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The Effect of CytoSorb on Inflammatory Markers in Critically Ill Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials*

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OBJECTIVES: The effectiveness of CytoSorb at removing inflammatory mediators in critically ill patients is controversial.

DATA SOURCES: Electronic databases were searched from inception to May 2023.

STUDY SELECTION: Randomized controlled trials reporting the effects of CytoSorb therapy on inflammatory parameters in critically ill patients with hyperinflammatory conditions were included.

DATA EXTRACTION: Two authors screened articles for eligibility, extracted data, and assessed the risk of bias, conflicts of interest, and certainty of evidence (CoE). The primary outcome was interleukin (IL)-6 at 1 day after initiation of the therapy. Secondary outcomes included various inflammatory markers at 1, 2, 3, and 5 days and mortality. Data were pooled if at least three trials reported the outcome of interest. We conducted meta-analyses of the data using a random-effects model.

DATA SYNTHESIS: Seventeen trials ($n = 855$) were included. Fourteen trials were judged to have notable concern about conflicts of interest. Seven trials were performed in medical ICU patients with hyperinflammatory conditions and 10 in complex cardiovascular surgery under cardiopulmonary bypass. Hemoadsorption with CytoSorb was not associated with lower IL-6 at 1 day (mean difference −5.98 [95% CI, −30.44 to 18.48] pg/mL), 2 days, 3 days, or 5 days after initiation of the treatment, as well as the concentration of procalcitionin. The levels of C-reactive protein were not lower with CytoSorb at 1, 2, and 3 days. The use of CytoSorb was associated with higher mortality at latest follow-up (relative risk = 1.22 [95% CI, 1.02–1.45]) and at 30 days. CoE ranged from low to very low.

CONCLUSIONS: The use of CytoSorb hemoadsorption in a mixed population of critically ill patients with hyperinflammatory conditions does not exhibit a consistent decrease in IL-6 and other inflammatory parameters within the first 5 days of treatment. The significant uncertainty surrounding these findings highlights the need for further investigations.

KEY WORDS: acute-phase proteins; critically illness; hemoperfusion; inflammation; sorption detoxification

Hemoadsorption is being studied as a treatment for severe inflammatory conditions, such as sepsis and cardiac surgery (1, 2). The treatment involves the extracorporeal removal of target specific molecules including endotoxins and cytokines, using a variety of devices (3). Although these treatment options are invasive and require extracorporeal pump circuits, they have the potential to improve outcomes for severely ill patients. However, randomized trials have not produced conclusive

***See also p. 1819.**

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KEY POINTS

Question: Is CytoSorb effective at removing inflammatory mediators in critically ill patients?

Findings: The present systematic review and meta-analysis of randomized trials found that the use of extracorporeal hemoadsorption CytoSorb was not associated with a consistent decrease in interleukin-6 and other inflammatory parameters up to 5 days in critically ill patients with hyperinflammatory conditions. Certainty of evidence ranged from low to very low.

Meaning: The association between CytoSorb and decrease in inflammatory markers is uncertain.

evidence to date (4). Over the previous 3 years, hemoadsorption has been particularly studied as a treatment option for COVID-19-related acute respiratory distress syndrome (ARDS).

One such device, CytoSorb (CytoSorbents, Monmouth Junction, NJ), consists of a polymer sorbent bead technology that is designed to filter out proinflammatory cytokines (5). In vitro studies indicate that CytoSorb reduces levels of inflammatory proteins during and after treatment (6, 7). Observational studies also suggest that CytoSorb may lower inflammatory parameters and improve outcomes in patients with various hyperinflammatory conditions (8–10). Nevertheless, a recent systematic review and meta-analysis of randomized controlled trials (RCTs) suggests, with low certainty of evidence (CoE), that CytoSorb may actually increase mortality rather than improve clinical outcomes (11). The same review also notes that several RCTs used different inflammatory markers, such as interleukin (IL)-6 or C-reactive protein (CRP), as primary outcomes (12–14).

Given the limited evidence, this systematic review and meta-analysis aim to provide a better understanding of the effectiveness of CytoSorb in reducing inflammatory mediator levels in critically ill patients. The research hypothesis is that the use of CytoSorb hemoadsorption will decrease inflammatory mediator levels.

MATERIAL AND METHODS

The authors of this systematic review followed a prepublished protocol (International Prospective Register of Systematic Reviews database, CRD42022350144) and adhered to the Cochrane methodology (15). The reporting followed the Preferred Reporting Items Systematic Reviews and Meta-Analysis (PRISMA) guidelines (PRISMA 2020 checklist, **Supplementary Table S1**, http://links.lww.com/CCM/H383) (16). This study received no funding and the authors declare no conflicts of interest.

Search Strategy

Two investigators (M.H. and A.P.) independently searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception to and including May 25, 2023, for appropriate articles. The search strategies are reported in **Supplementary Methods S1** (http://links.lww.com/CCM/H383). Unpublished trials were searched on Clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform. The bibliographies of the retrieved trials and the relevant reviews were also screened. All eligible studies published as full-text or abstracts only were included. No language restriction was enforced.

Study Selection

Relevant studies were identified through the examination of abstracts by two authors (M.H. and A.P.) and collected as full-text articles if potentially relevant. Eligible studies met the following PICOS criteria: 1) Population: adult critically ill patients with inflammatory conditions, 2) Intervention: extracorporeal hemoadsorption with CytoSorb, 3) Comparison intervention: standard treatment only or sham hemoadsorption, 4) Outcome: any primary, secondary, or tertiary outcome of the present review (see below), and 5) Study design: RCT. Trials with populations overlapping that of a previously included study and pediatric studies were excluded. Two authors (M.H., A.P.) independently assessed selected studies for the final analysis, with disagreements resolved by consensus.

Data Abstraction

Data extraction and entry were performed by one author (M.H.), and a second author (A.P.) verified the

data, with divergences resolved by consensus. Sources of significant clinical heterogeneity such as study design, clinical setting, inclusion and exclusion criteria, and hemoadsorption regimen were identified. Complete-case analysis was used to assess outcome data. Corresponding authors were not contacted in case of missing outcome data. Software was used to extract numerical values from images in case of a lack of raw data (WebPlotDigitizer, Ankit Rohatgi, Version: 4.5, Pacifica, CA). We transformed results reported as interquartile range in SD using the formula reported by Cochrane handbook (15). Data reported as median were converted into mean using a formula suggested for skewed outcomes that determined the less statistical heterogeneity in our study (15, 17). We excluded results with insufficient data to allow calculation of mean or SD, and reports with obvious errors.

Outcomes

The study's primary outcome was the level of IL-6 levels 1 day after initiation of the treatment. Secondary outcomes were CRP and procalcitonin (PCT) at 1, 2, 3, and 5 days and IL-6 at 2, 3, and 5 days after initiation of the treatment. Tertiary exploratory outcomes included the levels of the following mediators at 1, 2, 3, and 5 days after initiation of the treatment.: IL-1α, IL-2, IL-4, IL-1β, IL-8, IL-10, tumor necrosis factor (TNF)-α, IFN-γ, chemokine ligand (CCL)-2, and CCL-3. Post hoc secondary outcomes were mortality at 30 days or in-hospital and at the latest follow-up available.

Conflict of interest

Two authors (M.H. and A.P.) assessed potential financial and nonfinancial conflicts of interest according to a previously published methodology (11). Each study was categorized according to financial conflicts of interest into the following categories: "notable concern about conflicts of interest," "no notable concern about conflicts of interest," or "unclear concern about conflicts of interest."

Risk of Bias

One author (M.H.) evaluated the risk of bias of each included RCT according to the Cochrane Risk of Bias 2 tool, whereas another (A.P.) verified the assessment, with divergences resolved by consensus (15). The assessment was performed at the primary outcome level. The following sources of bias were evaluated for each trial: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The overall risk-of-bias judgment was categorized as: low risk of bias, some concerns, and high risk of bias.

Statistical Analysis

Mean difference (MD) and 95% CI were computed for continuous data as long as at least 3 trials reported the outcome of interest. Dichotomous data were reported as relative risk (RR) with 95% CI. Because of the expected substantial clinical heterogeneity, we used an inverse variance random-effects model for all of the analyses. A p value of 0.05 or less was considered statistically significant. Cochran's Q statistic and the I^2 statistic were used to evaluate heterogeneity (an I^2 larger than 50% and a p value of 0.10 or less indicated significant heterogeneity). A funnel plot was constructed for the primary outcome to assess reporting bias.

Some sensitivity and subgroup analyses for primary outcome were planned if at least 2 RCTs reported the outcome. Sensitivity analysis using a fixed-effects model was conducted. Subgroup analyses were performed according to setting (cardiovascular surgery vs medical ICU patients), risk of bias (low vs some concerns/high risk of bias), financial conflicts of interest (notable/unclear vs no notable concerns), and presence of an extracorporeal device also in the control group. A p value of 0.05 or less indicated statistically significant subgroup interaction. Meta-analyses and forest plots were computed using Review Manager software (RevMan [Computer program], version 5.4, The Cochrane Collaboration, 2020).

Trial sequential analysis (TSA) was conducted for the primary outcome, with the purpose of maintaining an overall 5% risk of type I error and a 20% risk of type II error (power of 80%). An MD of 30% of the control IL-6 levels was assumed as clinically plausible and significant. The resulting required information size was diversity-adjusted. Sensitivity analyses were performed using a diversity equal to 25% and an MD of 15% of the control group. The analysis was performed using the TSA software (TSA [Computer program], version

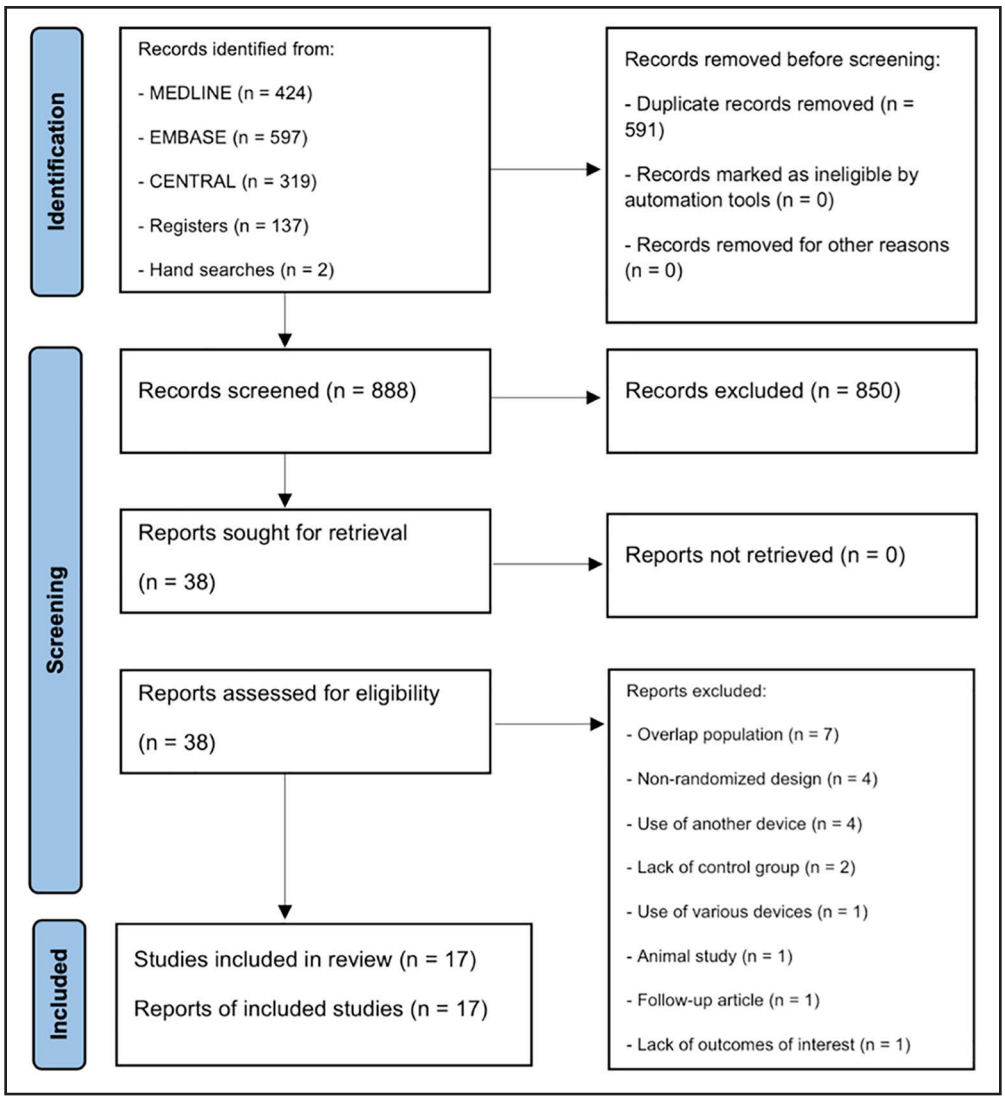

Figure 1. Flow diagram for the selection of studies. CENTRAL = Cochrane Central Register of Controlled Trials.

0.9.5.10 Beta, The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark, 2021). Protocol deviations are reported in **Supplementary Methods S2** (http://links.lww.com/CCM/H383).

Certainty of Evidence

The CoE for each outcome was assessed using the grading of recommendations assessment, development, and evaluation framework (18, 19). The CoE was categorized as very low, low, moderate, or high based on study limitations (risk of bias), imprecision, inconsistency, indirectness, publication bias, and large magnitude of effect.

RESULTS

Systematic Search

The systematic search in online databases produced 1,479 potential titles and abstracts from database and hand searches (**Fig. 1**). Thirty-eight articles were identified for review and after the exclusion of inadequate reports (**Supplementary Table S2**, http://links.lww.com/CCM/H383), we included 17 trials with a total of 855 patients (13, 14, 20–34).

Trials Characteristics

Trials' characteristics are shown in **Table 1** and **Supplementary Table S3** (http://links.lww.com/CCM/H383). Fourteen studies were single-center, whereas three were multicenter (13, 23, 34). Nine trials were performed in Germany, seven in other European countries, and one in the United States (23). The mean age ranged between 50 and 71 years old and the proportion of females ranged between 7% and 35%. Nine trials were performed in on-pump complex cardiac surgery (mean European System for Cardiac Operative Risk Evaluation II ranged between 3 and 20) and one in open on-pump thoracoabdominal aortic surgery, where the CytoSorb device was integrated into the cardiopulmonary bypass circuit.

Seven trials were performed in medical ICU patients with various hyperinflammatory conditions: two in sepsis and septic shock, two in COVID-19 ARDS, one in postcardiac arrest syndrome, one in COVID-19 needing renal replacement therapy or extracorporeal membrane oxygenation (ECMO), and one in extracorporeal cardiopulmonary resuscitation. In three studies control group patients did not receive any extracorporeal therapy (13, 20, 25).

TABLE 1.
Studies' Characteristics

Trial (Reference)	Country	Design	*n*	Population	CytoSorb Regimen	Control	Primary Outcome	Markers of Interest
Complex cardiovascular surgery								
Asch et al (30)	Germany	Single-center	20	Infective endocarditis undergoing cardiac surgery	CytoSorb was incorporated into the CPB circuit. Postoperatively, integrated into a hemodialysis circuit. Treatment duration: CPB time + 24 hr (cartridge change every 8 hr, 4 hr in total)	Conventional therapy (CPB without CytoSorb)	Selected cytokine and infection parameters levels	IL-6, CRP, PCT, TNFα
Bernardi et al (29)	Austria	Single-center	37	Elective CABG, valve surgery, or combined procedure with an expected CPB duration of more than 2 hr	CytoSorb was incorporated into the CPB circuit	Conventional therapy (CPB without CytoSorb)	Selected cytokine levels	IL-6, IL-10, CRP, PCT
Diab et al (34)	Germany	Multicenter	202	Cardiac surgery for infective endocarditis	CytoSorb was incorporated into the CPB circuit	Conventional therapy (CPB without CytoSorb)	Change in Sequential Organ Failure Assessment score	IL-1β, IL-6, IL-10, CRP, TNFα
Doukas et al (26)	Germany	Single-center	27	Open thoracoabdominal aortic surgery under CPB	CytoSorb was incorporated into the CPB circuit	Conventional therapy (CPB without CytoSorb)	Dynamics of inflammation markers, catecholamine requirements, and clinical parameters	CRP
Garau et al (31)	Germany	Single-center	40	Elective CABG, aortic valve replacement, or a combined procedure with an expected CPB time of more than 2 hr	CytoSorb was incorporated into the CPB circuit	Conventional therapy (CPB without CytoSorb)	Selected cytokine levels	IL-6, IL-8, PCT, TNFa
Gleason et al (23)	United States	Multicenter	46	Elective complex cardiac surgery with expected CPB duration equal or longer than 3 hr	CytoSorb was incorporated into the CPB circuit	Conventional therapy (CPB without CytoSorb)	Plasma-free hemoglobin levels	IL-6

(*Continued*)

TABLE 1. (*Continued*)
Studies' Characteristics

Trial (Reference)	Country	Design	*n*	Population	CytoSorb Regimen	Control	Primary Outcome	Markers of Interest
Holmén et al (22)	Sweden	Single-center	19	Cardiac surgery for infective endocarditis	CytoSorb was incorporated into the CPB circuit	Conventional therapy (CPB without CytoSorb)	Amount of norepinephrine	CRP
Poli et al (14)	Switzerland	Single-center	30	Elective cardiac surgery with expected long CPB duration and deemed at high risk of postoperative complications	CytoSorb was incorporated into the CPB circuit	Conventional therapy (CPB without CytoSorb)	Selected cytokine levels	IL-1β, IL-6, IL-10, TNFα
Taleska Stupica et al (27)	Slovenia	Singl-center	40	Elective complex cardiac surgery with an expected CPB time of more than 1.5 hr	CytoSorb was incorporated into the CPB circuit	Conventional therapy (CPB without CytoSorb)	Selected cytokine and infection parameters levels	IL-1β, IL-6, IL-8, IL-10, CRP, PCT, TNFα
Wagner et al (28)	Czech Republic	Single-center	28	Complex cardiac surgery (Ross operation 93%, David operation 7%)	CytoSorb was incorporated into the CPB circuit	Conventional therapy (CPB without CytoSorb)	Selected myocardial, monocyte and vascular miRNAs plasma levels	CRP, PCT
Medical ICU patients								
Hawchar et al (10)	Hungary	Single-center	20	Intubated patients with suspected septic shock of medical origin	CytoSorb was incorporated into a blood pump circuit using a renal replacement device. Treatment duration: 24 hr. Heparin anticoagulation. Hemodialysis catheter inserted into a central vein	Conventional therapy	Unclear	CRP, PCT
Jarczak et al (24)	Germany	Single-center		COVID-19 ARDS needs intubation with associated refractory shock requiring norepinephrine, elevated IL-6, and the need for RRT or ECMO	CytoSorb was incorporated either into either the RRT or the ECMO system. Filter replaced every 18–24 hr. Treatment duration: 5 d. Regional anticoagulation with citrate–calcium (92%) or heparin (8%)	Conventional therapy (RRT or ECMO without CytoSorb)	Sustained hemodynamic improvement (norepinephrine ≤ 0.05 µg/kg/min ≥ 24 hr)	IL-6, PCT

(*Continued*)

TABLE 1. (*Continued*)
Studies' Characteristics

Trial (Reference)	Country	Design	*n*	Population	CytoSorb Regimen	Control	Primary Outcome	Markers of Interest
Monard et al (25)	Switzerland	Single-center	21	Post-cardiac arrest syndrome (need for a vasoconstrictor, elevated serum lactate) and time to return of spontaneous circulation higher than 25 min	CytoSorb was integreted into a multiFiltrate monitor (Fresenius Medical Care, Bad Homburg, Germany) in hemoperfusion mode. Treatment duration: 12–24 hr. Regional anticoagulation with heparin–protamine. Dialysis catheter inserted in a femoral vein	Conventional therapy	Procedure's feasibility, safety, and efficacy	IL-6, IL-8, IL-10
Schädler et al (13)	Germany	Multicenter	97	Severe sepsis or septic shock in the setting of acute lung injury or ARDS	CytoSorb was either used alone in hemoperfusion mode or incorporated into the continuous venovenous hemofiltration/CVVHD circuit if RRT was indicated. Treatment duration: 6 hr/d, up to 7 consecutive days. Systemic heparin or regional citrate anticoagulation	Conventional therapy	IL-6 levels	IL-6, IL-8, IL-10, TNFα
Stockmann et al (22)	Germany	Single-center	49	COVID-19-associated vasoplegic shock requiring norepinephrine, elevated CRP, and indication for kidney replacement therapy	CytoSorb was incorporated into the CVVHD circuit. Treatment duration: 3–7 d according to the discretion of the treating physicians h (cartridge change every 24 hr)	Conventional therapy (CVVHD without CytoSorb)	Time until resolution of vasoplegic shock	IL-6, CRP, PCT, TNFα
Supady (12)	Germany	Single-center	34	Severe ARDS related to severe acute respiratory syndrome coronavirus 2 infections receiving venovenous ECMO	CytoSorb incorporated into the ECMO circuit. Treatment duration: 72 hr (cartridge change every 24 hr)	Conventional therapy (ECMO without CytoSorb)	IL-6 levels	IL-6
Supady et al (21)	Germany	Single-center	41	Extracorporeal cardiopulmonary resuscitation	CytoSorb incorporated into the ECMO circuit. Treatment duration: 72 hr (cartridge change every 24 hr)	Conventional therapy (ECMO without CytoSorb)	IL-6 levels	IL-6, CRP, PCT, TNFα

ARDS = acute respiratory distress syndrome, CABG = coronary artery bypass graft, CPB = cardiopulmonary bypass, CRP = C-reactive protein, CVVHD = continuous venovenous hemodialysis, ECMO = extracorporeal membrane oxygenation, IL = interleukin, PCT = procalcitonin, RRT = renal replacement therapy, TNFα = tumor necrosis factor α.

Risk of bias was assessed for the primary outcome. Five trials raised some concerns in at least one domain and 12 trials were judged at high risk of bias in at least one domain (**Supplementary Fig. S1**, http://links.lww.com/CCM/H383). Patient dropout was common, as were concerns regarding the selection of the reported result.

CoE results are reported after each estimate and summarized in **Supplementary Table S4** (http://links.lww.com/CCM/H383).

Conflicts of interest

Reported information on the author financial conflicts of interest and funding sources are reported in **Supplementary Table S5** (http://links.lww.com/CCM/H383). Fourteen trials were judged as raising notable concerns about conflicts of interest, with two trials raising no concerns (27, 28) and one having an unclear status (30).

Nine trials were financially supported by CytoSorbents Corporation. This varied from an unrestricted grant to partial support, including providing only the cartridges for example. The role of the funding body in the study was clearly reported in two trials.

Twelve trials had at least one author judged to have a financial conflicts of interest. In these studies, 28 of 163 authors (17.18%) had financial conflicts of interest and in most cases contributed to design, conduct, analysis, and reporting of the trial. In one trial, an author was reported to be a full-time employee of CytoSorbents Corporation (26). The clinicaltrials.gov registration (NCT02566525) of another study reported an employee from CytoSorbents Corporation as the study director; however, this information was not included in the final published article (23).

Nine trials had at least one author with a nonfinancial conflicts of interest. Sixteen authors (12 unique authors) had multiple publications and 11 authors (9 unique authors) were judged to be experts in the field.

Interleukin-6

The use of CytoSorb was not associated with a significant decrease in the primary outcome, IL-6 at 1 day after treatment (12 trials, $n = 441$, MD = −5.98 [95% CI, −30.44 to 18.48] pg/mL, CoE low) (**Fig. 2**). No significant subgroup interaction was found in trials enrolling complex cardiovascular surgery patients (six trials, $n = 212$, MD = −6.79 [95% CI, −31.70 to 18.11] pg/mL) versus trials enrolling medical ICU cases (six trials, $n = 229$, MD = 7.30 [95% CI, −153.59 to 168.19] pg/mL). Sensitivity and subgroup analyses were consistent with the main results and the funnel plot was symmetrical (**Supplementary Table S6** and **Figs. S2** and **S3**, http://links.lww.com/CCM/H383). TSA for the primary outcome found that the overall evidence is conclusive and no further trials are required (**Supplementary Figs. S4** and **S5**, http://links.lww.com/CCM/H383). Exploratory analyses are presented in **Supplementary Results S1** (http://links.lww.com/CCM/H383).

No significant decrease in IL-6 was found at 2 days (eight trials, $n = 267$, MD = 7 −0.30 [95% CI, −23.34 to 22.75] pg/mL, CoE low), 3 days (seven trials, $n = 215$, MD = 5.91 [95% CI, −20.68 to 32.50] pg/mL, CoE low), and 5 days (four trials, $n = 168$, MD = −5.22 [95% CI to −10.75, 0.31] pg/mL, CoE very low).

C-Reactive Protein

The concentration of CRP was not lower in patients receiving CytoSorb at 1 day (six trials, $n = 192$, MD = −0.27 [95% CI, −1.52 to 0.98] mg/dL, CoE low), 2 days (six trials, $n = 159$, MD = −0.88 [95% CI, −2.54 to 0.78] mg/dL, CoE low), and 3 days (three trials, $n = 95$, MD = −2.42 [95% CI, −5.32 to 0.48] mg/dL, CoE very low) (**Fig. 3**).

Procalcitonin

CytoSorb hemoadsorption was associated with no significant decrease in PCT at 1 day (eight trials, $n = 256$, MD = −0.07 [95% CI, −0.32 to 0.19] pg/mL, CoE very low), 2 days (six trials, $n = 164$, MD = −0.02 [95% CI, −0.25 to 0.21] pg/mL, CoE very low), 3 days (three trials, $n = 70$, MD = 0.41 [95% CI, −0.82 to 1.65] pg/mL, CoE very low), and 5 days (three trials, $n = 96$, MD = 0.01 [95% CI, −0.07 to 0.08] pg/mL, CoE very low) (**Fig. 4**).

Other Inflammatory Markers

Hemoadsorption with CytoSorb was not associated with lower IL-1β (three trials, $n = 120$, MD = −0.06 [−0.47 to 0.35] pg/mL, CoE very low), IL-8 (three trials, $n = 100$, MD = −2.68 [−8.50 to 3.14] pg/mL, CoE very low), IL-10 (four trials, $n = 140$, MD = 4.36 [95% CI, −1.19 to 9.91] pg/mL, CoE very low), and TNF-α

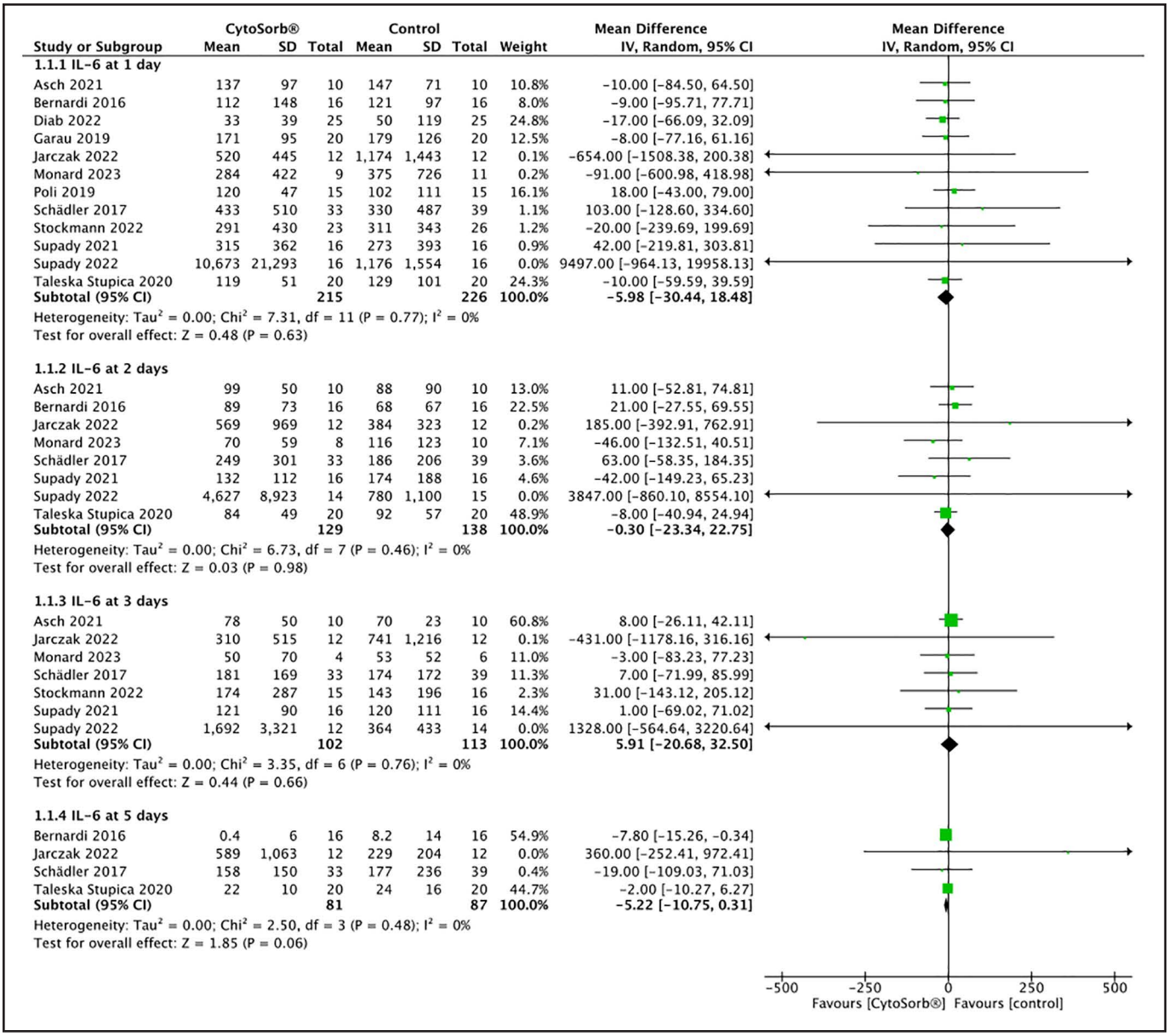

Figure 2. Interleukin-6 (IL-6). Forest plot of the mean difference in IL-6 levels at different time-points with CytoSorb hemoadsorption or conventional therapy.

(four trials, *n* = 130, MD = 0.31 [−1.85 to 2.48] pg/mL, CoE very low) at 24 hours (**Supplementary Fig. S6**, http://links.lww.com/CCM/H383).

Mortality

The use of hemoadsorption with CytoSorb device was associated with higher mortality at the latest follow-up compared with the control group (15 trials, *n* = 796, 127 of 391 [31.66%] patients in the CytoSorb group versus 106 of 405 [24.94%] patients in the control group, RR = 1.22 [95% CI, 1.02–1.45], CoE very low). The association was found also at 30-days (13 trials, *n* = 748; RR = 1.30 [95% CI, 1.04–1.63], CoE very low) (**Fig. 5**).

DISCUSSION

Key Findings

The aim of this meta-analysis was to study the relationship between the use of extracorporeal hemoadsorption CytoSorb and inflammatory markers in critically ill patients with hyperinflammatory conditions. The results indicated that there was no significant decrease in IL-6 levels up to 5 days after treatment. CRP and PCT were equally not affected, as well as other inflammatory

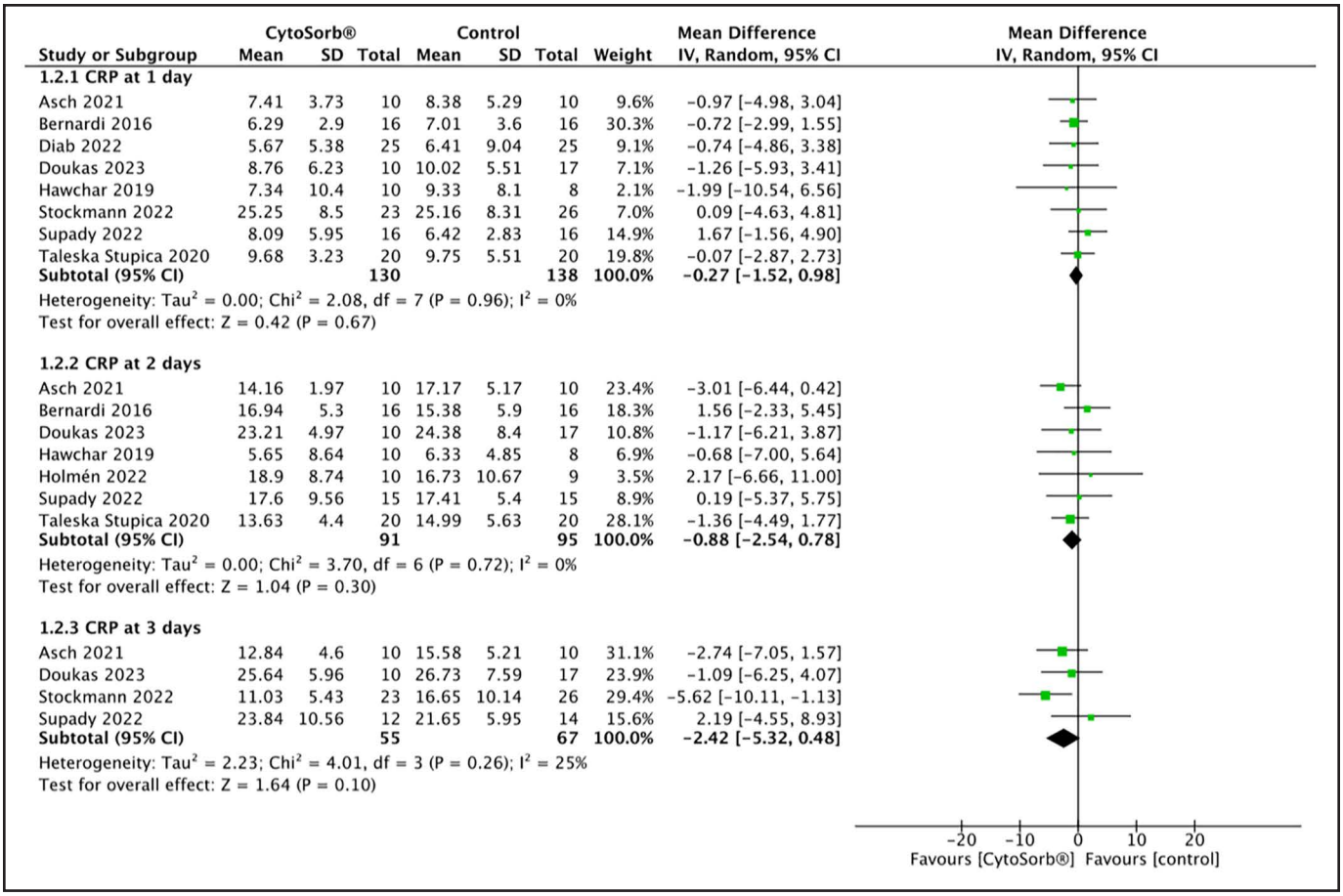

Figure 3. C-reactive protein (CRP) levels. Forest plot of the mean difference in CRP levels at different time-points with CytoSorb hemoadsorption or conventional therapy.

markers at 24 hours after treatment. CoE ranged from low to very low suggesting significant uncertainty of the findings, even if results were consistent in showing no impact of CytoSorb on inflammatory markers.

Relationship to Previous Studies

The study's findings align with previous RCTs, thus demonstrating that there is no consistent significant effect of CytoSorb treatment on IL-6 levels at various time points (13, 14, 21, 23, 24, 27, 29–34). IL-6 is released in response to infection and stimulates inflammatory pathways as part of the acute-phase response. This factor has been suggested to be an important marker of sepsis prognosis (35, 36). IL-6 levels rise significantly with the severity of postcardiac arrest syndrome and are associated with increased mortality (37). In COVID-19 patients, increased levels of IL-6 have been associated with severe disease and poor outcomes (38). Moreover, elevated levels of IL-6 are predictors of prolonged mechanical ventilation and a longer stay in the ICU after cardiac surgery (39). Administration of IL-6 antagonists was associated with lower mortality in patients hospitalized for COVID-19 (40). In sepsis; however, a recently published systematic review of RCTs investigating targeted therapies against the principal actors in the inflammatory pathway has demonstrated that up until now no single study was able to demonstrate the clinical relevance of such treatments (3).

The evidence on inflammatory markers should be interpreted in view of the effect of CytoSorb treatment on major outcomes. A recent publication shared data from the international CytoSorb Registry, which included observational information from over 1,400 patients with medical conditions like sepsis, cardiac surgery, ARDS on ECMO, liver failure, acute pancreatitis, or trauma (10). The primary objective of this registry was to compare the mortality predicted by the Acute Physiology and Chronic Health Evaluation II Score with the actual in-hospital mortality. Results showed no significant difference in mortality, which

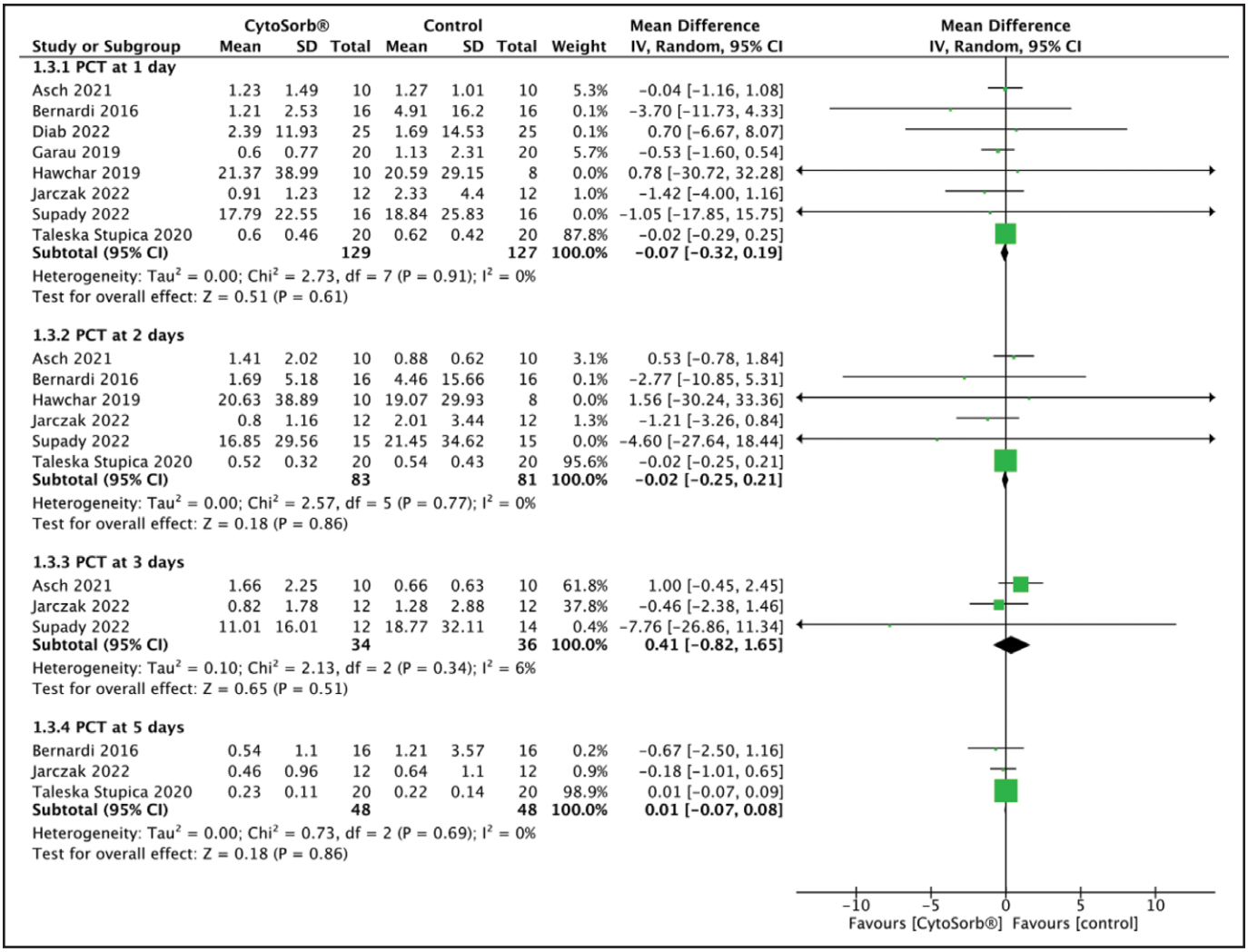

Figure 4. Procalcitonin (PCT). Forest plot of the mean difference in PCT levels at different time-points with CytoSorb hemoadsorption or conventional therapy.

was 50.1% with the use of CytoSorb. However, improvements were observed in cardiovascular and pulmonary Sequential Organ Failure Assessment Scores, along with reduced levels of PCT, CRP, and IL-6. Despite these findings, the study has limitations: observational design, lack of a control group, and risk of selection bias (10). Our present updated study aligns with our recent systematic review that evaluated mortality and adverse events in the same patient population, showing an increased mortality rate (11). Due to substantial uncertainty in the findings, firm conclusions cannot be drawn, highlighting the necessity for high-quality randomized trials to clarify the relationship between CytoSorb and mortality and more generally focusing on patient-centered outcomes. It is paramount to consider the importance of each clinical outcome when making decisions regarding the benefits and drawbacks of an intervention (i.e., improvement in mortality or organ dysfunction vs improvement in inflammatory markers), but this aspect falls outside the scope of the present study.

Significance of Study Findings

The present study found that CytoSorb does not significantly decrease levels of inflammatory mediators in a relatively large population of critically ill patients with hyperinflammatory conditions. The CoE was low to very low, but the data and the direction of the affect are important for some markers (IL-6, CRP, PCT) and need, while further evidence is needed for others, such as IL-1β, IL-8, TNF-α, and other unreported markers. Although it might be initially assumed that some

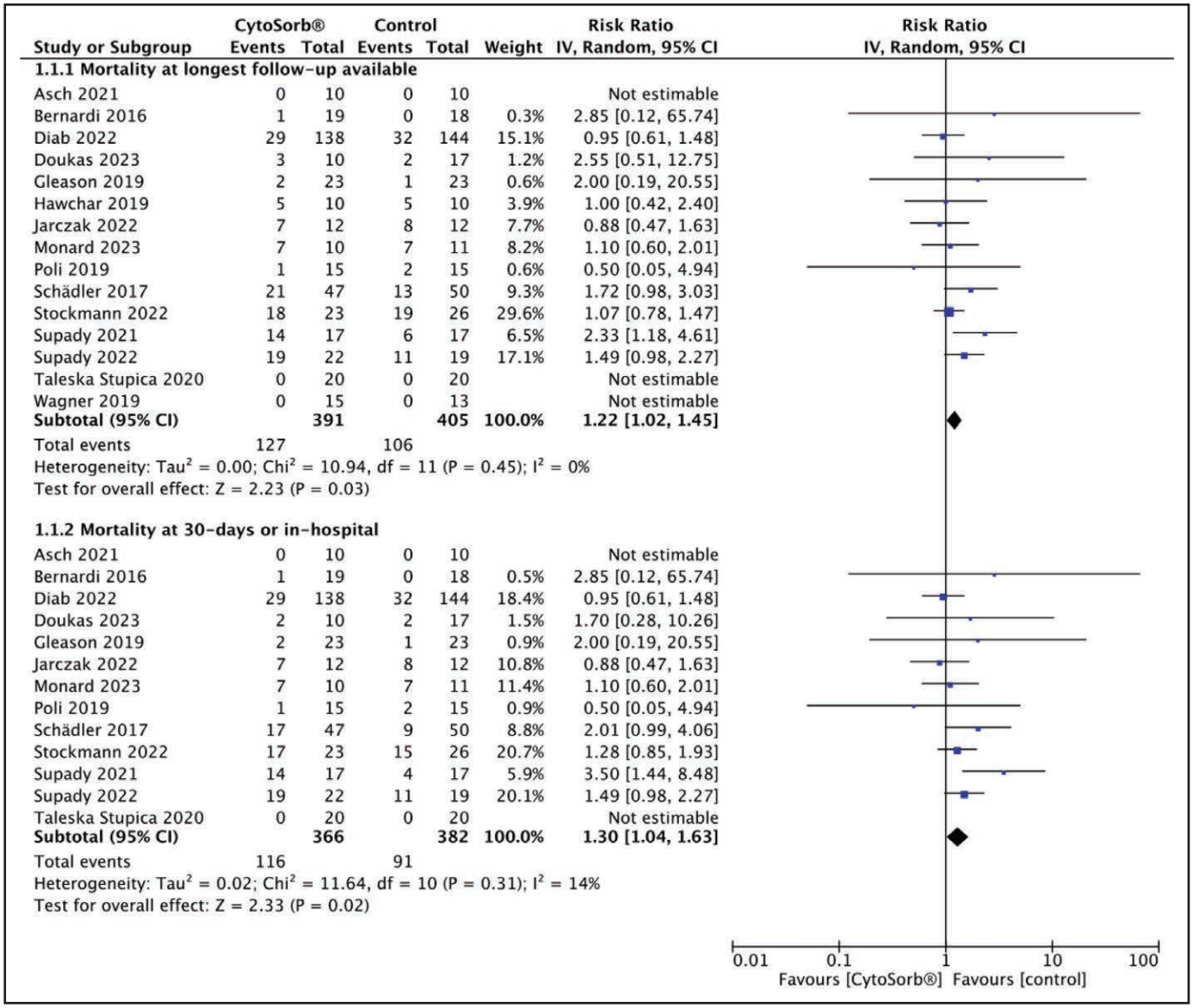

Figure 5. Mortality. Forest plot of the relative risk of mortality at 30 days/in-hospital and at longest follow-up available with CytoSorb hemoadsorption and control therapy.

inflammatory mediator levels decrease during the first hours of treatment (34), there is no evidence of lower levels in the following days. One possible explanation is that extracorporeal devices themselves trigger systemic inflammation and the net risk-benefit ratio is zero. This hypothesis is hard to explore, since only three small RCTs did not use an extracorporeal circuit in the control group. However, several studies have shown increased levels of inflammatory parameters such as IL-6 during treatment with ECMO and cardiopulmonary bypass, as summarized in a review on the pathophysiology of this response (41). Our findings do not support the use of CytoSorb therapy to decrease inflammatory mediators in critically ill patients.

Altering the levels of other molecules may have clinical relevance in some specific conditions. Like other hemoadsorption modalities (42, 43), CytoSorb appears to alter drug levels. Several antibiotics, antivirals, and antimycotics have been shown to be decreased in patients undergoing CytoSorb hemoadsorption (44–48). Similarly, some antiplatelets are also removed by CytoSorb and ongoing studies are investigating its potential use in emergency cardiac surgery (49). The impact on drugs is such that a recent review of the literature suggests that there may be a role of hemoadsorption with CytoSorb in severe intoxications (50).

The presence of financial support and conflicts of interest among authors was common, to the extent

that only two studies clearly reported the absence of industry funding or financial conflicts of interest. The development of medical devices necessitates collaboration between physicians and industry, which can give rise to conflicts of interest. This concern is well recognized in the field of extracorporeal therapy (51), but its association with study results remains unclear. Although the impact of nonfinancial conflicts of interest is uninvestigated, several reports examined financial conflicts of interest. Two Cochrane systematic reviews found that industry-sponsored studies or conflicts of interest leads to more favorable conclusions (52, 53). However, a large meta-epidemiological study of RCTs in critical care medicine found no evidence that industry-funded RCTs produce more favorable results or conclusions (54).

Strengths and Limitations of the Study

The strengths of this study include following a prepublished protocol, using the Cochrane methodology, and including a TSA and CoE assessment. In addition, a comprehensive literature search was performed. However, the study has some limitations, particularly concerning the quality and characteristics of the included RCTs. Most of the RCTs included were single-center studies, and there were some concerns regarding the risk of bias. Some studies included less than 20 patients per arm and had overdispersed data, so a non-Gaussian distribution could only be hypothesized in the absence of individual patient data. Dropouts of patients in relation to markers outcome was often underreported and unclear. Heterogeneity could arise from the different time points and techniques used to measure markers. An analysis based on changes from baseline is often more efficient and powerful than comparing postintervention values, but the lack of individual patient data or of aggregate change-from-baseline data did not allow further exploration. Consequently, the study is limited in its analysis of the absolute reduction of inflammatory markers from baseline.

Several RCTs reported multiple inflammatory markers at various time points and to ensure adequate data representation, we decided to pool data only if at least three trials reported the outcome of interest. Additionally, although all RCTs included patients suffering from hyperinflammatory syndromes, various settings such as high-risk cardiovascular surgery and medical ICU patients were represented. Stratification did not suggest any subgroup effect on the primary outcome, but a possible effect cannot be ruled out. Open questions still exist regarding whether hemoadsorption should be used in a prophylactic manner in hyperinflammatory conditions or tailored to individual patients, particularly in the subgroup of patients with very high inflammatory burden. Various exploratory outcomes are presented, and no adjustment was made to account for multiple hypothesis testing, which increases the risk of false-positive findings.

Conclusions

Hemoadsorption with CytoSorb does not consistently result in a decrease in IL-6 and various other inflammatory markers within the first 5 days after the initiation of treatment in a mixed population of critically ill patients with hyperinflammatory conditions. Mortality rates were increased with CytoSorb treatment. The certainty of the available evidence was graded low to very low, emphasizing the need for high-quality randomized trials to elucidate the impact of CytoSorb on inflammation and major outcomes.

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All authors involved in conceptualization; accessibility to data; interpretation of data; and article revision, editing, and approval. Drs. Heymann and Putzu were involved in literature search, hits screened and reviewed, data curation, and article drafting. Dr. Putzu was involved in analysis of data. Drs. Schorer and Putzu were involved in supervision.

The authors have disclosed that they do not have any potential conflicts of interest.

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Template data collection forms, data extracted from included studies, data used for all analyses, analytic code, any other materials used in the review: available from the corresponding authors on reasonable request.

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