS: cytokine release syndrome; DAMPs: Damage associated molecular patterns; DRG: Diagnosed Related Groups; FDA: U.S. Food and Drug Administration; G-CSF: Granulocyte-Colony Stimulating Factor; IL: Interleukin; ICD-10: International Code of Diseases-10; ICU: Intensive Care Unit; INF- γ : Interferon- γ ; LOS: length of stay in intensive care; IQR: interquartile range; MAP: Mean Arterial Pressure; MIP-1 α : Macrophage Inflammatory Protein 1-Alpha; MCP-1: monocyte chemotactic protein 1; NF κ B: Nuclear factor κ B; ns: not significant; NSURV: non-survivors; PAMPs: Pathogen associated molecular patterns; RCT: randomized controlled trial; SIRS: Systemic Inflammatory Response syndrome; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SOFA: Sequential Organ Failure Assessment; SURV: Survivors; TNF- α : Tumor necrosis factor alpha; TLR 4: Toll-like receptor 4; VV-ECMO: veno-venous extracorporeal membrane oxygenation.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional ethics committee of the Ruhr-University Bochum (reference number: 2019-450_1, from February 2, 2019). Due to the complete anonymised and non-traceable use of routine clinical parameters, in consultation with the Ethics Committee, the necessity to obtain consent from patients was waived.

Consent for publication

It is a retrospective investigation of parameters that have been routinely collected. All authors have approved the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

PS and TK have received lecture fees from Cytosorbent Europe. The Department of Anesthesiology at Klinikum Herford has received an unrestricted research grant from Cytosorbent Europe in 2018.

The authors declare that they have no other competing interests.

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The study was carried out without external funding.

Authors' contribution

PS participated in treatment of the patients, analyzing of data and reviewing of the manuscript.

ES performed literature research, helped with statistical analysis and reviewed the manuscript.

CE participated in clinical treatment and helped revising the manuscript.

DH conceived the study, analyzed and interpreted the data and participated in writing of the manuscript.

TK participated in treatment of the patients, analyzing and interpreting the data and was a major contributor in writing of the manuscript.

All authors read and approved the final manuscript.

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Figures

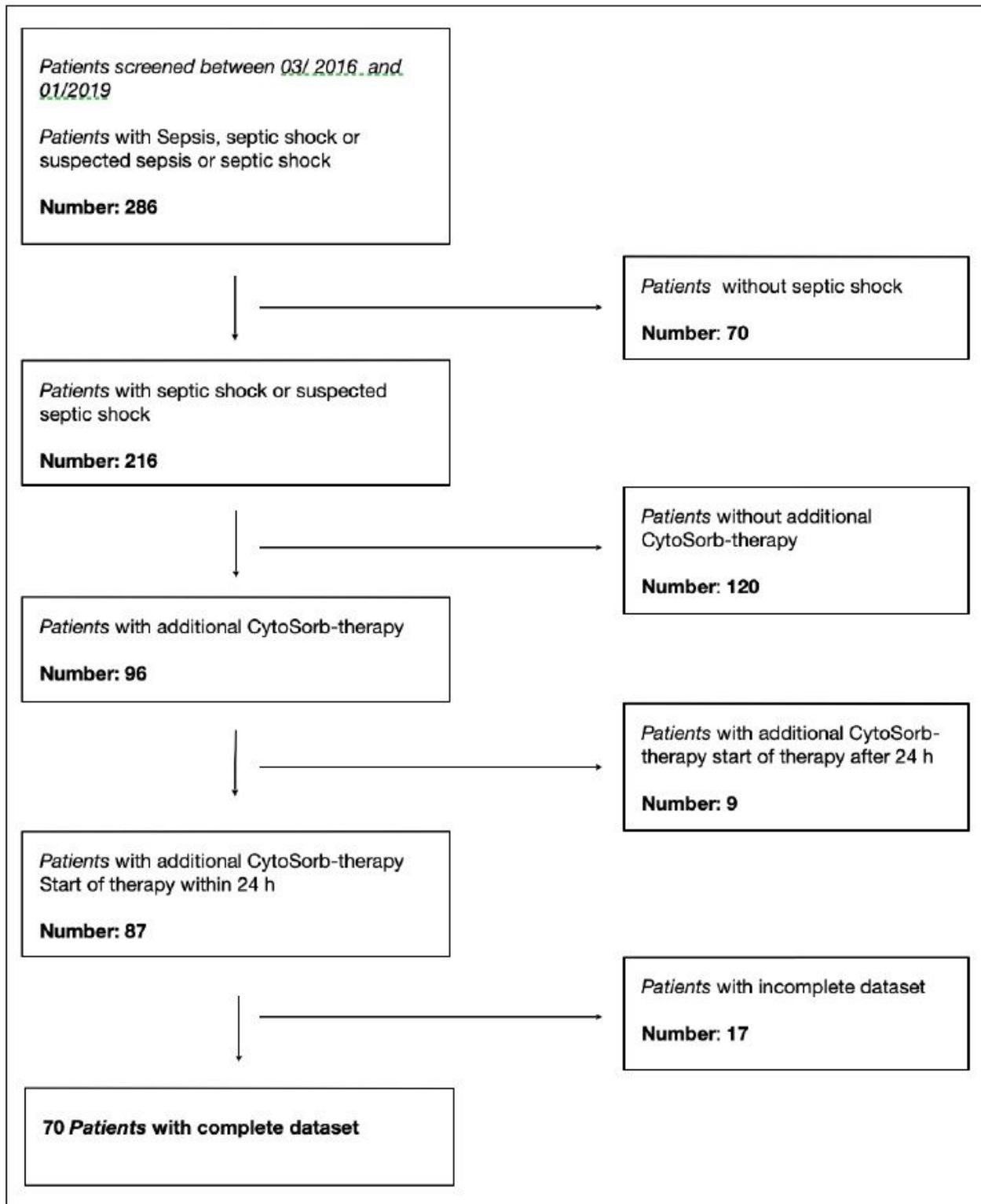


Figure 1

STROBE statement

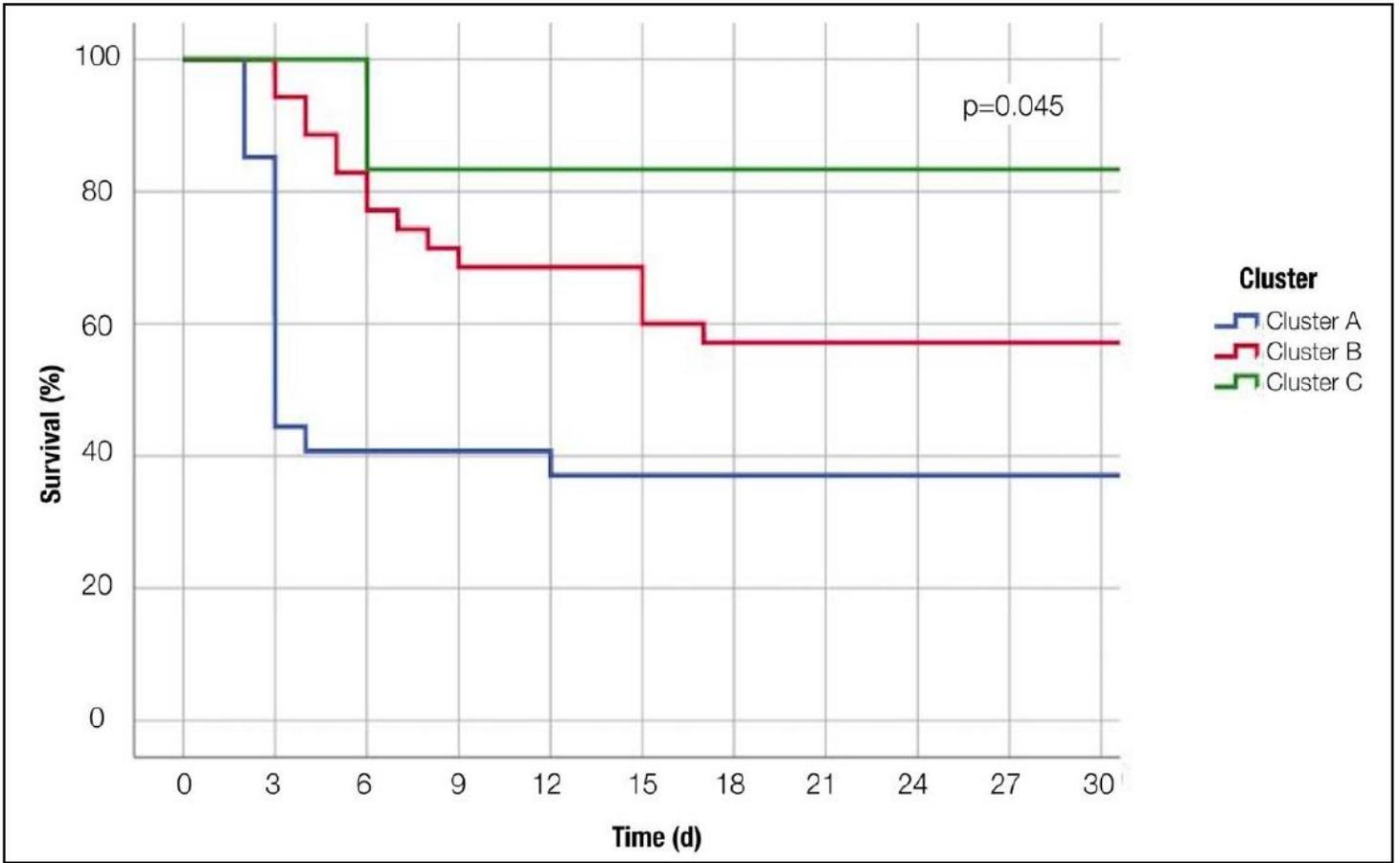


Figure 2

Survival curves according to amount of blood purified (ABP) Kaplan-Meier survival curves for different dosing clusters (blue curve: Cluster A, low ABP: < 6 l/kg BW; red curve: Cluster B, mid ABP: 6-13 l/kg BW; green curve: Cluster C, high ABP: ≥ 13 l/kg BW)

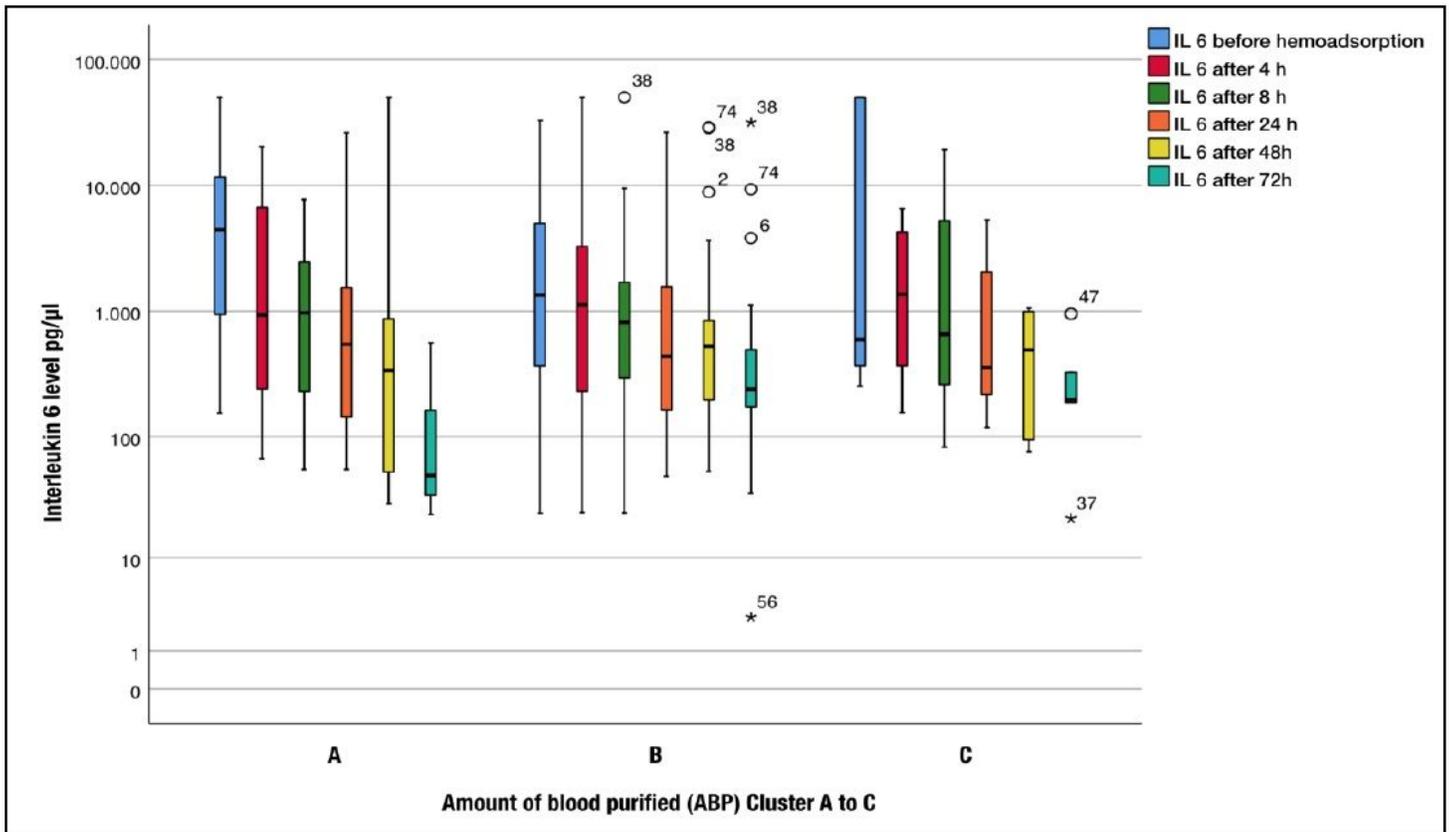


Figure 3

: Interleukin-6 course according to amount of blood purified (ABP) Box plot: Course of the Interleukin-6 serum concentration over the duration of CytoSorb® treatment (before connection; 4, 8, 24, 48 and 72 h after connection) taking into account the amount of purified blood (Cluster A, low ABP: < 6 l/kg BW, Cluster B, mid ABP: 6-13 l/kg BW, Cluster C, high ABP: ≥ 13 l/kg BW)

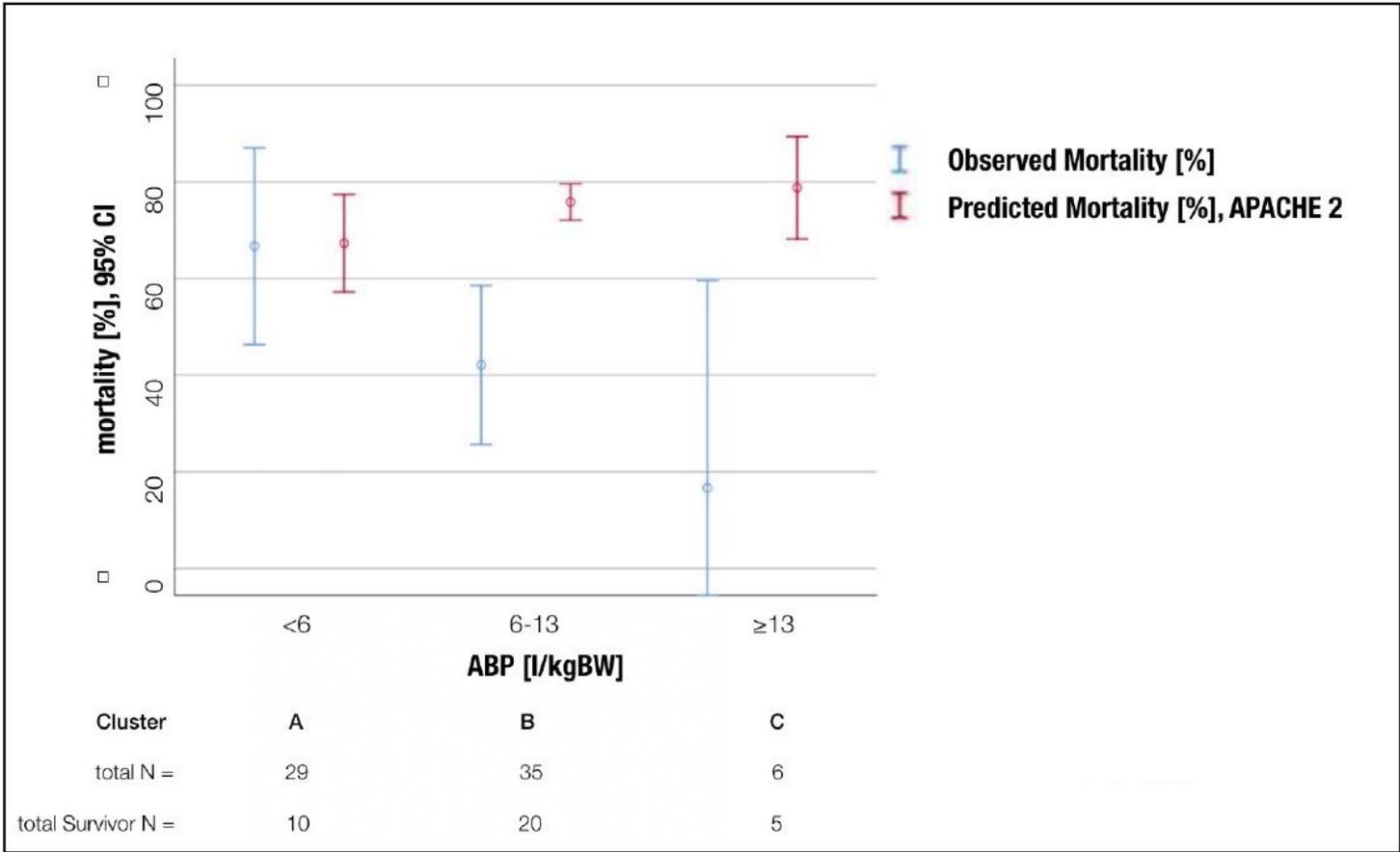


Figure 4

Predicted and observed mortality according to amount of blood purified (ABP) Predicted and observed mortality for different dosing cluster (Cluster A, low ABP: < 6 l blood/kg BW, Cluster B, mid ABP: 6-13 l blood/kg BW, Cluster C, high ABP: ≥13 l/kg BW)

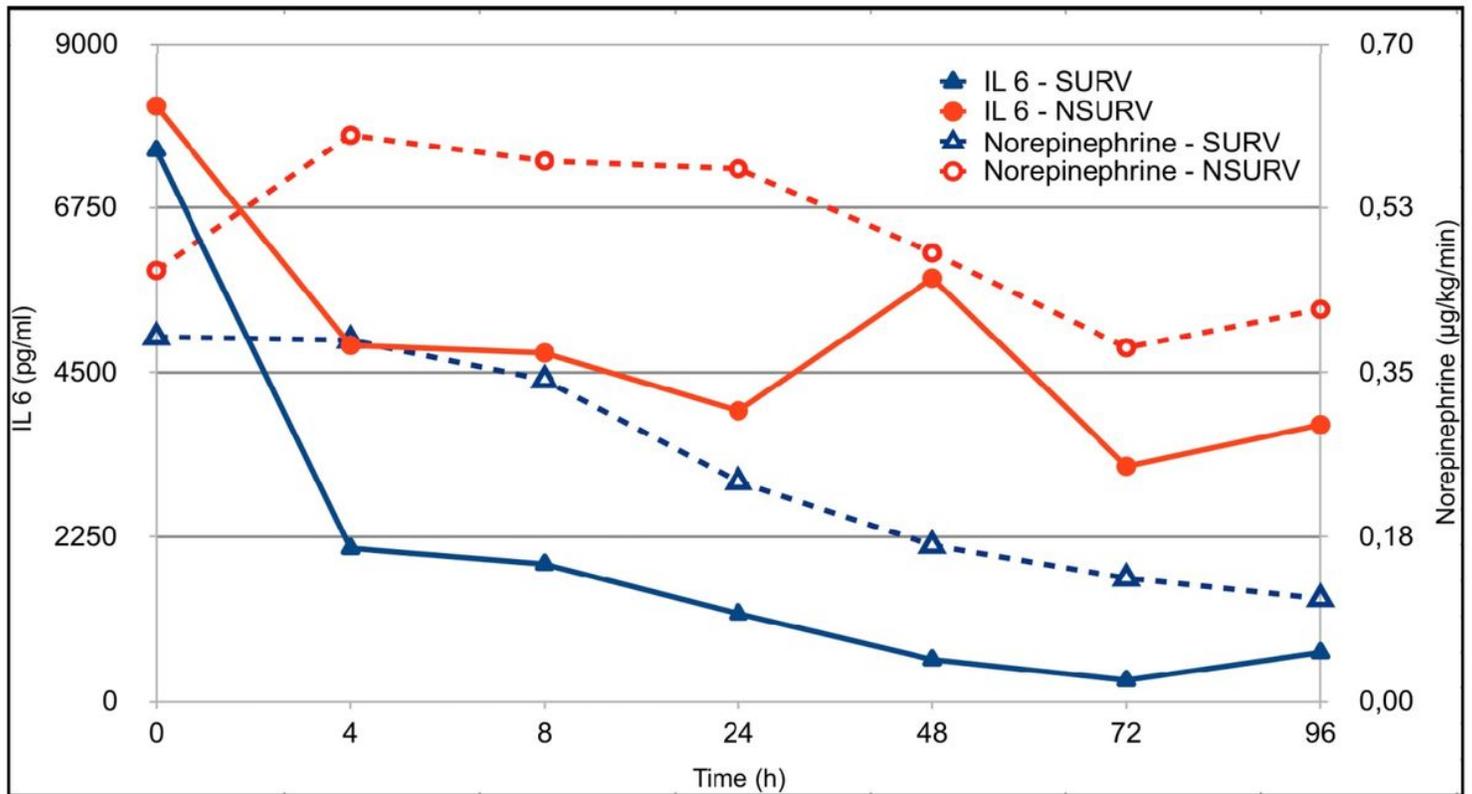


Figure 5

IL-6 and norepinephrine according to survival IL-6 concentration and norepinephrine doses for SURV and NSURV over time of treatment

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CytosorbCalculatorDH.xlsx](#)