Research Article

Improved Survival beyond 28 Days up to 1 Year after CytoSorb Treatment for Refractory Septic Shock: A Propensity-Weighted Retrospective Survival Analysis

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Abstract

Background and Aims: It is currently unknown whether CytoSorb treatment for septic shock improves long-term survival beyond 28 days from intensive care unit (ICU) admission and which factors determine outcome. ***Methods:*** This was a long-term follow-up retrospective analysis of patients with septic shock who were treated with continuous renal replacement therapy (CRRT) + CytoSorb ($n = 67$) or CRRT alone ($n = 49$). These patients were previously analyzed for 28-day mortality. The primary outcome was the time to long-term all-cause mortality. Factors associated with time to event were analyzed both weighted by stabilized inverse probability of treatment weights (sIPTW) as well as unweighted stratified by therapy received. ***Results:*** The median follow-up for the total cohort was 30 days (interquartile range [IQR]: 5–334, maximum 1,059 days) after ICU admission and 333 days (IQR: 170–583) for those who survived beyond 28 days ($n = 59$). Survival beyond 28 days was sustained up to 1 year after ICU admission for both treatment regimens: 80% (standard error [SE] 7%) vs. 87% (SE 7%), for CytoSorb vs. CRRT, respectively, $p = 0.853$. By sIPTW, CytoSorb was significantly associated with long-term outcome compared to CRRT (adjusted hazard ratio [aHR] 0.59, 95% confidence interval [CI] 0.37–0.93, $p = 0.025$). Independent factors associated with long-term outcome in CytoSorb-treated patients were baseline $\log_{10}$ lactate levels (aHR 5.1, $p = 0.002$), age in the presence of comorbidity (aHR 2.60, $p = 0.013$), and presence of abdominal sepsis (aHR 0.34, $p = 0.004$). A lactate level above 6.0 mmol/L at the start of CytoSorb therapy had a positive predictive value of 79% for mortality ($p = 0.013$). ***Conclusions:*** Survival is achieved with CytoSorb and CRRT for patients with septic shock beyond 28 days from ICU admission and may be improved for CytoSorb treatment. Lactate levels above 6.0 mmol/L at the start of CytoSorb therapy are predictive of worse outcome with high specificity and positive predictive value.

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Introduction

Worldwide, approximately 45 million patients suffer from sepsis with an estimated 11 million deaths each year [1–4]. Sepsis and septic shock are the leading causes of mortality with an amplified incidence due to increased aging of populations, comorbidities, and greater awareness of sepsis, but also because of emerging pandemics [5,

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6]. Septic shock arises from a derailed host response to infection, with consequently a condition what is known as a "cytokine storm" leading to shock [6]. Sepsis is generally treated with early resuscitation and antibiotics, which is strongly associated with an improved outcome [5]. More innovative treatment options have been evaluated, most with disappointing results. Continuous renal replacement therapy (CRRT) proved able to clear cytokines from serum and possibly improve the cytokine storm; however, a clinical benefit seems to be lacking [7–9]. Recently, we have shown that CytoSorb treatment may lead to an improved clinical outcome at 28 days from intensive care unit (ICU) admission for refractory septic shock [10]. CytoSorb has been developed and approved for use in patients with severe cytokinemia [11–13]. It is an adsorber which can be used in addition to CRRT and has been shown to be able to reduce circulating cytokines by >90% [13]. It is currently not known whether CytoSorb therapy for refractory septic shock is associated with an improved survival beyond the first month of ICU admission. Moreover, factors determining (un)favourable outcomes and the optimal timing of CytoSorb therapy are currently not known. Therefore, the aim of the current study was to investigate the long-term outcome of the septic shock patients we had previously investigated for 28-day survival who were treated with CytoSorb and/or CRRT and to study factors associated with outcome in CytoSorb-treated patients.

Patients and Methods

Patients

This is a long-term follow-up of a retrospective cohort study, in which patients were treated at the ICU for septic shock with CytoSorb and/or CRRT. Here, we further studied the cohort of patients we had previously studied for 28-day survival. The selection methods and inclusion and exclusion criteria are described elsewhere in detail [10]. In short, patients admitted to the ICU with septic shock who were treated with CytoSorb or CRRT in the period from January 1, 2014, to April 1, 2017, were eligible for inclusion in the study. These patients were treated at the discretion of the attending intensive care physician according to local protocol. Patients were excluded from the analysis in case the primary reason for therapy was not septic shock. In case of improvement of septic shock or renal function, CytoSorb or CRRT was discontinued. CytoSorb was used according to the manufacturer's protocol. It was placed in a blood-pump circuit with an optimal ultrafiltration rate of 250–400 mL/min. The CytoSorb adsorber was changed after 24 hours of use.

Definitions

Septic shock was defined as persisting hypotension requiring vasopressive medication to maintain mean arterial pressure

(MAP) ≥65 mmHg and having a serum lactate level of >2 mmol/L despite adequate volume resuscitation [6]. Shock reversal was defined as a serum lactate level of ≤2 mmol/L and discontinuation of vasopressive medication [14].

Endpoints

The primary endpoint was the time to all-cause mortality compared for CytoSorb versus CRRT alone. Also, factors associated with all-cause mortality during long-term follow-up were analyzed separately. All-cause mortality was measured from ICU admission until the last follow-up date known (irrespective of ICU, in-hospital, or out-of-hospital mortality).

Statistical Analysis

A survival analysis was employed with application of the inverse probability of treatment weights (IPTW), including a stabilizing method to avoid bias from extreme weights. Stabilized IPTW (sIPTW) is applied to overcome differences in baseline patient characteristics, to mimic a randomized controlled trial [15]. The sIPTW was previously constructed [10] and contains the following variables at the start of therapy: age, presence of any comorbidity, SOFA score, lactate level, noradrenalin level, type of sepsis, and medical or surgical treatment. Since mean arterial pressure (MAP) at the start of therapy was at imbalance between the 2 treatment groups and associated with outcome, it was additionally accounted for in the final analysis [10, 15]. Factors associated with all-cause mortality in CytoSorb-treated patients were analyzed as well without application of sIPTW. For this, factors with a p value of <0.2 in univariate Cox regression analysis were considered for multivariate analyses, where a full, forced and final model was constructed. Using the same variables from the full model, the final model was constructed using the back step and forward step likelihood ratio method, where the model with the highest χ^2 value was selected. Moreover, factors determining outcome were selected and inspected for optimal clinical use by analyzing tests' characteristics with Harrell's C-statistic and for laboratory values choosing the optimal cutoff using the highest sensitivity and specificity sum. Laboratory values and variables with a skewed normal distribution were log-transformed prior to the analysis. SAS Enterprise version 9.4 and SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) were used to perform the statistical analyses. All statistical tests were two-sided and evaluated at the 0.05 level of significance.

Results

Patient and Follow-Up Characteristics

In total, 67 patients with septic shock were treated with CytoSorb, versus 49 with CRRT. Table 1 shows the patient characteristics at the start of therapy [10]. Patients were followed for a median duration of 30 days (interquartile range [IQR]: 5–334) with a maximum of 1,059 days after ICU admission. For those patients followed beyond 28 days after ICU admission (n = 59), the median follow-up duration was 333 days (IQR: 170–583). There was no difference in median follow-up duration between the 2 treatment groups (p = 0.880). Median ICU and hospital admission were 9 and

Table 1. Patient characteristics at the start of therapy*

Characteristics	CytoSorb (n = 67)	CRRT only (n = 49)	sIPTW-adjusted p value
Demography			
Age, years, mean (SD)	61.1 (14.7)	68.7 (9.6)	0.410
Male, *n* (%)	37 (55)	30 (61)	0.008
Any comorbidity, *n* (%)	43 (64)	42 (88)	0.601
Diabetes mellitus type 2	14 (21)	20 (41)	0.778
Hypertension	23 (34)	26 (53)	0.409
Coronary heart disease	9 (13)	8 (16)	0.064
Heart failure (systolic/diastolic)	4 (6)	10 (20)	0.501
Prior chronic kidney disease	8 (12)	18 (37)	0.002
Peripheral artery disease	10 (15)	8 (16)	0.021
Cerebrovascular accident	6 (9)	3 (6)	0.369
COPD	8 (12)	10 (20)	0.002
Surgical (otherwise medical), *n* (%)	27 (40)	6 (12)	0.930
Sepsis origin, n (%)			
Abdominal sepsis	31 (46)	12 (25)	0.809
Pneumosepsis	14 (21)	21 (43)	0.914
Others	22 (33)	16 (33)	0.883
Hemodynamics, mean (SD)			
Lactate level, mmol/L	6.9 (5.6)	2.9 (3.1)	0.560
Noradrenaline, µg/kg/min	0.96 (0.73)	0.28 (0.36)	0.943
Mean arterial pressure	69 (15)	77 (18)	0.015
SOFA at start of treatment	13.8 (2.8)	12.8 (3.2)	0.164

CRRT, continuous renal replacement therapy; sIPTW, stabilized inverse probability of treatment weights.
* Table 1 characteristics have been previously published elsewhere [10].

17–22 days, respectively, for both groups ($p = 0.735$ and $p = 0.991$). The mean duration from ICU admission to the start of treatment was 2.1 (SE 0.36) versus 1.66 (SE 0.38) days ($p = 0.416$) for CRRT versus CytoSorb, respectively. In the CRRT group, CRRT was given for a mean duration of 4.96 (SE 0.63) days versus 4.97 (SE 0.55) days in the Cyto-Sorb group ($p = 0.990$). The mean treatment duration for the CytoSorb group was 2.34 (SE 0.16) days.

CytoSorb and CRRT Lead to a Durable Response beyond 28 Days of ICU Admission

For the total group, at 1 year after ICU admission, the unweighted survival rate was similar in both groups with CytoSorb-treated patients being 42% (standard error [SE] 6%) and CRRT-treated patients, 43% (SE 7%) (Fig. 1a), while CytoSorb-treated patients had a more severe shock as mentioned before. For those patients who survived beyond 28 days of ICU admission, survival for CytoSorb and CRRT at 1 year after ICU admission was comparable at 80% (SE 7%) and 87% (SE 7%), respectively ($p = 0.853$).

CytoSorb May Improve Long-Term Outcome Compared to CRRT Alone

By Kaplan-Meier analysis applying sIPTW, the 1-year survival was 37% (SE 7%) versus 26% (SE 12%) for Cyto-Sorb versus CRRT, respectively (log-rank $p = 0.21$). By Cox regression analysis adjusted for the MAP at baseline of therapy, CytoSorb treatment showed a significantly higher survival rate compared to CRRT (adjusted HR [aHR] 0.59, 95% Wald confidence interval [CI]: 0.37–0.93, $p = 0.025$; Fig. 1b). In this model, presence of chronic kidney disease (aHR 1.10, $p = 0.736$) or gender (aHR 1.02, $p = 0.940$) were not significantly associated with outcome.

Factors Associated with Long-Term Outcome in the CytoSorb Group

Factors in univariable and multivariable analyses associated with outcome in the CytoSorb group can be found in Table 2. Noradrenaline levels did not significantly interfere with lactate levels ($p = 0.496$). However, there was evidence of collinearity for noradrenaline and lactate levels. When lactate was replaced by noradrenaline, the multivariate Cox
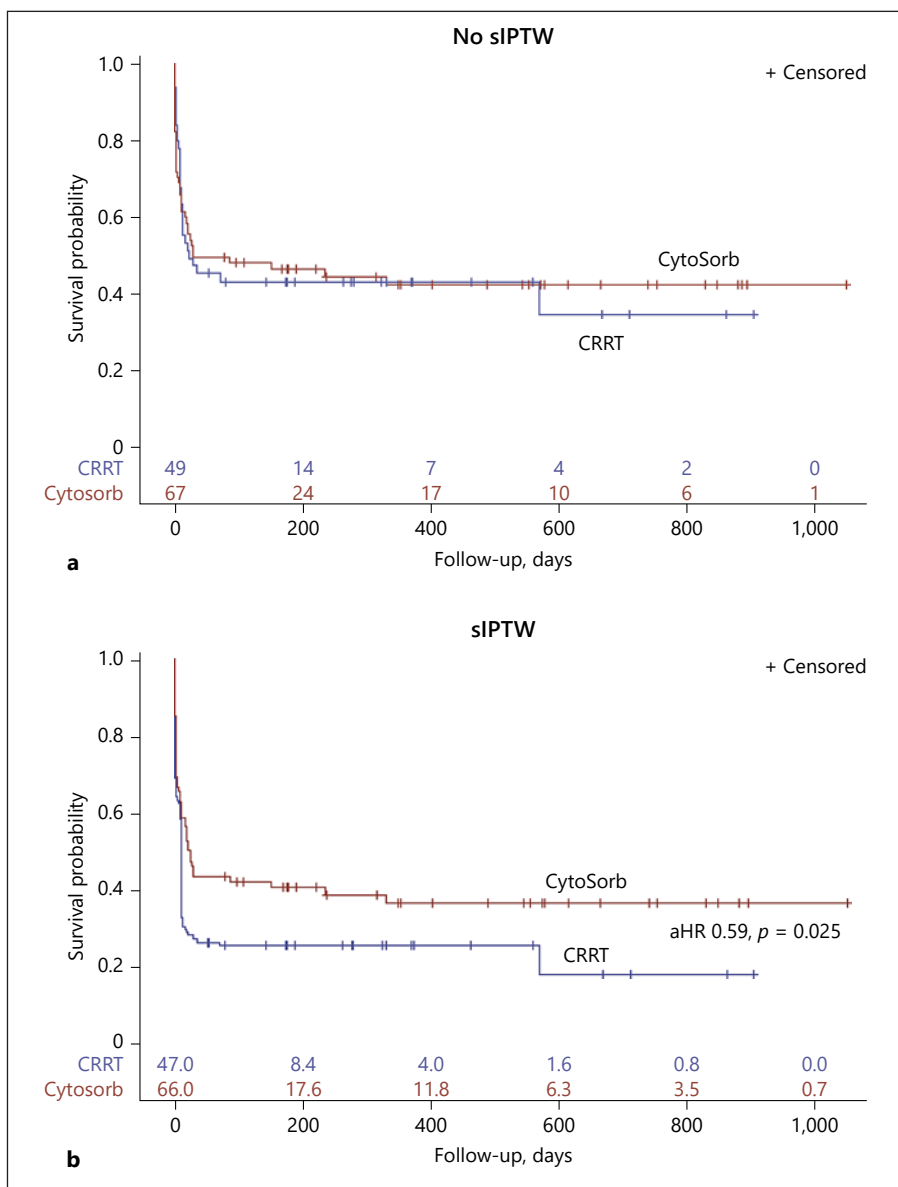
Fig. 1. Survival plots for CytoSorb versus CRRT therapy without sIPTW (**a**) and with sIPTW (**b**). CRRT, continuous renal replacement therapy; sIPTW, stabilized inverse probability of treatment weights; aHR, adjusted hazard ratio.

regression model showed a slight weaker χ^2 and noradrenaline was not significantly associated with outcome (HR 2.86, 95% CI: 0.99–8.21, $p = 0.051$). The final model (Table 2) had a Harrell C-statistic of 0.80 (SE 0.04, $p < 0.001$) for mortality prediction in the long term, but also in the short term (28-day mortality C-statistic 0.81, SE 0.04, $p < 0.001$). For a simple and practical approach, the most important factor from this model was selected for mortality prediction: it was observed that a lactate level cutoff of 6.0 mmol/L (HR 3.1, SE 0.33, $p < 0.001$) had the highest specificity (79%) and sensitivity (58%) sum and positive predictive value (79%) for long-term mortality, Harrell C-statistic 0.67 (95% CI: 0.54–0.80, $p = 0.013$). Figure 2 shows the Ka-

plan-Meier curve for the CytoSorb cohort stratified by lactate below or above 6.0 mmol/L. This same cutoff of lactate level also had the highest sensitivity (63%) and specificity (77%) for 28-day mortality where the positive predictive value was slightly lower (71%).

Discussion

In this long-term follow-up study, we have shown that long-term survival with either CytoSorb or CRRT beyond 28 days of ICU admission is achievable. In a weighted analysis, CytoSorb showed an improved long-term outcome
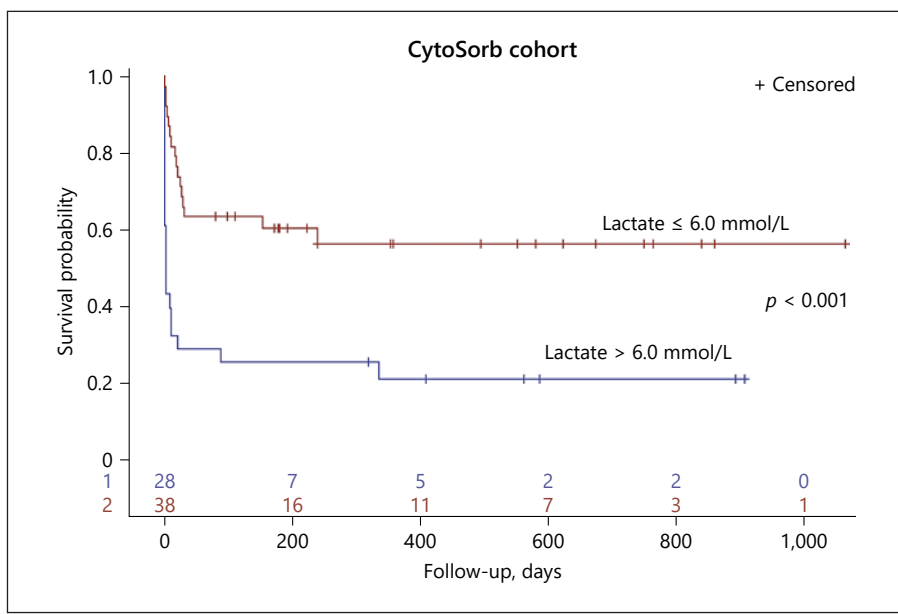
Fig. 2. Survival plot within CytoSorb-treated patients according to lactate level at the start of treatment.

Table 2. Cox regression analysis for all-cause mortality in CytoSorb-treated patients

Variables at start of therapy	Univariable model		Full multivariable model (forced)		Final multivariable model	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age per 10 years older	**1.53 (1.16–2.01)**	**0.003**	–		–	
Any comorbidity*	**2.97 (1.35–6.52)**	**0.007**	–		–	
Yes, age per 10 years older	–		**2.53 (1.12–5.72)**	**0.025**	**2.60 (1.22–5.52)**	**0.013**
No, age per 10 years older	–		1.05 (0.73–1.50)	0.808	1.04 (0.75–1.45)	0.817
Ethnicity	1.21 (0.59–2.47)	0.606	–		–	
Female gender	0.89 (0.47–1.68)	0.715	–		–	
Body mass index	0.97 (0.92–1.02)	0.213	–		–	
CRRT duration	0.94 (0.86–1.03)	0.201	–		–	
Log creatinine	0.76 (0.25–2.25)	–	–		–	
SOFA	**1.15 (1.03–1.29)**	**0.014**	1.08 (0.95–1.22)	0.275	–	
MAP	**0.99 (0.96–1.01)**	**0.197**	1.01 (0.98–1.04)	0.532	–	
Log10lactate level	**4.14 (1.58–10.86)**	**0.004**	**4.15 (1.13–15.3)**	**0.033**	**5.05 (1.77–14.4)**	**0.002**
Log10noradrenaline, yr/kg/min	**3.13 (1.28–7.65)**	**0.012**	1.46 (0.44–4.80)	0.536	–	
Noradrenaline duration	1.02 (0.97–1.08)	0.393	–		–	
Admission ICU to treatment	1.01 (0.91–1.11)	0.913	–		–	
Admission hospital to treatment	1.02 (0.96–1.09)	0.517	–		–	
Surgery	**0.57 (0.29–1.14)**	**0.113**	0.96 (0.42–2.21)	0.924	–	
Type of sepsis						
Pneumosepsis	**1.69 (0.81–3.51)**	**0.159**	0.78 (0.29–2.12)	0.623	–	
Abdominal sepsis	**0.62 (0.32–1.19)**	**0.152**	**0.41 (0.18–0.98)**	**0.044**	**0.34 (0.17–0.70)**	**0.004**

CRRT, continuous renal replacement therapy; MAP, mean arterial pressure; ICU, intensive care unit. Any comorbidity (n = 43, 64%): hypertension (n = 23, 34%), prior heart failure (n = 4, 6%), chronic kidney (any KDIGO class) disease including hemodialysis (n = 8, 12%), peripheral artery disease (n = 10, 15%), chronic obstructive lung disease (n = 8, 12%), diabetes mellitus type 2 (n = 14, 21%), coronary artery disease (n = 9, 13%), and cerebrovascular accident (n = 6, 9%). Note that these factors on their own do not show significance in these analyses. * p value = 0.029 for interaction between comorbidity and age.

compared to CRRT alone. In CytoSorb-treated patients, it was observed that age, lactate level at the start of therapy, presence of any comorbidity, and abdominal sepsis were factors associated with long-term and also short-term all-cause mortality. This is the first study to show that the benefit achieved with CytoSorb in the first month of ICU admission is enduring in the long term and that a lactate level above 6.0 mmol/L is an important determinant of outcome.

It is currently not known what the best timing for CytoSorb therapy in septic shock is. In the current study, we have shown that lower levels of lactate or noradrenaline were associated with an improved outcome. A lactate level above 6.0 mmol/L had a positive predictive value for long-term all-cause mortality of almost 80%. Indeed, this is a retrospective analysis and confounding by indication may have an impact on the current data. Nevertheless, it was observed that patients more often were treated with CytoSorb as a last-resort option when lactate and noradrenaline levels were already (too) high, as >50% of the CytoSorb-treated patients already had lactate levels above 6.0 mmol/L at the start of treatment. In line with our findings, a current report also showed that initiation of CytoSorb within 48 h of admission was associated with better outcome [16]. Given these lines of evidence, it seems reasonable to suggest that CytoSorb should be initiated earlier in the disease course rather than in case of refractory sepsis with high lactatemia. The timing should be further evaluated in future studies.

As was shown in our previous publication, before applying weights CytoSorb-treated patients were not comparable to those treated with CRRT alone at the start of therapy as they had worse hemodynamic characteristics including higher levels of lactate, need for vasopressors, lower MAP, and higher SOFA scores. Nonetheless, they still had a similar outcome to those treated with CRRT alone. Indeed patients treated with CRRT more often showed chronic kidney disease; however, this factor was not associated with long-term outcome in our analysis. When we applied IPTW adjusting for MAP, it was shown that CytoSorb-treated patients had an improved survival. Presence of chronic kidney disease, male gender, or other factors (peripheral artery disease or COPD) which were at imbalance did not show significant associations with outcome.

The current data show that, not unexpectedly, the first days of ICU admission were most important in the determination of clinical outcome. It is important to underline that the 28-day mortality rate showed to be a good surrogate for overall outcome as >80% of patients who survived up to 28 days after ICU admission also survived in the long term. There are some important limitations of the current study. Next to the retrospective nature of the study, we did not have inflammatory cytokines such as IL-6 or procalcitonin levels available. In addition, although this is currently the largest cohort study of septic shock patients treated with CytoSorb analyzed for mortality, the number of patients assessed is still relatively small and the results are partly obtained from a propensity score analysis. Moreover, we were not able to perform an analysis for fluid balances as this would entail a dynamic analysis and this falls outside the scope of the current article. The results obtained from this study should be further confirmed in randomized clinical trials.

In conclusion, we have shown that the survival achieved with both CRRT and CytoSorb for patients with septic shock leads to an improved outcome beyond 28 days of ICU admission and may be enhanced for CytoSorb treatment. Importantly, lactate levels above 6.0 mmol/L were predictive for mortality with a 79% specificity and 80% positive predictive value. Therefore, for patients with septic shock not responding to fluid therapy and with a lactate level below 6.0 mmol/L, CytoSorb therapy should be considered, especially for young patients with abdominal sepsis. Future randomized trials should take into account this lactate level since too high lactate levels are associated with poor treatment response.

Statement of Ethics

All patients, their relatives, or legal representatives gave their informed consent for the admission to the ICU and to undergo specific interventions. Patients were not recontacted for the purpose of this study. Recontacting patients for informed consent for the current retrospective chart study would introduce a serious bias because a large proportion is out of follow-up or deceased. All procedures were carried out per standard of care per protocol. This retrospective cohort study was performed in accordance with the protocol, the principles of the Declaration of Helsinki 1964 as modified by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013, with notes of clarification on paragraphs 29 and 30 added by the WMA General Assembly, and the local national laws governing the conduct of clinical research studies. This study was approved by the ethics committee of the Maasstad Hospital Rotterdam, the Netherlands (MZ0582-07-14 and L2017-030).

Conflict of Interest Statement

W.P.B. and S.D. have received speaker's fee from CytoSorb. C.I. has received a grant from CytoSorb to commence a randomized controlled trial on the effect of the adsorber on the microcirculation of critically ill patients at the Department of Intensive Care of the Erasmus Medical Center, Rotterdam.

Funding Sources

Author Contributions

W.P.B.: study design, data collection, statistical methods and analysis, writing of the manuscript, and approval of the final version. S.D. and C.I.: study design, critical review of the manuscript, and approval of the final version. W.P.B., S.D., and C.I. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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