Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): a single centre, open-label, randomised, controlled trial

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Summary

Background We sought to clarify the benefit of cytokine adsorption in patients with COVID-19 supported with venovenous extracorporeal membrane oxygenation (ECMO).

Methods We did a single-centre, open-label, randomised, controlled trial to investigate cytokine adsorption in adult patients with severe COVID-19 pneumonia requiring ECMO. Patients with COVID-19 selected for ECMO at the Freiburg University Medical Center (Freiburg, Germany) were randomly assigned (1:1) to receive cytokine adsorption using the CytoSorb device or not. Randomisation was computer-generated, allocation was concealed by opaque, sequentially numbered sealed envelopes. The CytoSorb device was incorporated into the ECMO circuit before connection to the patient circuit, replaced every 24 h, and removed after 72 h. The primary endpoint was serum interleukin-6 (IL-6) concentration 72 h after initiation of ECMO analysed by intention to treat. Secondary endpoints included 30-day survival. The trial is registered with ClinicalTrials.gov (NCT04324528) and the German Clinical Trials Register (DRKS00021300) and is closed.

Findings From March 29, 2020, to Dec 29, 2020, of 34 patients assessed for eligibility, 17 (50%) were treated with cytokine adsorption and 17 (50%) without. Median IL-6 decreased from 357·0 pg/mL to 98·6 pg/mL in patients randomly assigned to cytokine adsorption and from 289·0 pg/mL to 112·0 pg/mL in the control group after 72 h. One patient in each group died before 72 h. Adjusted mean log IL-6 concentrations after 72 h were 0·30 higher in the cytokine adsorption group (95% CI −0·70 to 1·30, p=0·54). Survival after 30 days was three (18%) of 17 with cytokine adsorption and 13 (76%) of 17 without cytokine adsorption (p=0·0016).

Interpretation Early initiation of cytokine adsorption in patients with severe COVID-19 and venovenous ECMO did not reduce serum IL-6 and had a negative effect on survival. Cytokine adsorption should not be used during the first days of ECMO support in COVID-19.

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Introduction

COVID-19 can lead to severe respiratory tract infections and acute respiratory distress syndrome (ARDS). About 17% of patients with COVID-19 treated in hospital require invasive mechanical ventilation; venovenous extracorporeal membrane oxygenation support (ECMO) is applied in 1%.[1,2] Survival of patients with COVID-19 supported with venovenous ECMO was reported to be approximately 60%.[3,4]

Observations during the first months of the pandemic suggested that severe COVID-19 was associated with an uncontrolled cytokine response.[5–8] Furthermore, increased serum concentrations of interleukin-6 (IL-6) were associated with poor outcome in severe COVID-19 ARDS.[9,10] Previous observations in diseases other than COVID-19 indicated that extracorporeal adsorption of IL-6 and other vasoactive substances using a CytoSorb adsorber (CytoSorbents Corporation, Monmouth Junction, NJ, USA) might lead to a reduction of circulating cytokine concentrations with a positive effect on survival.[11–13] The CytoSorb adsorber consists of porous polymer beads that adsorb hydrophobic molecules within the 5–55 kDa range, including cytokines, myoglobin, or bilirubin and various therapeutic drugs.[14] The adsorber can be integrated in an extracorporeal blood pump circuit, such as ECMO or continuous renal replacement therapy.[15,16] In several countries, the CytoSorb adsorber is an approved treatment option for extracorporeal adsorption of circulating cytokines. In 2020, the US Food and Drug Administration issued an emergency use authorisation for the CytoSorb adsorber for the treatment of COVID-19.[17]

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Research in context

Evidence before this study

Observations during the first months of the pandemic suggested that severe COVID-19 was associated with an uncontrolled cytokine response. Increased interleukin-6 (IL-6) concentrations have been related to higher mortality. Cytokine adsorption using the CytoSorb device has been reported to reduce circulating concentrations of cytokines in the patient blood, including IL-6, in COVID-19 and in other diseases.

Added value of this study

The results from this randomised, controlled trial question the efficiency of cytokine adsorption to reduce concentrations of circulating IL-6 in the patient blood. Early initiation of cytokine adsorption in patients with severe COVID-19 and venovenous ECMO did not reduce serum IL-6 compared with the control group without cytokine adsorption. Most importantly, we observed a negative effect of cytokine adsorption on survival at 30 days.

Implications of all the available evidence

To date, a purported benefit of cytokine adsorption with the CytoSorb adsorber has been described primarily in case reports, case series, and retrospective analyses, which are highly susceptible to selection bias. The results of this trial highlight the utility of randomised, controlled trials. Owing to the small case number in our trial, these results should be viewed with caution and further assessed, but we urge against uncritical use of cytokine adsorption outside of clinical trials and suggest that cytokine adsorption should not be used during the first days of ECMO support in COVID-19.

Use of cytokine adsorption in severe COVID-19 ARDS yielded promising results in terms of IL-6 reduction similar to treatment observations in ARDS not related to COVID-19.[18,19] The aim of the CYCOV trial was to analyse the efficiency of extracorporeal cytokine adsorption in patients with severe COVID-19 and venovenous ECMO in reducing concentrations of circulating IL-6.

Methods

Study design and participants

The CYCOV trial was a single-centre, randomised, controlled, parallel group, open-label, superiority trial. All adult patients (≥18 years of age) admitted to the participating intensive care units (ICUs) of the Freiburg University Medical Center with reverse transcriptase (rt) PCR-confirmed SARS-CoV-2 infection who were selected to receive venovenous ECMO were eligible. Exclusion criteria were a known patient will against study participation or study interventions and a decision made before inclusion to stop further treatment of the patient within the next 24 h.

See Online for appendix

The trial conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional ethics committee of the University of Freiburg (EK 168/20). Patients eligible for study participation were usually unable to give informed consent. Therefore, a legal representative was informed and had to give consent to study participation.

Randomisation and masking

EG prepared a computer-generated randomisation list with 1:1 treatment allocation, stratified for age (<65, ≥65 years).[10,20] The block sizes (8 and 2) were not disclosed to the investigators. Allocation was concealed by opaque, sequentially numbered sealed envelopes. Details are described in the study protocol (appendix). Neither participants nor care providers or the study team were masked to treatment.

Procedures

In the intervention group, a CytoSorb adsorber was incorporated into the ECMO system and replaced every 24 h for a total treatment duration of 72 h. Routinely, the adsorber was installed in the ECMO as part of the system setup before connecting it to the patient circuit, but at the latest within 4 h after initiation of the ECMO (for example, in case of initiation of ECMO in another hospital by the mobile ECMO retrieval team).[16] The adsorber could be replaced or removed without stopping the ECMO system. Envisioned flow rates through the adsorber were between 100 mL/min and 700 mL/min. Early replacement was indicated when blood flow through the adsorber decreased below 100 mL/min, for example, owing to blood clotting within the device. The control group had no CytoSorb adsorber incorporated into the ECMO system.

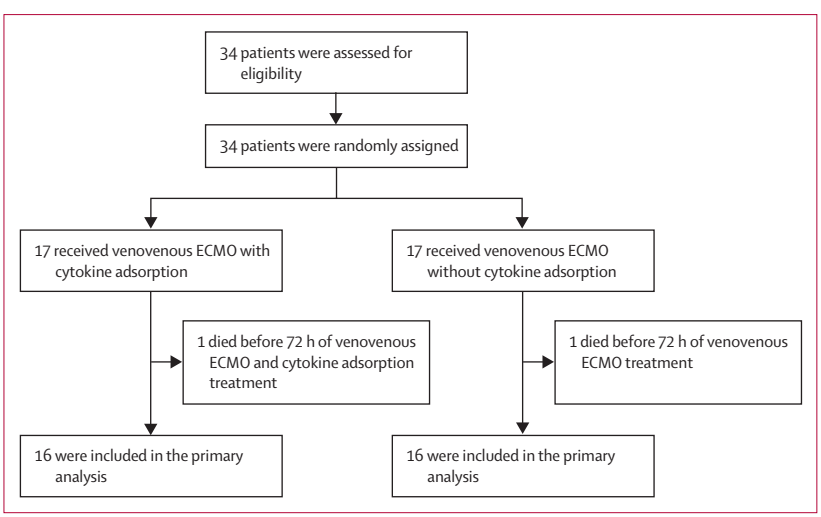

Figure 1: **Trial profile**
ECMO=extracorporeal membrane oxygenation.

Blood samples were taken via an arterial catheter (radial or brachial artery) before initiation and 1 h, 24 h, 48 h, and 72 h after initiation of ECMO and analysed for clinical laboratory parameters, such as blood count, electrolytes, kidney, liver function and coagulation parameters, and IL-6. The reference time (t_0) was the start of cytokine adsorption in the intervention group and the start of ECMO in the control group. Patient follow-up was 30 days after initiation of ECMO.

Outcomes

The primary endpoint was serum IL-6 after 72 h of ECMO with or without cytokine adsorption. Secondary endpoints were ICU survival and 30-day survival, days on ECMO, days on mechanical ventilation, serum lactate, Willebrand factor, D-dimers, vasopressor dosage, amount of fluid substitution, fluid balance after 72 h, and Sequential Organ Failure Assessment score after 24, 48, and 72 h.[21]

Statistical analysis

Sample size estimation was based on the results of the international CytoSorb registry, according to which serum IL-6 in patients with severe infections could be reduced by more than 80% by adsorption in the CytoSorb adsorber.[12] A two-group Satterthwaite t test with two-sided 5% significance level and a sample size of 15 per group yielded 80% power to detect a difference, assuming that the mean logarithmic IL-6 values at 72 h would differ by 1·33 SDs of the intervention group, with a 1·4 ratio of SDs in the control versus intervention group (nQuery version 8.5.1.0).

In the primary analysis, the effect of cytokine adsorption compared with control on IL-6 after 72 h (logarithmic scale) was estimated and tested by linear regression. Log-transformation was prespecified in the trial protocol to obtain a more symmetric distribution. The model included treatment, age group (<65, ≥65 years) and baseline IL-6 values as independent variables, coefficients were estimated with robust standard errors. The test for a difference between treatment groups was based on the corresponding two-sided 95% CI. Secondary endpoints were evaluated by the Mann-Whitney test, Fisher's exact test, the Kaplan-Meier method, Cox regression, and competing risk regression, as appropriate. Owing to unexpected differences in mortality, the primary endpoint and survival outcomes were subjected to extensive exploratory post-hoc analyses, including linear and logistic regression analyses, and single and multiple Cox regression analyses. Statistical tests were two-sided with a 5% significance level and with nominal p values reported for description outside the primary analysis. No interim analysis was planned or done. Statistical analyses were done using R version 3.6.0 (R Foundation for Statistical Computing) and GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). The trial is registered with ClinicalTrials.gov (NCT04324528) and the German Clinical Trials Register (DRKS00021300).

	Cytokine adsorption group (n=17)	Control group (n=17)
Age, years	62·0 (54·0–71·5)	59·0 (43·5–66·5)
Sex		
Female	5 (29%)	4 (24%)
Male	12 (71%)	13 (76%)
Body-mass index, kg/m²	29·41 (24·69–33·20)	29·68 (26·41–36·48)
Laboratory values		
Interleukin-6, pg/mL	357·0 (177·4–1186·0)	289·0 (84·7–787·0)
C-reactive protein, mg/L	254·9 (148·0–374·4)	169·3 (128·6–342·2)
Procalcitonin, ng/mL	0·73 (0·50–1·84)	1·34 (0·37–5·98)
Ferritin, ng/mL	2172·0 (883·5–3706·0)*	1489·0 (938·5–2543·0)
Leukocytes, ×10³/µL	10·03 (8·22–19·92)	14·43 (8·40–16·48)
Neutrophils, ×10³/µL	9·12 (6·59–14·84)*	11·86 (7·18–13·92)
Lymphocytes, ×10³/µL	0·67 (0·44–1·15)*	0·59 (0·39–0·88)
Monocytes, ×10³/µL	0·51 (0·20–0·98)*	0·46 (0·22–0·90)
Willebrand factor antigen, %	603·5 (458·5–642·5)†	399·0 (362·0–542·5)*
D-dimers, mg/L FEU	9·1 (4·5–21·0)*	4·7 (3·4–13·5)
Scores		
SOFA	9·0 (8·0–10·0)	9·0 (7·0–10·5)
RESP	1·0 (0·5–2·0)	1·0 (0–3·5)
PRESERVE	4·0 (3·0–5·0)	4·0 (2·0–6·0)
Comorbidities		
Hypertension	9 (53%)	7 (41%)
Diabetes	5 (29%)	3 (18%)
Coronary heart disease	3 (18%)	1 (6%)
Chronic lung disease	1 (6%)	3 (18%)
Liver cirrhosis	0	0
Haematological malignancy	1 (6%)	1 (6%)
Solid malignant tumour	0	0
Immunosuppressive therapy	1 (6%)	0
Active smoker	2 (12%)	1 (6%)
Any comorbidity	12 (71%)	10 (59%)
Pre-ECMO treatment		
Time from hospital admission to ECMO, days	6·0 (4·0–13·5)	8·0 (4·5–14·0)
Time from intensive care unit admission to ECMO, days	5·0 (2·5–11·5)	6·0 (4·0–14·0)
Duration of mechanical ventilation (including non-invasive and invasive ventilation) before ECMO, days	6·0 (3·5–12·0)	5·0 (2·0–14·0)
Duration of invasive ventilation before ECMO, days	5·0 (0·5–11·0)	4·0 (1·0–8·5)
Prone positioning	11 (65%)‡	12 (71%)
Renal replacement therapy	1 (6%)	0
Hydroxychloroquine	4 (24%)	5 (29%)
Lopinavir–ritonavir	3 (18%)	1 (6%)
Tocilizumab	2 (12%)	0
Remdesivir	5 (29%)	1 (6%)
Methylprednisolone	9 (53%)	10 (60%)§
Norepinephrine support, µg/kg per min	0·15 (0·04–0·22)	0·03 (0·00–0·36)

(Table 1 continues on next page)

	Cytokine adsorption group (n=17)	Control group (n=17)
(Continued from previous page)		
Ventilation parameters		
FiO_2, %	100·0 (95·0–100·0)	100·0 (85·0–100·0)
Positive end-expiratory pressure, mbar	15·0 (14·0–17·0)	15·0 (12·5–18·0)
Peak pressure, mbar	34·0 (29·5–36·0)	32·0 (31·0–35·0)
Dynamic driving pressure, mbar	18·0 (15·0–20·0)	20·0 (14·0–20·0)
Tidal volume, mL	460·0 (354·0–576·5)	417·0 (334·3–479·5)*
Tidal volume, mL/kg	5·30 (3·90–6·25)	3·85 (2·95–4·83)*
Breathing rate, 1/min	25·0 (21·5–31·0)	25·0 (21·0–29·0)
Last blood-gas values pre-ECMO		
pH	7·34 (7·17–7·39)	7·28 (7·16–7·41)
PaO_2, mm Hg	57·3 (48·5–70·7)	75·1 (52·1–88·4)
$PaCO_2$, mm Hg	65·5 (42·5–80·1)	61·9 (55·1–73·8)
PaO_2/FiO_2, mm Hg	62·7 (48·5–72·7)	84·2 (59·9–95·6)
Plasma bicarbonate, mmol/L	25·3 (20·9–29·5)¶	24·6 (20·6–31·8)*
Arterial lactate, mmol/L	1·8 (1·2–2·3)	1·4 (0·9–1·8)

Data are median (IQR) or n (%), unless otherwise specified. FEU=fibrinogen equivalent unit. SOFA=Sequential organ failure assessment. RESP=Respiratory extracorporeal membrane oxygenation survival prediction. PRESERVE=Predicting death for severe ARDS on venovenous ECMO. ECMO=extracorporeal membrane oxygenation. *n=16. †n=14. ‡Two additional patients were treated in a RotoRest bed (ArjoHuntleigh, Malmö, Sweden) allowing kinetic therapy and lateral patient positioning up to 62°. §One additional patient received high-dose prednisolone. ¶n=15.

Table 1: **Baseline characteristics**

Role of the funding source

There was no funding source for this study.

Results

34 patients were screened and enrolled in the trial, from March 29, 2020, to Dec 29, 2020 (figure 1). The trial ended on Jan 27, 2021. During the trial period, all patients who tested positive for SARS-CoV-2 and received venovenous ECMO on the participating ICUs were screened for study participation and finally included in the trial.

17 (50%) of 34 patients were randomly assigned to receive venovenous ECMO in combination with cytokine adsorption for 72 h and 17 (50%) of 34 to standard venovenous ECMO support without cytokine adsorption. In 10 (59%) of 17 patients in the cytokine adsorption group, at least one adsorber needed to be replaced earlier than 24 h, because of a decrease of the blood flow rate through the adsorber to below 100 mL/min due to clotting in the device. In 17 patients allocated to cytokine adsorption, 62 adsorbers were used for a cumulative treatment duration of 1194 h, therefore, the mean operating time of each adsorber in this trial was 19 h (SD 7).

The median age of the study cohort was 61 years (IQR 53–68), nine (26%) of 34 patients were female. Baseline characteristics, including demographics, past medical history, and preceding or concomitant drug treatment specifically for COVID-19 were balanced between the two groups (table 1).

Of all 34 patients enrolled, the primary outcome measure (IL-6 after 72 h) was obtained in 32 patients. Two patients died before 72 h: one patient in the control group after 55 h on ECMO and one patient in the cytokine adsorption group after 67 h on ECMO and cytokine adsorption. In one surviving patient, cytokine adsorption was terminated after 47 h owing to successful weaning of ECMO therapy. Nevertheless, IL-6 was assessed after 72 h in this patient.

No significant differences for IL-6 were detected between the two groups after 72 h of ECMO. Median IL-6 concentrations decreased from 357·0 pg/mL (IQR 177·4–1186·0) to 98·6 pg/mL (71·0–192·8) in the cytokine adsorption group and from 289·0 pg/mL (84·7–787·0) to 112·0 pg/mL (48·7–198·5) in the control group (table 2, figure 2). In the analysis adjusting for baseline IL-6 concentrations and age group, the mean log IL-6 concentration after 72 h was estimated to be 0·30 higher in the cytokine adsorption group than in the control group (95% CI –0·70 to 1·30, p=0·54; appendix p 5).

SARS-CoV-2 test results in two patients turned out to be uncertain. In one patient (in the control group) a positive rtPCR-test for SARS-CoV-2 could not be confirmed in subsequent tests, however, this patient was diagnosed positive for SARS-CoV-2-IgG antibodies. In another patient (cytokine adsorption group), supposedly tested positive in another hospital before transfer to our hospital, it turned out that there had been a mix-up of test results from another patient. Although we assumed a positive test result at the time of study inclusion, this patient had never tested positive, either in repeated rtPCR-tests or in SARS-CoV-2-IgG antibody tests, and he was suffering from ARDS of unknown cause. Both patients were included in the intention-to-treat cohort.

The linear regression for the primary endpoint was repeated excluding eight patients with various particularities (two patients with uncertain test results, two patients who received IL-6 receptor antagonist tocilizumab before cytokine adsorption, and five patients treated on the cardiosurgical ICU; appendix p 5). Furthermore, instead of excluding the two deaths before 72 h as in the primary analysis, for these cases, IL-6 concentrations at 48 h were used in another linear regression analysis (appendix p 5). Finally, we included the ICU (cardiosurgical *vs* medical–anesthesiological) as an additional factor in the primary regression model (appendix p 6). Interpretation of the results from these analyses remained unchanged compared with the primary analysis.

Secondary outcomes are listed in table 2. 13 (76%) of 17 patients survived until day 30 after initiation of ECMO in the control group, three (18%) of 17 patients survived until day 30 in the cytokine adsorption group (p=0·0016, table 2). Kaplan-Meier survival curves separated beyond day 10 (figure 3).

Additional exploratory post-hoc analyses were done owing to these unexpected findings. In a logistic regression analysis adjusted for age group, only the investigational treatment had an effect on 30-day survival. This was also true when this analysis was done excluding the patients treated on the cardiosurgical ICU (appendix p 7).

	Cytokine adsorption group (n=17)	Control group (n=17)	p value
Primary endpoint			
Serum interleukin-6 after 72 h	98·6 (71·0 to 192·8)*	112·0 (48·7 to 198·5)*	0·54†
Other endpoints			
30-day survival	3 (18%)	13 (76%)	0·0016‡
Discharged from intensive care unit until day 30	0	3 (18%)	0·23‡
Serum lactate after 72 h, mmol/L	1·35 (1·05–1·58)*	1·25 (0·93–1·85)*	0·80§
Willebrand factor antigen after 72 h, %	426·0 (396·0–501·0)¶	311·5 (287·8 to 405·8)*	0·021§
D-dimers after 72 h, mg/L FEU	8·77 (3·90 to 35·19)*	15·23 (5·79 to 34·23)*	0·48§
SOFA score after 24 h	7·0 (6·0 to 9·5)	8·0 (6·0 to 10·0)	0·59§
SOFA score after 48 h	8·0 (6·5 to 9·5)	8·0 (6·0 to 10·5)	0·95§
SOFA score after 72 h	7·5 (6·0 to 10·8)*	8·5 (6·0 to 10·0)*	0·81§
Norepinephrine support at 72 h, µg/kg per min‖	0·07 (0·03 to 0·13)*	0·00 (0·00 to 0·10)*	0·04§
Cumulative fluid balance for 72 h after initiation of ECMO, mL	2665·0 (663·5 to 5152·0)	2145·0 (−92·5 to 3002·0)	0·29§
Fluid substitution during the first 72 h after implementation of venovenous ECMO, mL	11 773 (8959 to 13 468)	8344 (7304 to 10 866)	0·0068§
Intensive care unit and ECMO treatment			
Prone positioning after initiation of ECMO	15 (88%)	15 (88%)	0·99‡
Retrieval on ECMO by mobile ECMO retrieval team from another hospital	3 (18%)	4 (24%)	0·99‡
Cytokine adsorption treatment			
Cytokine adsorption	17 (100%)	..	..
Delay between initiation of ECMO and start of cytokine adsorption, h	0·00 (0·00 to 0·75)**	..	..
Duration of cytokine adsorption, h	72·00 (68·66 to 72·34)	..	..
Number of cytokine adsorbers used, per patient	3·0 (3·0 to 4·0)	..	..
Causes of death			
Respiratory failure	3 (18%)	0	0·23‡
Respiratory failure due to pulmonary haemorrhage	3 (18%)	0	0·23‡
Septic shock	5 (29%)	2 (12%)	0·40‡
Multiorgan failure	1 (6%)	0	0·99‡
Intracranial haemorrhage	2 (12%)	2 (12%)	0·99‡

Data are median (IQR) or n (%), unless otherwise specified. Missing values—2 (6%) of 34 patients died before reaching the 72-h primary endpoint. For these patients, no endpoint data besides 30-day survival, SOFA scores at 24 and 48 h and cumulative fluid balance were available. For competing risk analysis including secondary endpoint days on ECMO see appendix (p 4). FEU=fibrinogen equivalent unit. SOFA=Sequential organ failure assessment. ECMO=extracorporeal membrane oxygenation. *n=16. †Linear regression (see appendix p 5). ‡Fisher's exact test. §Mann-Whitney test. ¶n=15. ‖One patient in the cytokine adsorption group received dobutamine (3·7 µg/kg per min) in addition to norepinephrine (0·22 µg/kg per min) before initiation of ECMO. Dobutamine was ended immediately after initiation of venovenous ECMO. One patient in the control group received adrenaline (0·02 µg/kg per min) in addition to norepinephrine (0·52 µg/kg per min) before initiation of ECMO. Adrenaline was ended immediately after initiation of venovenous ECMO. Three patients received argipressin (all of them in the cytokine adsorption group) before initiation of ECMO, in two patients in addition to norepinephrine, in one patient as the only vasopressor. In one of these patients argipressin could be ended after 48·5 h, the others received it longer than 72 h. **in 10 (59%) of 17 patients, cytokine adsorption was started immediately after initiation of venovenous ECMO.

Table 2: **Endpoints and treatment characteristics**

Multiple regression analyses including various baseline characteristics in addition to age group did not show any statistically significant factor other than treatment, with estimated odds of 30-day survival at least 14 times higher in the control group compared with the cytokine adsorption group (appendix pp 7–9). In further multiple regression analyses with mediation variables (change from baseline to value at 72 h), the effect of treatment on survival remained statistically significant in all models. Change of neutrophils from baseline to 72 h was the only mediation variable with a statistically significant effect on survival, however its change did not depend on the investigational treatment (appendix pp 3, 9–11).

Analogously, in single and multiple Cox regression analyses of survival time after ECMO implantation, only cytokine adsorption treatment showed a statistically significant, harmful effect on survival. The hazard ratio was estimated as 6·46 (95% CI 1·64–25·42, p=0·0075; figure 3; appendix p 11).

Discussion

In this randomised, controlled pilot trial, cytokine adsorption during the first 72 h after initiation of

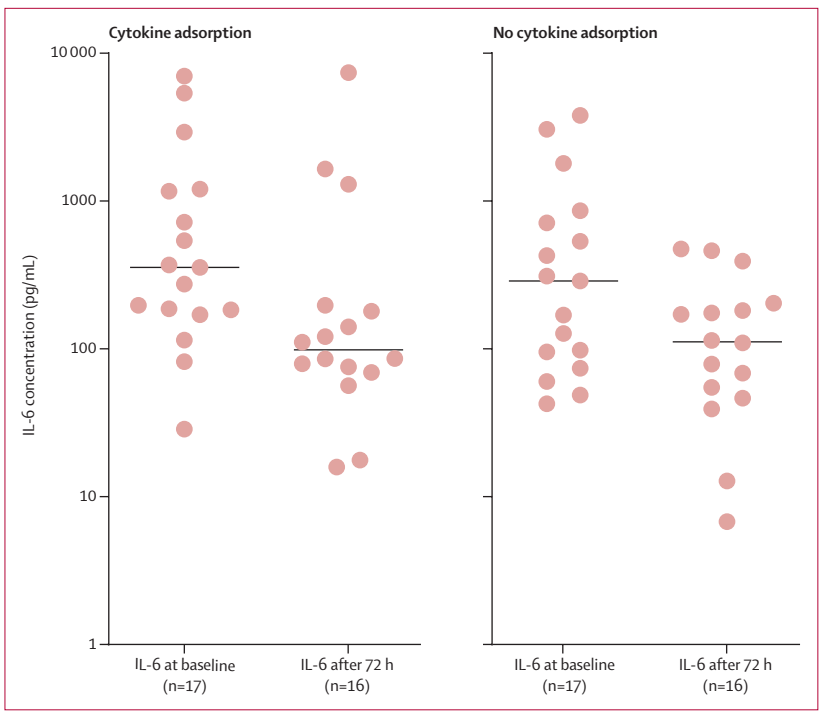

Figure 2: **IL-6 concentrations at baseline and after 72 h of venovenous ECMO with or without cytokine adsorption**

IL-6 values in the cytokine adsorption group and control group before and 72 h after initiation of venovenous ECMO are displayed on the logarithmic scale. Medians are shown as horizontal lines. No significant differences were detected between the two groups after 72 h of ECMO (p=0·54). IL-6=interleukin-6.

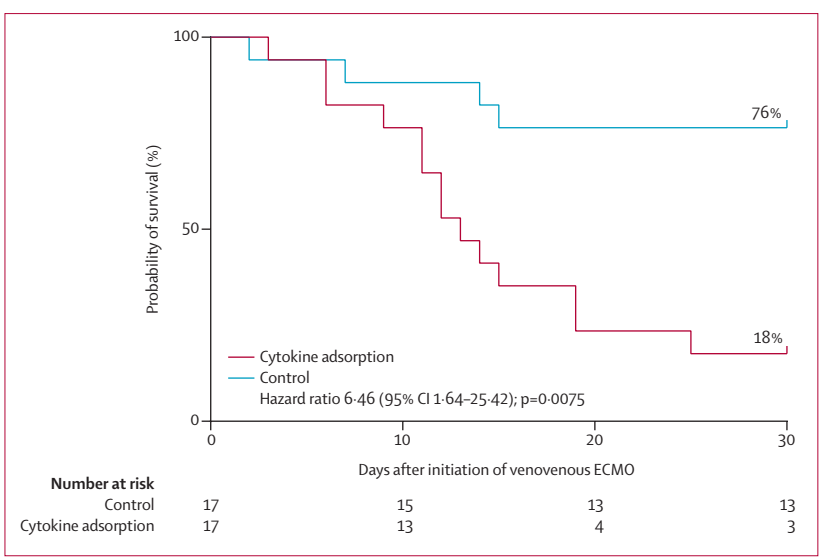

Figure 3: **Kaplan–Meier curves for survival in the cytokine adsorption group and control group**

Survival in the group receiving cytokine adsorption during the first 72 h of venovenous ECMO support was lower. ECMO=extracorporeal membrane oxygenation.

venovenous ECMO in severe COVID-19 did not result in reduced interleukin-6 concentrations after 72 h, compared with the control group. Notably, survival in the cytokine adsorption group was considerably lower than in the control group (18% *vs* 76%). These findings were in contrast with our hypothesis of a treatment benefit for patients in the cytokine adsorption group.

Data from the international CytoSorb registry suggest that serum IL-6 concentrations can be reduced from a median of 5000 pg/mL down to 289 pg/mL after 24 h of cytokine adsorption in patients with severe infections.[12] Use of cytokine adsorption in patients with severe COVID-19 ARDS supported with venovenous ECMO suggested successful reduction of IL-6 in this cohort, too, and encouraged further investigation.[18,19]

Our study, however, did not detect a meaningful effect of cytokine adsorption on IL-6 concentrations in patients with COVID-19 requiring ECMO support. Critical evaluation of available evidence might help understand this finding. Contrary to observations from the CytoSorb registry, from case reports and small case series, in a prospective observational study of nine patients, cytokine adsorption did not lead to a significant reduction of IL-6 concentrations in septic patients, and in two small prospective randomised, controlled trials on cytokine adsorption, no significant effects on patient IL-6 concentrations were observed.[22–24] In 2021, similar observations have been described for patients with COVID-19 treated with ECMO.[25]

Beneficial effects of cytokine adsorption have primarily been described in numerous single-case reports, case series, and small retrospective registry analyses. In these reports, haemodynamic stabilisation and clinical improvement under cytokine adsorption in patients with and without venovenous ECMO have been reported.[16,26–28] However, these reports are probably subject to selection bias, and the observed effects might at least partially be due to concomitant standard treatment rather than cytokine adsorption.

We observed lower survival in the patient cohort treated with cytokine adsorption. Although our trial was not designed to assess mortality, we consider this a major finding. This finding is in line with a 2020 study, describing a lower 30-day survival in patients treated with cytokine adsorption after cardiac arrest compared with a matched control group without cytokine adsorption (17% *vs* 35%).[29]

In our trial, most patients in the cytokine adsorption group died between day 10 and day 20 after initiation of ECMO and cytokine adsorption, that is, the excess in mortality compared with the control group occurred after the end of the 72-h period of cytokine adsorption. The 76% survival rate on day 30 in the control group was in line with previous findings in large cohorts of patients with COVID-19 treated with venovenous ECMO.[3,4] The data collected during this trial do not allow further analysis and understanding of the reasons and pathophysiological basis explaining the increased mortality in patients treated with cytokine adsorption. Since cytokine adsorption using the CytoSorb device is non-specific, it might have affected concentrations of protective factors as well, but these are yet to be identified. Potential activation of the coagulation

system by the CytoSorb device might be a factor that is particularly relevant in light of the previously described coagulopathy in severe COVID-19.[30,31] However, our data provides no evidence for bleeding or thromboembolism causing excess mortality in the CytoSorb group. Extensive post-hoc analyses failed to identify any random imbalances between the treatment groups or short-term treatment effects explaining inferior survival in the intervention group.

Severe COVID-19 was associated with increased concentrations of IL-6, according to previous studies, however, this was not specific for COVID-19, and IL-6 concentrations in COVID-19 are probably lower than in other forms of severe ARDS.[6,32–35] The degree of systemic inflammation in our patient cohort was variable, as reflected by the large variability of IL-6, C-reactive protein, or procalcitonin. The extent of adsorption of a given factor by the CytoSorb device is concentration dependent. The small number of patients in our trial does not allow meaningful sub-group analyses with respect to patient response on cytokine adsorption based on different baseline concentrations for IL-6.

Furthermore, the timing of initiation and duration of cytokine adsorption and replacement intervals could play an important role. Our trial does not allow inferences about cytokine adsorption for shorter or longer periods during ECMO support in COVID-19 nor about cytokine adsorption at different timepoints during the course of the disease.

Future investigations of cytokine adsorption in COVID-19 should consider the three major findings from our study: first, early initiation of cytokine adsorption together with initiation of ECMO appears to have a negative effect on patient survival; second, factors that could explain why most patients in the cytokine adsorption group died within the second week of ECMO support need to be studied, such as a possible inflammatory or haemostatic activation several days after termination of cytokine adsorption, including functional assessments of immune cells; third, overall, serum concentrations of IL-6 were lower than usually observed in severe septic shock and it is conceivable that cytokine adsorption might not be beneficial if this surrogate parameter is below a yet to be defined threshold.

Our results do not allow us to draw conclusions about treatment with cytokine adsorption in patients with COVID-19 without venovenous ECMO, nor do they allow us to draw conclusions about treatment with cytokine adsorption in patients with venovenous ECMO for ARDS of causes other than COVID-19. Nevertheless, treatment with cytokine adsorption in patients with COVID-19 requiring venovenous ECMO support has to be considered carefully. We have stopped recruitment for our previously planned multicentre CYCOV-II trial (NCT04385771) and we urge against uncritical use outside of clinical trials.[36]

In severe COVID-19 supported with venovenous ECMO, cytokine adsorption with a CytoSorb adsorber during the first 72 h of ECMO support did not result in reduced IL-6 concentrations after 72 h. Cytokine adsorption was associated with an increased mortality risk within 30 days after initiation of ECMO. Therefore, early cytokine adsorption should be avoided in patients with COVID-19 requiring venovenous ECMO support.

Contributors

ASu was principal investigator of the trial, he wrote the study protocol, designed and supervised the trial, and wrote the first draft of the manuscript. ASu and DD accessed and verified the data. Statistical analyses were done by EW, EG, and AS. MR, AL, TN, TZ, FF, SMü, MK, CBe, SMa, GT, AF, KK, ASe, PS, VZ, CBo, PMB, DS, TW, and DD supported acquisition, analysis, and interpretation of the data. All authors had full access to all the data and the corresponding author had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

Declarations of interests

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Data sharing

Data will not be made available.

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